Published in final edited form as:
Cancer Epidemiol Biomarkers Prev. 2013 October ; 22(10): 1853–1861. doi: 10.1158/1055-9965.EPI-13-0560.

Reproductive Factors, Heterogeneity, and Breast Tumor Subtypes in Women of Mexican Descent

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Abstract

Background—Published data support the presence of etiologic heterogeneity by breast tumor subtype, but few studies have assessed this in Hispanic populations.

Methods—We assessed tumor subtype prevalence and associations between reproductive factors and tumor subtypes in 1041 women of Mexican descent enrolled in a case-only, binational breast cancer study. Multinomial logistic regression comparing human epidermal growth factor receptor 2 positive (HER2+) tumors and triple negative breast cancer (TNBC) to luminal A tumors was conducted.

Results—Compared to women with luminal A tumors, those with a later age at first pregnancy were less likely to have TNBC (odds ratio [OR], 0.61; 95% CI, 0.39–0.95), whereas those with ≥ 3 full-term pregnancies were more likely to have TNBC (OR, 1.68; 95% CI, 1.10–2.55). A lower odds of TNBC was shown for longer menstruation duration, whether prior to first pregnancy (OR, 0.78; 95% CI, 0.65–0.93 per 10 years) or menopause (OR, 0.79; 95% CI, 0.69–0.91 per 10 years). Patients who reported breastfeeding for >12 months were over twice as likely to have TNBC than luminal A tumors (OR, 2.14; 95% CI, 1.24–3.68). Associations comparing HER2+ to luminal A tumors were weak or non-existent except for the interval between last full-term pregnancy and breast cancer diagnosis.

Conclusions—Findings show etiologic heterogeneity by tumor subtype in a population of Hispanic women with unique reproductive profiles.

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Conflicts of Interest: The authors have no disclosures or conflicts of interest.

Impact—Identification of etiologically distinct breast tumor subtypes can further improve our understanding of the disease and help provide personalized prevention and treatment regimens.

Keywords

Breast cancer; Breastfeeding; Hispanics; Parity; Reproductive Factors; Tumor Subtype

Introduction

Established risk factors for breast cancer include older age, family history, high mammographic density, and obesity in post- but not pre-menopausal disease [1]. In addition, a number of reproductive factors, including earlier menarche, nulliparity, older age at first pregnancy, and use of hormone replacement therapy (HRT) containing synthetic progestins, have been associated with higher risk of developing breast cancer [1]. Although data are scarce, longer menstruation duration has also been associated with higher risk [2, 3].

Differences in patient outcomes based on tumor hormone receptor status, estrogen receptor (ER) and progesterone receptor (PR), as well as the expression level of human epidermal growth factor receptor 2 (HER2) has resulted in routine clinical stratification of tumors in the treatment setting. Gene expression studies have confirmed the existence of distinct and reproducible breast cancer subtypes with molecular differences aligning on hormone receptor and HER2 status and at least four major disease subtypes [4]. In parallel, epidemiological studies provide evidence supporting differential effects of reproductive and genetic risk factors on the risk of developing hormone receptor positive or negative tumors, which further support etiologic heterogeneity among breast tumors.

As we have previously noted [5], case-only studies can serve as a useful initial step in understanding the extent of etiologic heterogeneity by identifying correlations between risk factor and disease subtypes. Furthermore, much can be learned by assessing disease risk or etiologic heterogeneity in populations with unique risk factor distributions. Here we report on reproductive differences by tumor subtype in a high-fertility patient series of breast cancer cases from women of Mexican descent, including a novel exploration of menstruation history.

Materials and Methods

Study Population

The *Ella* Binational Breast Cancer Study is a case-only study of invasive breast cancer; details of the study have been previously described [6]. Briefly, using the same protocol and data collection instruments, Mexican and Mexican-American women age ≥ 18 y were recruited within 24 months of diagnosis. Recruitment sites included two in the U.S. (the Arizona Cancer Center, which recruited from throughout Arizona; and the M.D. Anderson Cancer Center in Houston, Texas) and three in Mexico (the Universidad de Sonora in Hermosillo, Sonora; the Instituto Tecnológico de Sonora in Ciudad Obregón, Sonora; and the Universidad de Guadalajara in Guadalajara, Jalisco). All recruitment sites used a predominately clinic-based recruitment strategy. Recruitment took place from March 2007 through June 2011, with response rates ranging from 95–99% [6]. Of 1151 total eligible cases, 110 (9.6%) had unknown ER status, yielding a sample size of 1041 for the present analysis (559 U.S. and 482 Mexico). The Institutional Review Board from each participating institution approved the study protocol, and all women provided informed consent.

