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Parity and lactation in relation to estrogen receptor negative breast cancer in African American women

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Abstract

Background—Estrogen receptor (ER) negative, progesterone receptor (PR) negative breast tumors occur more commonly in women of African ancestry. Recent research indicates that the effects of reproductive factors may differ by hormone receptor status. We assessed the relation of parity and lactation to incidence of ER−/PR− and ER+/PR+ breast cancer in a cohort of African American women.

Methods—From 1995–2009, 457 incident cases of ER+/PR+ and 318 cases of ER−/PR− breast cancer were confirmed by review of pathology data among 59,000 African American women followed in the Black Women's Health Study through biennial questionnaires. Hazard ratios (HR) and two-sided 95% confidence intervals (CI) for the incidence of breast cancer subtypes were derived from proportional hazards regression models that controlled for age, reproductive variables, and breast cancer risk factors.

Results—Higher parity was associated with an increased risk of ER−/PR− breast cancer (HR = 1.48, 95% CI 0.98–1.84 for 3+ versus 0 births, p trend = 0.009), and with a reduced risk of ER+/PR+ cancer (HR = 0.53, 95% CI 0.39–0.73 for 3+ versus 0 births, p trend = 0.0002). Among women who had breastfed, high parity was no longer associated with increased incidence of ER−/PR− breast, but the inverse association with ER+/PR+ cancer persisted.

Conclusions—The higher incidence of ER−/PR− breast cancer in African American women may be explained in part by their higher parity and lower prevalence of breastfeeding relative to white women.

Impact—Increased breastfeeding may lead to a reduction in the incidence of this breast cancer subtype.

Keywords

Estrogen receptors; breast cancer; parity; lactation; disparities

INTRODUCTION

Tumors characterized by a lack of estrogen receptors (ER) and progesterone receptors (PR) are associated with an aggressive pathology and poor prognosis and occur in African American women more frequently than in white women at every age level.(1–3) Numerous

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risk factors for ER+ breast cancer, many of them hormonal, have been identified, but the causal etiology of ER− breast cancer is largely unexplained.

A dual effect of parity on overall breast cancer incidence is widely recognized. In the first years following a full-term pregnancy, and possibly extending for as long as 10–15 years, there is an increased risk of developing breast cancer.(4–7) Possible contributors are pregnancy-related hormones (estrogens, progesterone, and IGF-1) that promote previously initiated cells, immune suppressive effects of pregnancy, and inflammatory effects of the post-partum involution process. After the 10–15 year period of increased risk of breast cancer, parous women subsequently have a reduced risk.(8–11) This pattern holds for ER positive breast cancer,(12–18) but full-term pregnancy may have a sustained adverse effect on risk of ER− breast cancer.(18–23)

We previously observed that high parity was associated with increased risk of breast cancer before age 45 and with a reduced risk at older ages in African American women.(24) We now have sufficient data to investigate the effects of parity separately for ER−/PR− and ER +/PR+ breast cancers.

METHODS

Study population and data

The Black Women's Health Study (BWHS) began in 1995 when 59,000 African American women aged 21–69 from across the U.S. completed mailed health questionnaires. Participants have completed follow-up questionnaires every two years. Over 80% of participants in the original cohort were successfully followed through the most recent completed questionnaire cycle. The Institutional Review Board of Boston University approved the protocol and reviews the study annually.

At baseline, participants were asked about the number of births, timing of each full-term birth, whether they had ever breastfed, and total duration of breast feeding. There were also asked their height and weight, age at menarche, oral contraceptive use, breast cancer in first degree relatives, vigorous physical activity, alcohol consumption, menopausal status, age at menopause, supplemental female hormone use, and years of education. The biennial follow-up questionnaires ascertained occurrences of incident breast cancer and updated information on births, breast-feeding, oral contraceptive use, weight, vigorous physical activity, alcohol consumption, menopausal status, and supplemental female hormone use.