Data Collection and Variable Definition

Risk factor data were ascertained from an interview-administered questionnaire and included age at menarche, age at menopause, number of full-term pregnancies (pregnancies lasting greater than 5 months regardless of outcome), age at first full-term pregnancy, breastfeeding history, HRT use, and hormone contraceptive use (including birth control pills, injections, implants, patches, and vaginal ring). To assess the association between menstruation history and tumor subtype, we derived three variables after excluding women who reported irregular menstrual cycles (n=62): 1) interval between age at menarche and age at first full-term pregnancy; 2) duration of menstruation taking into account number of pregnancies: [(age at menopause – age at menarche) – (0.75 y * number of pregnancies)]; and 3) duration of menstruation taking into account pregnancies and breastfeeding, derived as follows: [(age at menopause – age at menarche) – (0.75 y * number of pregnancies)] – (breastfeeding duration). In the last two variables, we substituted age at diagnosis for age at menopause for premenopausal women.

Age at diagnosis and tumor marker data for ER, PR, and HER2 were abstracted from medical records. In the abstraction, priority was given to a numeric value for the percent of cells staining, where ER and PR positivity was based on ≥ 1% cell staining by immunohistochemistry (IHC). Cases were considered HER2+ if amplified as determined by fluorescence *in situ* hybridization (FISH; ratio ≥ 2.2). If no FISH results were available, an IHC intensity score of 3/3+ was considered positive, 2/2+ equivocal, and 0/1/1+ negative. For HER2 classification, we excluded cases with an equivocal IHC intensity score and no FISH data from the analyses (n=53). Cases were assigned to one of three tumor marker categories: luminal A (ER+ and/or PR+ and HER2−), HER2+ (regardless of ER or PR status), and TNBC (ER−, PR−, and HER2−). We classified HER2+ tumors independent of hormone receptor status based on data that HER2 mediates endocrine independence [7] and would likely be a shared etiologic factor. In a sensitivity analyses, we classified cases with equivocal IHC score and no FISH data for HER2 as HER2− and included them in the analyses; results were unchanged when compared to those presented in the tables.

Statistical Analysis

Descriptive statistics (mean ± SD and proportions) for risk factor characteristics and tumor markers were calculated for the total study population and separately by country of residence (U.S. or Mexico). Associations between reproductive factors and tumor subtypes were tested using multinomial logistic regression, considering luminal A tumors as the comparison group. Each model generated an odds ratio (OR) and 95% confidence interval (CI). Since the primary objective was to quantify the associations between reproductive factors and tumor subtype as a means of understanding tumor heterogeneity rather than building risk models, the ORs were adjusted only for age at diagnosis (continuous) and recruitment country (U.S. or Mexico). We did, however, explore parity and breastfeeding together in one model given the interest in understanding the independent effect of each. Tests for trend were conducted by modeling risk factors as continuous variables. All statistical analyses were performed using Stata 12.1 (StataCorp, College Station, TX).

Results

Table 1 presents the risk factor distributions for the 1041 study participants by tumor subtype. Participants with TNBC were younger at diagnosis than those with luminal A or HER2+ tumors. Duration of menstruation and the interval between menarche and first pregnancy were shortest for patients with TNBC. Age at first full-term pregnancy was lowest among women with TNBC. Parity was high in the total population (mean 3.6 births) and it was highest among women with TNBC. Breastfeeding was more prevalent and longer

in duration for women with TNBC. Women with TNBC had the youngest age at menopause and the lowest prevalence of hormone contraceptive use.

We observed variations in the prevalence of tumor markers by country (Table 2). A higher proportion of ER- tumors was shown for women in Mexico compared to those in the U.S. Slightly higher proportions of luminal A and HER2+ tumors were observed in the U.S. versus Mexico. Prevalence of TNBC was 16.7% overall; however, the percentage was higher in cases in Mexico (19.5%) than in the U.S. (14.5%).