The present analyses are based on follow-up from 1995 through 2009. We excluded women who reported any cancer at baseline (N=1,476), had missing data on number of births (N=124) or missing data on age at first birth (N=374). We identified 1,692 incident cases of breast cancer among the remaining participants and obtained pathology data from either medical records or cancer registries for 1,332 cases. The present analyses are based on the 922 incident breast cancer cases with known receptor status. The proportion of cases on which such data were available increased over the course of follow-up to >80% in the last completed cycle of follow-up as ascertainment of hormone receptor status became the standard of care in hospitals nationwide. The proportions with ER+PR+, ER+PR−, ER−PR +, and ER−PR− tumors were 50%, 14%, 2%, and 34%, respectively, similar to the distributions observed for African American women in SEER registry and other population-based data.(25–27) Information on HER2 expression was unavailable for most BWHS breast cancer cases. A comparison of the 922 cases with known receptor status to the 770 cases with unknown receptor status with regard to reproductive factors and other breast cancer risk factors indicated that the cases included in this analysis were similar to the excluded cases. Prevalences of parity ≥2, age at first birth ≥25, years since last birth <10,

and ever lactation for cases with known receptor status versus case with unknown status were, respectively, 40.6, 42.8, p=0.77; 35.9, 35.1, p=0.17; 35.2, 37.9, p=0.26; and 42.6, 40.0, p=0.75. Means for age, age at menarche, and body mass index were 45.3, 44.9, p=0.39; 12.2, 12.2, p=0.47; and 27.4, 27.6, p=0.67, respectively, for included versus excluded cases.

Statistical analysis

Each participant contributed person-time from baseline in 1995 until diagnosis of breast cancer, death, loss to follow-up, or end of follow-up in 2009, whichever came first. We used Cox proportional hazards regression, stratified by age in one-year intervals and questionnaire cycle, to estimate hazard ratios (HR) and 95% confidence intervals (CI) for breast cancer incidence, with adjustment for number of births, age at first birth, years since last birth, lactation, age at menarche (<12, 12–13, ≥14 years), oral contraceptive use (never, <5 years, ≥5 years), body mass index (<25, 25–29, ≥30 kg/m^2), family history of breast cancer, vigorous exercise (none, <5, ≥5 hours/week), current alcohol consumption (<1, 1–6, ≥7 drinks/week), age at menopause (premenopausal, <45, 45–49, ≥50 years), and menopausal female hormone use (never, <5, ≥5 years of use). Covariates were selected a priori based on having an established or suspected causal association with breast cancer incidence. Indicator terms were included for missing data. Covariates that changed over time were treated as time-dependent variables. Women who reported a hysterectomy but retained one or both ovaries were classified as premenopausal if their current age was less than the 10th percentile of age at natural menopause in the BWHS (<43 years), as postmenopausal if their age was greater than the 90th percentile of age at natural menopause in the cohort (>56years), and as having unknown age at menopause if their age was 43–56 years. Educational status, which may be correlated with reproductive factors, was not independently associated with breast cancer incidence; HRs were the same with and without control for education.

To test for trend across categories of parity, age at first birth, and years since last birth, we numbered each category to create an ordinal term in the regression. Departures from the proportional hazards assumption (i.e., a constant HR across age and time) were tested by the likelihood ratio test comparing models with and without interaction terms for age and calendar time with the main exposure variables.

RESULTS

As shown in Table 1, relative to women with only one birth, women with two or more births were older, more likely to have had their first birth before age 25 and to have breastfed, and had fewer years of oral contraceptive use and fewer years of education. Women with an early age at first birth were less likely to have breastfed and had fewer years of oral contraceptive use and fewer years of education than those with first birth at age ≥25. The prevalence of ever lactation was lower in women with ≤12 years of education but was not associated with oral contraceptive use.

As shown in Table 2, higher parity was associated with an increased risk of ER−/PR− breast cancer (HR = 1.48, 95% CI 0.98–1.84 for 3+ relative to 0 births; p trend = 0.009) but with a reduced risk of ER+/PR+ cancer (HR = 0.53, 95% CI 0.39–0.73; p trend = 0.0002;) and ER +/PR− cancer (HR = 0.62, 95% CI 0.35–1.11; p trend= 0.08). Later age at first birth was associated with an increased risk of breast cancer for all subtypes examined, ER+/PR+, ER +/PR, and ER−/PR− (p trend = 0.05, 0.18, 0.04, respectively). Time since last birth was associated with both ER+/PR+ and ER−/PR− breast cancer: the HRs for recent birth (<10 years since last birth) relative to a birth at least 15 years previously were 1.69 (95% CI 1.08–2.63) and 1.61 (0.97–2.68), respectively. There was no association of time since last birth

with ER+/PR− subtype, but there were only 9 cases in the <10 year category. HRs for the association of breastfeeding with subtypes of breast cancer were 1.13 (95% CI 0.91–1.42) for ER+/PR+, 1.25 (95% CI 0.83–1.89) for ER+/PR−, and 0.78 (95% CI 0.60–1.03) for ER −/PR− cancers. HRs were essentially the same for total duration of lactation 1–5 months and total duration ≥6 months.

We stratified the lactation analyses on family history of breast cancer. HRs for ever-lactation in relation to ER+/PR+ breast cancer among women with and without a family history of breast cancer were 0.91 (95% CI 0.51–1.61) and 1.22 (95% CI 0.94–1.60), respectively. Ever-lactation was associated with a significantly reduced risk of ER−/PR− breast cancer among women with a family history of breast cancer (HR = 0.33, 95% CI 0.15–0.72, based on 9 exposed cases) and but not among those without (HR =0.91, 95% CI 0.68–1.22, based on 86 exposed cases) (data not shown).

The inverse association of high parity with ER+/PR+ breast cancer appeared stronger among the older women (ages 45–78), whereas the positive association with older age at first birth appeared stronger among the younger women (Table 3). For ER−/PR− cancer, the associations with parity, age at first birth, and years since last birth were all stronger among women under age 45. However, none of the tests for interaction by age were statistically significant.

Table 4 shows HRs for joint exposure categories of parity with age at first birth, time since last birth, and lactation relative to a reference category of nulliparity. Number of births appeared to be a more important risk factor for ER−/PR− breast cancer than age at first birth or recency of last birth: IRRs for ≥2 births relative to nulliparity were significantly elevated regardless of timing of the first birth and regardless of recency of the last birth. The highest HR (2.20, 95% CI 1.47–3.29) was for women who had their first birth at age 25 or later and had at least two births. For ER+/PR+ breast cancer, age at first birth was a more important factor than parity: women who had their first birth before age 25 had a 30–40% reduced risk of ER+/PR+ breast cancer relative to nulliparous women, regardless of the number of births.

Among women who had never breastfed, having ≥2 births was associated with a 50% increase in risk of ER−/PR− cancer (HR = 1.53, 95% CI 1.09–2.23), whereas there was little increase in risk associated with parity ≥2 births among those who had breastfed (HR = 1.16, 95% CI 0.80–1.69) (Table 4). To test the significance of this interaction by lactation, we estimated the HR for parity ≥2, no breastfeeding relative to a reference category of parity ≥2, ever breastfed; the HR was 1.32 (95% CI 0.98–1.78). For ER+/PR+ breast cancer, parous women had a decreased risk relative to nulliparous women regardless of whether or not they had breastfed.

DISCUSSION

The present results suggest that higher parity is associated with an increased risk of ER−/PR − breast cancer, but that breastfeeding ameliorates this adverse effect. Analyses stratified by time last since birth indicated that the association is not accounted for by the transient increase in risk in the period immediately following a full-term pregnancy. Results for parity and lactation in relation to ER+/PR+ subtype were strikingly different. Higher parity was associated with a reduced risk of ER+/PR+ breast cancer, and breastfeeding did not alter this association.