Reproductive risk factor associations for HER2 subtype and TNBC were conducted using luminal A tumors as the reference group (Table 3). Patients with ≥ 3 full-term pregnancies were more likely to have TNBC than luminal A tumors (OR, 1.68; 95% CI, 1.10–2.66). Women with a later age at first pregnancy were less likely to have TNBC than luminal A tumors (OR, 0.61; 95% CI, 0.39–0.95). When compared to cases who never breastfed, those who reported breastfeeding for > 12 months were over twice as likely to have TNBC than luminal A tumors (OR, 2.14; 95% CI, 1.24–3.68); a similar association was observed for breastfeeding duration per birth. A longer interval between menarche and first pregnancy was significantly associated with lower odds of having TNBC than luminal A tumors (OR=0.47; 95% CI, 0.65–0.93 for 13+ vs. <8 years). Likewise, TNBCs were less likely in women with longer menstruation duration, whether considering pregnancies or pregnancies and breastfeeding duration. An inverse association between hormone contraceptive use and TNBC was observed but the point estimate was imprecise. Associations comparing HER2+ to luminal A tumors were weak or non-existent, except for a higher likelihood of having HER2+ tumors among women whose interval between last full-term pregnancy and breast cancer diagnosis was within 10 years, which we have previously reported [8]; no association was shown for TNBC. When we considered hormone receptor status of HER2+ tumors in the reported associations, we found no evidence of a difference by hormone receptor status (data not shown).

In an effort to elucidate the association between breastfeeding and TNBC, we explored confounding and effect modification by parity in this association. Nulliparous women were excluded from these analyses. We observed no significant interaction between parity and breastfeeding (P=0.751). Associations between parity and TNBC were fairly consistent across breastfeeding categories, as were associations between breastfeeding and TNBC across parity categories (Table 4). When we included parity and breastfeeding in the same model, the ORs for TNBC and parity and breastfeeding were fairly consistent with the positive associations observed in the models that included these variables separately.

Discussion

In this case-only study in women of Mexican descent, several reproductive factors, including age at first full-term pregnancy, parity, interval between menarche and first pregnancy, duration of menstruation, and breastfeeding, differed in their distribution by tumor subtype. Despite the vast amount of published reports on breast cancer risk factors, relatively few have investigated associations by tumor subtypes. With few exceptions [8–11], most of these study populations comprise predominately or exclusively non-Hispanic white (NHW) women. Consistent with a recent report of Hispanic women [12], the reproductive pattern of participants in our study with breast cancer would classify them as low risk (i.e., high parity, early age at first pregnancy, high breastfeeding rates, and low HRT use).

Our findings add to the growing evidence that reproductive risk factors have divergent effects on breast tumors according to subtype. These differences likely contribute to

population-specific disease patterns, which, given the effect of subtype on prognosis, have direct impact on population disease outcomes. For example, the observation that patients with high parity are more likely to present with poor prognosis TNBC than with hormone-responsive luminal A tumors could partly explain the higher cancer-specific mortality in Mexican women compared to lower parity NHWs [13]. These results suggest that differences in reproductive patterns across racial/ethnic groups are key contributors to population differences in breast phenotype and burden.

Emerging patterns of breast cancer subtype-specific risk associated with reproductive history are complex. It has been hypothesized that breast epithelial cells undergo differentiation following pregnancy, making them less susceptible to the effect of carcinogens [14], which suggests that the period of relevant exposure is that prior to initiation of pregnancy [15]. However, results from other studies show that both number of menstrual cycles before first full-term pregnancy and total menstrual cycles are positively associated with risk of breast cancer [2, 3]. A more recent case-control study [16] showed that the interval between menarche and first pregnancy was inversely associated with risk of TNBC but not ER+ tumors. Our results are consistent with this degree of heterogeneity, which applies to both duration of menstruation before first pregnancy as well as that extending to menopause.

Case-control and cohort studies have shown positive associations between parity and risk of ER- tumors or TNBC [17–25]. Studies extending outcome to include the intrinsic subtypes also find basal-like tumors associated with higher parity [9, 17, 26]. Our results are in agreement with four case–case analyses that reported positive associations between parity and TNBC compared to hormone receptor positive or luminal A tumors [10, 18, 19, 26, 27]; one of these was conducted in Mexican women [10]. The literature on age at first pregnancy and tumor subtype is mixed. Our results show that women with later age at first full-term pregnancy (≥ 25 years) have a lower odds of having TNBC than luminal A tumors, consistent with data from a case-control study of younger women [16] and a large pooled analysis [17] but not with others [9, 11, 21, 25, 26, 28, 29]. Differences in the findings across studies could be due in part to variation in the age cut-off used to define later age at first pregnancy as well as whether nulliparous or women with younger age at first birth is used as the referent group.

A pooled analysis of 47 studies showed that the relative risk of breast cancer decreased by 4.3% for every 12 months of breastfeeding [30]. This protective effect could be due to breastfeeding's induction of final differentiation of the terminal duct epithelium, making it less sensitive to hormonal stimulation [31], or through delay in return of ovulation, reducing the cumulative number of menstrual cycles and exposure to ovarian hormones. Relatively fewer studies have reported associations between breastfeeding and tumor subtype. Although not all associations are statistically significant, several studies have reported a lower risk of ER−, TNBC, or basal-like breast cancer in parous women who breastfed compared to those who do not [9, 10, 16, 20–22, 28, 29, 32]; one exception is a study among younger women [33]. Three studies found a protective effect of breastfeeding but no difference in risk by tumor subtype [23, 24, 34]. Likewise, case-only studies have shown lower odds of having TNBC or ER− breast cancer than luminal A tumors associated with breastfeeding [18, 19, 27]. However, a clinic-based study from Turkey reported a positive association between breastfeeding and TNBC compared to luminal subtype, although the odds ratio was imprecise [35]. Our results show a higher likelihood of TNBC than luminal A tumors associated with breastfeeding for >12 months. Reasons for this opposing observation are unclear. Although some have explored the independent risk of parity and breastfeeding [11, 19], challenges occur due to their natural co-occurrence. This is even more challenging in the *Ella* Study population, since highly parous women tend to also breastfeed. Our

stratified analyses support the positive association for parity and TNBC since the ORs among women who never breastfed are similar to those who breastfed for > 12 months. Likewise, our stratified analyses for breastfeeding are consistent with a positive association with TNBC, which is also supported in the multivariate analyses that adjusted for parity. Given the higher parity and breastfeeding duration in the *Ella* Study, future studies among populations with similar exposures should assess these associations. As we have previously noted [5], we must emphasize that our case-case ORs can only point to degree of heterogeneity by tumor subtype, and it is not possible for us to assess risk by subtype.

Data on risk factor associations with breast tumors overexpressing HER2 are sparse. Phipps et al., [21], reported a higher risk for HER2+ tumors associated with a later age at first birth (compared to younger women) whereas Kwan et al., [18] showed that a younger age at first pregnancy (compared to nulliparous women) was associated with higher odds of HER2+ tumors than luminal A breast cancers. Two case-control studies [22, 24] showed a lower risk for HER2+ tumors associated with breastfeeding. Our results do not support any associations for the reproductive risk factors assessed, with the exception of time since last birth, which we have previously reported [8].

Strengths of our study relate to the large sample of women of Mexican descent residing in the U.S. or Mexico and the well-characterized risk factor data and tumor phenotypes. Though recruitment was not population-based, participation was very high (95–99%), which is a challenge in population-based studies. The value of a case-only study design continues to be appreciated, particularly for understanding etiologic heterogeneity [5, 17, 36]. Recognizing the limitations of this design, we were careful not to interpret the associations as indicators of risk. Finally, despite the value in assessing the unique distribution of risk factors by tumor subtype, we were unable to assess these in the context of nulliparity due to its low prevalence in the *Ella* Study.

In summary, unique reproductive risk factor distributions in a population of Hispanic women indicate substantial heterogeneity in associations between reproductive risk factors and luminal A and TNBC breast cancers. Such heterogeneity was less evident for HER2+ tumors, with the exception of the interval between last birth and breast cancer diagnosis. Given the case-only design, these results must be replicated in populations including non-diseased groups. Identification of distinct breast tumor subtypes with discrete natural histories will continue to be helpful in identifying alternate mechanisms of etiopathogenesis for specific tumor phenotypes. This, in turn, can aid in identifying target populations for optimal prevention, diagnosis, and treatment.