An inverse association of parity with risk of ER+ breast cancer has been consistently found, (12–15, 18) whereas studies of ER− breast cancer indicate either no association(12–15) or a positive association.(18, 19, 22, 23) Among studies that also considered HER2 status, one found higher parity to be strongly associated with increased risk of both ER−/ PR−/ HER2−

("triple negative") cancer and ER−/PR−/HER2+ cancer,(22) one found high parity to be associated with increased risk of triple negative breast cancer only, (18) and two studies were null.(16, 28) In two case-case analyses that compared the triple negative breast cancer subtype with ER+/PR+ subtype, one found a strong positive association of parity with the triple negative subtype, (21) and the other found a similar positive association of parity with ER−/PR−/HER2+ tumors.(20) Results of studies of "intrinsic" breast cancer subtypes (19, 23, 29) as characterized by immunohistochemistry of several additional molecular markers also support these associations. The basal-like subtype characterized by ER−, PR−, HER2−, HER1+ and/or CK5/6 occurs more frequently in African Americans than in other ethnic groups and carries a poorer prognosis.(3) In a case-control study from Poland, high parity was associated with an increased risk of basal-like breast cancer and a reduced risk of luminal A breast cancer (ER+ and/or PR+, HER2−).(23) In the Carolina Breast Cancer Study, high parity was also positively associated with basal-like breast cancer and inversely associated with luminal A cancer.(19)

The limited data from previous studies regarding the association of both lactation and parity with incidence of the ER− subtype are generally consistent with our findings. In the Carolina Breast Cancer Study,(19) breastfeeding was associated with a reduced risk of basal-like but not luminal A subtype. In addition, the increased risk associated with parity was present only among women who had never breast fed; among women who had breast fed, there was essentially no association of parity with risk of basal-like breast cancer. The two case-only studies described above both observed a reduced risk of triple negative breast cancer associated with lactation,(20, 21) and, in one, the positive association of parity with triple negative breast cancer was present only among women who had never breastfed.(20)

Why might full-term pregnancy, in the absence of breastfeeding, lead to an increased risk of ER− breast cancer? Schedin et al. hypothesized that the adverse effect of pregnancy may relate to immune system / inflammatory processes that occur during post-partum involution. (30–32) Involution involves processes of wound healing and immunosuppression, both of which are known to be pre-tumorigenic. During involution, there is an influx of immune cells, activation of fibroblasts, and extracellular matrix deposition which resembles a pre-tumorigenic wounding environment.(33) Mouse studies have shown that numerous immune-related genes are upregulated during involution.(34) Lactation may mitigate the increased risk from full-term pregnancy by increasing the time between pregnancy and involution, thus lessening the chances that these two events (increase in estrogen levels during pregnancy and postpartum wound healing) will act synergistically to promote progression of previously initiated cells. Further, lactation may prevent disordered involution, characterized by increased inflammation of the mammary tissue. In women who breastfeed, involution is more likely to occur over a period of weeks or months as physiologic weaning takes place; thus, mammary tissue returns to its prepregnant state in a more coordinated process of apoptosis and remodeling.(35) Under these postulated mechanisms, lactation could have a protective effect on all subtypes of breast cancer. We did not, however, observe an association of lactation with risk of ER+/PR+ breast cancer; it is possible that the beneficial effects of lactation on involution may be less important for hormone-positive breast cancer where hormonal influences have a dominant role.

In our analyses of ER− breast cancer, the inverse association with lactation was strongest in the group of women who had a first degree family history of breast cancer. This finding is consistent with a recent report from the Nurses' Health Study II,(36) which showed that among young women with a family history of breast cancer, those who had breastfed or used lactation suppression medications had a reduced risk of breast cancer compared with women who neither breastfed nor used such medications. The authors hypothesized that

both lactation and use of lactation suppression medications could reduce breast cancer risk by preventing disordered involution.

Differences in inflammatory profiles between women of African ancestry and other women may be relevant to our finding of an association of parity in the absence of lactation with risk of ER− breast cancer in African American women. Several markers of inflammation, including C-reactive protein, serum amyloid, and IL-6, are elevated in African Americans.(37–41) A robust immune system has an evolutionary advantage for populations living in sub-Saharan Africa where there has been endemic infectious disease. Genetic profiles have developed over millennia to adapt to these conditions. While these characteristics are advantageous for women living in Africa, the very strong immune response may be disadvantageous in other situations and could lead to an increased risk of aggressive breast tumors following pregnancy without lactation, due to the inflammatory processes accompanying involution. There have been several examples of genetic traits that are beneficial in some environments but detrimental in others. Murine studies show that specific malaria-driven genetic changes, such as loss of the Duffy antigen receptor, result in higher serum chemokine levels and an increased inflammatory milieu, predisposing to the development of more aggressive prostate tumors.(42) More recently, two *APOL1* variants that are common in African chromosomes but absent from European chromosomes were shown to be strongly associated with kidney disease.(43) The variants reside within haplotypes that harbor signatures of positive selection. The protein ApoL1 is a trypanolytic factor that confers resistance to the otherwise deadly infection from the *trypanosoma brucei brucei* parasite. We hypothesize that interactions of immune profiles with pregnancy and lactation may lead to an increased risk of ER− and basal-like breast cancers; the association may be seen most clearly in African Americans, who typically have a more robust inflammatory response. As discussed above, similar mechanisms may be involved in the etiology of ER+ breast cancer as well but may have a minor role relative to the powerful impact of hormone levels on this subtype.