Acknowledgments

We are indebted to Erin Ashbeck, Julie Buckmeier, Carole Kepler, and Fang Wang for their contribution.

Grant support: NIH/NCI grants UO1CA153086, CA023074-2953, CA116199-02S1; the Avon Foundation, and the Susan G. Komen for the Cure® (KG090934).

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Table 1

Risk Factors in the *Ella* Study, by Breast Cancer Tumor Subtype

	Luminal A n=571	HER2+ n=225	TNBC n=159
Age at diagnosis, y			
<50	250(43.8)	93 (41.3)	93(58.5)
50 to 59	169 (29.6)	73 (32.4)	30 (18.9)
≥60	152 (26.6)	59 (26.2)	36 (22.6)
Mean ± SD	52.3 ± 12.2	53.2 ± 12.2	50.1 ± 13.3
Age at menarche, y			
<13	261 (45.7)	104 (46.2)	64 (40.5)
≥13	310 (54.3)	121 (53.8)	94 (59.5)
Unknown	0	0	1
Mean ± SD	12.7 ± 1.6	12.7 ± 1.7	13.0 ± 1.7
Parity			
Nulliparous	58 (10.2)	25 (11.1)	9 (5.7)
1 to 2 children	176 (30.8)	74 (32.9)	39 (24.5)
≥3 children	337 (59.0)	126 (56.0)	111 (69.8)
Mean ± SD (excludes nulliparous)	3.5 ± 2.2	3.5 ± 2.1	3.7 ± 2.1
Age at first full-term pregnancy, y			
<21	201 (39.2)	77 (38.5)	68 (45.6)
21–24	133 (25.9)	55 (27.5)	42 (28.2)
≥25	179 (34.9)	68 (34.0)	39 (26.2)
Nulliparous	58	25	9
Unknown	0	0	1
Mean ± SD	23.1 ± 5.6	23.0 ± 5.3	21.9 ± 4.9
Time since last full-term pregnancy, y			
>10	159 (64.4)	53 (57.0)	48 (60.0)
≤10	88 (35.6)	40 (43.0)	32 (40.0)
Postmenopausal (or unknown)	293	122	71
Premenopausal but nulliparous	31	10	8
Mean ± SD	13.5 ± 7.6	13.5 ± 8.2	12.1 ± 7.7
Time from menarche to first pregnancy, y			
<8	179 (34.9)	71 (35.5)	69 (46.6)
8–12	172 (33.5)	68 (34.0)	49 (33.1)
≥13	162 (31.6)	61 (30.5)	30 (20.3)
Nulliparous	58	25	9
Unknown	0	0	2
Mean ± SD	10.3 ± 5.8	10.2 ± 5.5	8.9 ± 5.2
Lifetime duration of breastfeeding, mo			
Never	134 (26.1)	58 (29.0)	23 (15.3)
Up to 12	188 (36.7)	63 (31.5)	52 (34.7)
>12	191 (37.2)	79 (39.5)	75 (50.0)

	Luminal A n=571	HER2+ n=225	TNBC n=159
Nulliparous	58	25	9
Mean ± SD	18.3 ± 28.7	21.5 ± 36.5	24.8 ± 34.9
Breastfeeding duration per birth, mo			
Never	134 (26.1)	58 (29.0)	23 (15.3)
>0 to 5	206 (40.2)	66 (33.0)	60 (40.0)
>5	173 (33.7)	76 (38.0)	67 (44.7)
Nulliparous	58	25	9
Mean ± SD	4.7 ± 6.5	5.1 ± 6.3	6.4 ± 7.4
Duration of menstruation, y			
7.6–27.35	172 (32.4)	59 (28.8)	64 (42.4)
27.4–33.45	174 (32.8)	62 (30.2)	60 (39.7)
33.5–50.5	185 (34.8)	84 (41.0)	27 (17.9)
Periods never regular	35	14	7
Unknown	5	6	1
Mean ± SD	30.1 ± 7.2	30.9 ± 6.4	27.5 ± 7.1
Duration of menstruation, y			
0–25.23	150 (31.5)	56 (30.8)	58 (40.9)
25.23–31.75	160 (33.6)	55 (30.2)	57 (40.1)
31.85–50.5	166 (34.9)	71 (39.0)	27 (19.0)
Periods never regular	35	14	7
Unknown	60	29	10
Mean ± SD	28.4 ± 7.5	28.8 ±6.9	25.8 ± 7.6
Menopausal status at diagnosis			
Premenopausal	278 (49.2)	103 (47.0)	88 (55.7)
Postmenopausal	287 (50.8)	116 (53.0)	70 (44.3)
Unknown	6	6	1
Age at menopause, y			
<50	164 (57.1)	68 (58.6)	48 (68.6)
≥50	123 (42.9)	48 (41.4)	22 (31.4)
Premenopausal at diagnosis	278	103	88
Unknown	6	6	1
Mean ± SD	47.3 ± 6.7	47.7 ± 6.1	45.9 ± 7.1
Hormone replacement therapy			
Never	490 (86.9)	192 (85.7)	142 (89.3)
Ever	74 (13.1)	32 (14.3)	17 (10.7)
Unknown	7	1	0
Hormone contraceptive use			
Never	244 (42.8)	102(45.3)	78 (49.1)
Ever	326 (57.2)	123 (54.7)	81 (50.9)
Unknown	1	0	0

Abbreviations: SD, standard deviation; U.S., United States; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer.

[A] Textile categories; duration accounts for pregnancy. Excludes 56 women never having a regular period and 12 women with unknown age at menopause or menopausal status.

[b] Tertile categories; duration accounts for pregnancy and breastfeeding. Excludes 56 women never having a regular period, 12 women with unknown age at menopause/menopausal status, and 87 women with unknown lifetime duration breastfeeding.

Table 2

Distribution of Breast Cancer Tumor Subtypes in the *Ella* Study by Country

Tumor subtype	No. of patients (%)		
	Total n = 1041	US n = 559	Mexico n = 482
ER^-	347 (33.3)	152 (27.2)	195 (40.5)
ER^+	694 (66.7)	407 (72.8)	287 (59.5)
PR^-	408 (39.8)	209 (37.8)	199 (42.2)
PR^+	617 (60.2)	344 (62.2)	273 (57.8)
PR unknown	16	6	10
luminal A	571 (59.8)	330 (61.2)	241 (57.9)
$HER2^-$	735 (72.6)	410 (74.6)	325 (70.2)
$HER2^+$	225 (22.2)	131 (23.8)	94 (20.3)
HER2 equivocal	53 (5.23)	9 (1.64)	44 (9.50)
$HER2+^a$	225 (23.6)	131 (24.3)	94 (22.6)
HER2 unknown	28	9	19
TNBC	159 (16.7)	78 (14.5)	81 (19.5)
Subtype unknown	86	20	66

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; luminal A, hormone receptor; PR, progesterone receptor; TNBC, triple negative breast cancer; US, United States.

[a]Excludes women with equivocal immunohistochemistry scores.

Table 3

Adjusted Odds[a] for TNBC and HER2+ Compared to Luminal A Tumors and Reproductive and Hormonal Factors