Late age at first birth and recent birth (within 10 years) were associated with increased risk of both ER+ and ER− breast cancer in the present study. Most previous studies have found later age at first birth to be positively associated with ER+ breast cancer only or with both ER+ and ER− breast cancer.(12–17) In contrast, the Carolina Breast Cancer Study observed an association with basal-like but not luminal-A cancers.(19) Most studies to date have not reported on time since last pregnancy by ER/PR status.

Strengths of the present study include the prospective data collection, high response rate, large sample size, and control for a large number of breast cancer risk factors. Notably, this is the first prospective study with sufficient numbers to assess reproductive factors in relation to ER−/PR− breast cancer among African American women. A limitation is that data on ER/PR status were unavailable for 40% of breast cancer cases because many cases were diagnosed before immunohistochemistry was routinely carried out on tumor tissue. However, cases with and without hormone receptor status data were closely similar with regard to reproductive factors and other breast cancer risk factors, mitigating concern about selection bias. We were unable to assess subtypes according to HER2 expression, but previous studies suggest that HER2 status does not modify associations with the ER− subtype. Our ability to assess associations by duration of breastfeeding was limited because most participants who had breastfed had done so for less than 12 months total.

In summary, the present findings suggest that higher parity is associated with an increased risk of ER−/PR− breast cancer in African American women. Since African American women have had more births on average than U.S. white women,(44) this association may explain, in part, why incidence of ER−/PR− breast cancer is higher in African American

than white women. Further, the results provide evidence of a protective effect of lactation on ER−/PR− cancer, at least among women who have a family history of breast cancer. Uptake of breastfeeding has been considerably lower in African American women than in other ethnic groups in spite of efforts to convince women of its numerous health benefits.(45–47) Our results, taken together with recent results from studies of triple negative and basal-like breast cancer, suggest that breastfeeding can reduce risk of developing the aggressive, difficult-to-treat breast cancers that disproportionately affect African American women.

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Table 1

Baseline characteristics according to parity, age at first birth, and lactation[1]

	Parity			Age at first birth[2]		Lactation[2]	
	0	**1**	**≥2**	**<25**	**≥25**	**Never**	**Ever**
N	20,480	12,439	24,123	25,966	10,596	21,343	14,717
Parity ≥ 2 births, %	-	-	-	69.7	41.0	57.5	67.6
Age at first birth ≥ 25 years, %	-	43.9	18.6	-	-	22.4	36.2
Ever lactation, %	-	33.8	45.0	36.2	52.5	-	-
Years since last birth < 10, %	-	41.4	49.4	39.0	60.2	41.5	52.2
Age (years), mean	33.0	38.6	43.7	42.2	41.5	42.4	41.3
Age at menarche (years), mean	12.3	12.4	12.4	12.4	12.4	12.4	12.3
Postmenopausal, %	18.2	17.2	16.5	17.3	15.6	17.5	15.5
Family history of breast cancer, %	6.7	6.5	6.4	6.5	6.3	6.6	6.2
Oral contraceptive use ≥5 years, %	33.7	35.7	25.7	25.7	39.3	30.1	29.3
Ever female hormone use, %	17.0	16.1	15.0	16.1	13.3	15.9	14.2
Body mass index (kg/m^2), mean	27.7	27.8	28.4	28.5	27.5	28.5	27.8
Alcohol ≥ 1 drink/day, %	6.0	6.0	5.7	6.3	4.5	6.5	4.7
Smoking ≥ 15 cigarettes/day, %	5.3	5.9	6.2	6.9	4.1	7.1	4.6
Education ≤ 12 years, %	11.7	18.4	28.4	29.5	10.7	29.6	16.6

[1] All means and proportions, with the exception of age, are standardized to the age distribution of the baseline cohort.