	Luminal A n = 571	HER2+ n = 225		TNBC n = 159	
	No. (%)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
Age at diagnosis, y					
< 50	250 (43.8)	93 (41.3)	1.00	93 (58.5)	1.00
50 to 59	169 (29.6)	73 (32.4)	1.17 (0.81–1.68)	30 (18.9)	0.44 (0.28–0.70)
≥ 60	152 (26.6)	59 (26.2)	1.05 (0.71–1.56)	36 (22.6)	0.57 (0.36–0.88)
Per 5 y			1.01 (0.95–1.08)		0.89 (0.83–0.96)
Age at menarche, y					
< 13	261 (45.7)	104 (46.2)	1.00	64 (40.5)	1.00
≥ 13	310 (54.3)	121 (53.8)	0.98 (0.71–1.33)	94 (59.5)	1.27 (0.88–1.82)
Per 5 y			0.93 (0.58–1.50)		1.64 (0.95–2.82)
Parity					
Nulliparous	58 (10.2)	25 (11.1)	1.02 (0.59–1.75)	9 (5.66)	0.71 (0.32–1.57)
1 to 2 children	176 (30.8)	74 (32.9)	1.00	39 (24.5)	1.00
≥ 3 children	337 (59.0)	126 (56.0)	0.87 (0.61–1.24)	111 (69.8)	1.68 (1.10–2.55)
Per birth (excludes nulliparous)			0.99 (0.91–1.08)		1.07 (0.98–1.18)
Age at first full-term pregnancy, y					
< 21	201 (39.2)	77 (38.5)	1.00	68 (45.6)	1.00
21–24	133 (25.9)	55 (27.5)	1.08 (0.72–1.63)	42 (28.2)	0.90 (0.58–1.41)
≥ 25	179 (34.9)	68 (34.0)	0.99 (0.68–1.46)	39 (26.2)	0.61 (0.39–0.95)
Per 5 y			1.00 (0.97–1.03)		0.95 (0.92–0.99)
Time since last full-term pregnancy[b], y					
> 10	159 (64.4)	53 (57.0)	1.00	48 (60.0)	1.00
≤ 10	88 (35.6)	40 (43.0)	1.83 (0.96–3.48)	32 (40.0)	0.76 (0.38–1.52)
Per 5 y			0.97 (0.78–1.21)		0.99 (0.78–1.26)
Lifetime duration of breastfeeding[c], mo					
Never	134 (26.1)	58 (29.0)	1.00	23 (15.3)	1.00
Up to 12	188 (36.7)	63 (31.5)	0.77 (0.50–1.18)	52 (34.7)	1.44 (0.83–2.49)

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	Luminal A n = 571	HER2+ n = 225		TNBC n = 159	
	No. (%)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
> 12	191 (37.2)	79 (39.5)	0.97 (0.63–1.50)	75 (50.0)	2.14 (1.24–3.68)
Per 6 mo			1.03 (0.99–1.06)		1.04 (1.01–1.08)
Breastfeeding duration per birth[c], mo					
Never	134 (26.1)	58 (29.0)	1.00	23 (15.3)	1.00
> 0 to 5	206 (40.2)	66 (33.0)	0.74 (0.49–1.13)	60 (40.0)	1.52 (0.89–2.60)
> 5	173 (33.7)	76 (38.0)	1.03 (0.67–1.59)	67 (44.7)	2.07 (1.20–3.58)
Per 6 mo			1.06 (0.91–1.24)		1.20 (1.03–1.41)
Time from menarche to first pregnancy, y					
< 8	179 (34.9)	71 (35.5)	1.00	69 (46.6)	1.00
8–12	172 (33.5)	68 (34.0)	1.00 (0.67–1.48)	49 (33.1)	0.75 (0.49–1.15)
≥ 13	162 (31.6)	61 (30.5)	0.95 (0.63–1.42)	30 (20.3)	0.47 (0.29–0.77)
Per 10 y			0.99 (0.85–1.14)		0.78 (0.65–0.93)
Duration of menstruation[d], y					
7.6–27.35	172 (32.4)	59 (28.8)	1.00	64 (42.4)	1.00
27.4–33.45	174 (32.8)	62 (30.2)	1.04 (0.68–1.59)	60 (39.7)	0.99 (0.65–1.53)
33.5–50.5	185 (34.8)	84 (41.0)	1.33 (0.87–2.03)	27 (17.9)	0.43 (0.25–0.74)
Per 5 y			1.09 (0.95–1.24)		0.79 (0.69–0.91)
Duration of menstruation[e], y					
0–25.23	150 (31.5)	56 (30.8)	1.00	58 (40.9)	1.00
25.25–31.75	160 (33.6)	55 (30.2)	0.92 (0.60–1.43)	57 (40.1)	0.96 (0.62–1.49)
31.85–50.5	166 (34.9)	71 (39.0)	1.15 (0.75–1.78)	27 (19.0)	0.47 (0.28–0.79)
Per 5 y			1.04 (0.92–1.18)		0.82 (0.72–0.93)
Age at menopause, y					
< 50	164 (57.1)	68 (58.6)	1.00	48 (68.6)	1.00
≥ 50	123 (42.9)	48 (41.4)	0.97 (0.62–1.52)	22 (31.4)	0.59 (0.33–1.04)
Per 5 y			1.07 (0.90–1.27)		0.82 (0.67–1.01)
Hormone replacement therapy					
Never	490 (86.9)	192 (85.7)	1.00	142 (89.3)	1.00
Ever	74 (13.1)	32 (14.3)	1.09 (0.69–1.72)	17 (10.7)	0.99 (0.56–1.77)

	Luminal A n = 571	HER2+ n = 225		TNBC n = 159	
	No. (%)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
Hormone contraceptive use					
Never	244 (42.8)	102 (45.3)	1.00	78 (49.1)	1.00
Ever	326 (57.2)	123 (54.7)	0.91 (0.66–1.26)	81 (50.9)	0.70 (0.49–1.01)

Abbreviations: CI, confidence interval; HER2, human epidermal growth factor receptor 2; OR, odds ratio; TNBC, triple negative breast cancer.

[a] Adjusted for age at diagnosis (continuous) and country (U.S. vs. Mexico).

[b] Among pre-menopausal women only.

[c] Excludes nulliparous women.

[d] Tertile categories; duration accounts for pregnancy. Excludes 62 women never having a regular period and 13 women with unknown age at menopause or menopausal status.

[e] Tertile categories; duration accounts for pregnancy and breastfeeding. Excludes 62 women never having a regular period, 13 women with unknown age at menopause/menopausal status, and 99 women with unknown lifetime duration breastfeeding.

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Table 4

Adjusted Odds for TNBC Compared to Luminal A Tumors for Subgroups of Parity and Breastfeeding

	Luminal A n = 571	TNBC n = 159	
	No. (%)	**No. (%)**	**OR (95% CI)**
Multivariate Model[a]			
Breastfeeding			
Never	134 (26.1)	23 (15.3)	1.00
Up to 12 mos	188 (36.6)	52 (34.7)	1.40 (0.81–2.43)
>12 mos	191 (37.2)	75 (50.0)	1.91 (1.09–3.36)
Parity			
1 to 2 children	176 (30.8)	39 (24.5)	1.00
≥ 3 children	337 (59.0)	111 (69.8)	1.41 (0.91–2.20)
Parity[b] stratified by Breastfeeding			
Among never breastfed			
1 to 2 children	65 (48.5)	10 (43.5)	1.00
≥ 3 children	69 (51.5)	13 (56.5)	1.47 (0.57–3.78)
Per birth (excludes nulliparous)			1.27 (0.95–1.70)
Among breastfed ≤ 12 mo			
1 to 2 children	80 (42.6)	20 (38.5)	1.00
≥ 3 children	108 (57.5)	32 (31.5)	1.29 (0.67–2.48)
Per birth (excludes nulliparous)			1.08 (0.89–1.31)
Among breastfed > 12 mo			
1 to 2 children	31 (16.2)	9 (12.0)	1.00
≥ 3 children	160 (83.8)	66 (88.0)	1.54 (0.68–3.47)
Per birth (excludes nulliparous)			0.95 (0.83–1.08)
Breastfeeding[b] stratified by parity			
Among 1–2 children			
Never	65 (36.9)	10 (25.6)	1.00
Up to 12	80 (45.5)	20 (51.3)	1.46 (0.63–3.41)
> 12	31 (17.6)	9 (23.1)	1.66 (0.60–4.64)
Per 6 mo			1.04 (0.89–1.20)
Among 3+ children			
Never	69 (20.5)	13 (11.7)	1.00
Up to 12	108 (32.1)	32 (28.8)	1.39 (0.67–2.87)
> 12	160 (47.5)	66 (59.5)	2.00 (1.00–4.03)
Per 6 mo			1.04 (1.00–1.08)

Abbreviations: CI, confidence interval; HER2, human epidermal growth factor receptor 2; OR, odds ratio; TNBC, triple negative breast cancer.

[a] Breastfeeding and parity included in a single model, adjusted for age at diagnosis (continuous) and country (U.S. vs. Mexico).

[b] Adjusted for age at diagnosis (continuous) and country (U.S. vs. Mexico).