[2] Restricted to parous women.

Table 2

Reproductive factors in relation to breast cancer subtypes*

	ER + / PR +				ER + / PR −				ER − / PR −			
	Cases	**P-Years**	**HR**	**95% CI**	**Cases**	**P-Years**	**HR**	**95% CI**	**Cases**	**P-Years**	**HR**	**95% CI**
Number of births												
0	110	212,629	1.00	Reference	29	212,495	1.00	Reference	56	212,539	1.00	Reference
1	112	161,964	0.77	0.56–1.04	35	161,835	0.86	0.48–1.53	64	161,887	1.04	0.69–1.56
2	136	171,818	0.76	0.57–1.01	35	171,649	0.70	0.40–1.22	107	171,771	1.54	1.07–2.21
≥ 3	99	144,765	0.53	0.39–0.73	32	144,649	0.62	0.35–1.11	89	144,749	1.48	0.98–1.84
		P trend = 0.0002				P trend = 0.08				P trend = 0.009		
Age at 1st birth												
< 20	103	150,943	1.00	Reference	26	150,808	1.00	Reference	82	150,906	1.00	Reference
20–24	106	162,425	0.90	0.68–1.19	35	162,306	1.21	0.72–2.04	82	162,387	0.97	0.71–1.33
25–29	80	100,093	1.23	0.90–1.68	25	100,004	1.54	0.85–2.79	59	100,064	1.32	0.92–1.90
≥ 30	58	65,086	1.34	0.93–1.94	16	65,016	1.45	0.72–2.94	37	65,050	1.47	0.94–2.29
		p trend = 0.05				P trend = 0.18				P trend = 0.04		
Years since last birth												
≥ 15	264	278,425	1.00	Reference	85	278,121	1.00	Reference	184	278,295	1.00	Reference
10–14	26	65,208	0.93	0.60–1.57	8	65,179	0.96	0.42–2.21	29	57,214	1.30	0.82–2.08
< 10	51	128,913	1.69	1.08–2.63	9	128,121	0.89	0.34–2.34	44	128,901	1.61	0.97–2.68
		p trend = 0.03				P trend = 0.82				P trend = 0.08		
Lactation, parous women only												
No	192	269,725	1.00	Reference	56	269,493	1.00	Reference	162	269,675	1.00	Reference
Yes	151	203,135	1.13	0.91–1.42	46	202,960	1.25	0.83–1.89	95	203,047	0.78	0.60–1.03
<6 mos	85	112,008	1.11	0.86–1.44	27	111,912	1.30	0.81–2.08	51	111,956	0.78	0.56–1.08
≥6 mos	66	91,127	1.17	0.87–1.57	19	91,048	1.18	0.68–2.06	45	91,091	0.79	0.56–1.13

* 18 breast cancer cases were classified as ER−/PR+ and were omitted from this table.

HRs were derived from models that adjusted for age, time, geographic region, age at menarche, age at menopause, use of menopausal hormone supplements, use of oral contraceptives, body mass index, physical activity, alcohol intake, cigarette smoking, family history of breast cancer, and each of the other reproductive factors.

Table 3

Reproductive factors in relation to ER+/PR+ and ER−/PR− breast cancer by age

	ER + / PR +				ER − / PR −			
	Age < 45		Age ≥ 45		Age < 45		Age ≥ 45	
	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)
Number of births								
0	31	1.00 (Reference)	79	1.00 (Reference)	29	1.00 (Reference)	27	1.00 (Reference)
1	36	0.90 (0.47–1.71)	76	0.68 (0.48–0.98)	22	0.81 (0.41–1.59)	42	1.17 (0.69–1.96)
2	25	0.71 (0.37–1.39)	111	0.73 (0.53–1.01)	31	1.37 (0.74–2.56)	76	1.61 (1.01–2.57)
≥ 3	14	0.76 (0.36–1.59)	85	0.47 (0.33–0.66)	23	1.89 (1.00–3.59)	66	1.39 (0.86–2.25)
	P trend = 0.32		P trend < 0.0001		P trend = 0.02		P trend = 0.11	
Age at 1st birth								
< 20	16	1.00 (Reference)	87	1.00 (Reference)	17	1.00 (Reference)	65	1.00 (Reference)
20–24	13	0.69(0.33–1.46)	93	0.93 (0.69–1.26)	19	1.13 (0.52–1.99)	63	0.93 (0.65–1.33)
25–29	20	1.23 (0.61–2.49)	60	1.22 (0.86–1.73)	21	1.66 (0.61–2.59)	38	1.21 (0.79–1.86)
≥ 30	26	1.75 (0.85–3.61)	32	1.14 (0.73–1.79)	19	2.24 (0.76–3.86)	18	1.16 (0.65–2.07)
	P trend = 0.04		P trend = 0.31		P trend = 0.03		P trend = 0.42	
Years since last birth								
≥ 15	20	1.00 (Reference)	244	1.00 (Reference)	14	1.00 (Reference)	170	1.00 (Reference)
10–14	11	0.71 (0.33–1.51)	15	1.15 (0.65–2.03)	20	1.84 (0.90–3.74)	9	1.01 (0.49–2.05)
< 10	43	1.61 (0.88–2.95)	8	1.51 (0.71–3.23)	42	2.18 (1.08–4.41)	2	0.66 (0.16–2.79)
	P trend = 0.08		P trend = 0.23		P trend = 0.03		P trend = 0.66	
Ever breastfed								
No	32	1.00 (Reference)	160	1.00 (Reference)	40	1.00 (Reference)	122	1.00 (Reference)
Yes	43	1.30 (0.80–2.12)	108	1.10 (0.85–1.42)	36	0.78 (0.48–1.26)	59	0.79 (0.57–1.09)

HRs were derived from models that adjusted for age, time, geographic region, age at menarche, age at menopause, use of menopausal hormone supplements, use of oral contraceptives, body mass index, physical activity, alcohol intake, cigarette smoking, family history of breast cancer, and each of the other reproductive factors.

Table 4

Joint effects of parity and other reproductive variables on risk of ER+/PR+ and ER−/PR− breast cancer.

		ER + / PR +			ER − / PR −		
Number of births		**Cases**	**HR**	**95% CI**	**Cases**	**HR**	**95% CI**
Nulliparous		110	1.00	Reference	56	1.00	Reference
	Age at 1st birth						
1	<25	46	0.78	(0.55–1.11)	29	1.16	(0.73–1.83)
1	≥25	66	1.06	(0.76–1.43)	35	1.34	(0.86–2.07)
≥ 2	<25	163	0.64	(0.48–0.84)	135	1.48	(1.04–2.09)
≥ 2	≥25	72	0.96	(0.69–1.34)	61	2.20	(1.47–3.29)
	Years since last birth						
1	<10	24	1.95	(1.22–3.11)	12	1.27	(0.67–2.41)
1	≥10	88	0.93	(0.69–1.26)	52	1.23	(0.82–1.85)
≥ 2	<10	27	1.24	(0.79–1.94)	32	2.05	(1.29–3.26)
≥ 2	≥10	202	0.86	(0.64–1.16)	161	1.66	(1.13–2.44)
	Lactation						
1	Never	73	0.76	(0.55–1.05)	44	1.00	(0.65–1.52)
1	Ever	38	0.75	(0.50–1.14)	20	0.85	(0.48–1.48)
≥ 2	Never	119	0.64	(0.48–0.85)	118	1.53	(1.09–2.23)
≥ 2	Ever	113	0.73	(0.54–0.97)	75	1.16	(0.80–1.69)

HRs were derived from models that adjusted for age, time, geographic region, age at menarche, age at menopause, use of menopausal hormone supplements, use of oral contraceptives, body mass index, physical activity, alcohol intake, cigarette smoking, family history of breast cancer, and each of the other reproductive factors.