Breast cancer risk and hormone receptor status in older women by parity, age of first birth, and breastfeeding - a case-control study

Running title: Parity and breast cancer risk

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ACKNOWLEDGEMENT

The Women's CARE Study was funded by the National Institute of Child Health and Human Development, with additional support from the National Cancer Institute, through contracts with Emory University (N01-HD-3-3168), Fred Hutchinson Cancer Research Center (N01-HD-2-3166), Karmanos Cancer Institute at Wayne State University (N01-HD-3-3174), University of Pennsylvania (NO1-HD-3-3276) and University of Southern California (N01-HD-3-3175) and through an interagency agreement with the Centers for Disease Control and Prevention (Y01-HD-7022). The Centers for Disease Control and Prevention contributed additional staff and computer support. General support through SEER contract numbers N01-PC-67006 (Atlanta), N01-CN-65064 (Detroit), N01-PC-67010 (Los Angeles), and N01-CN-0532 (Seattle) is also acknowledged. The collection of cancer incidence data in California used in this publication (University of Southern California Los Angeles County portion of the Women's CARE Study) was also supported by the California Department of Health Services as part of the statewide cancer reporting program mandated by the California Health and Safety Code Section 103885. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention or endorsement by the State of California, Department of Health Services.

Abstract

Background: Early age at first birth and multiparity reduce the risk of estrogen receptor and progesterone receptor (ERPR) positive breast cancer, whereas breastfeeding reduces the risk of both ERPR-positive and ERPR-negative cancers.

Methods: We used multivariable logistic regression analysis to investigate whether age at first birth (</≥25 years) and breastfeeding (ever/never) modify the long-term effect of parity on risk of ERPR-positive and ERPR-negative cancer using 1457 incident breast cancer cases and 1455 controls aged ≥ 55 years who participated in the Women's Contraceptive and Reproductive Experiences Study.

Results: Women who gave birth before age 25 years had a 36% reduced risk of breast cancer compared to nulligravida that was not observed for women who started their families at an older age (*P* heterogeneity=0.0007). This protective effect was restricted to ERPR-positive breast cancer (*P* heterogeneity=0.004). Late age at first birth increased the risk of ERPR-negative cancers.

Additional births reduced the risk of ERPR-positive cancers among women with an early first birth (*P* trend=0.0001) and among women who breastfed (*P* trend=0.004), but not among older mothers or those who never breastfed. In women with a late first birth who never breastfed, multiparity was associated with increased risk of breast cancer.

Conclusions: These findings suggest that the effect of parity on a woman's long-term risk of breast cancer is modified by age at first full-term pregnancy and possibly by

breastfeeding.

Introduction

Epidemiological studies have provided consistent evidence that reproductive factors are associated with breast cancer risk. Some of these associations vary depending on the hormone-receptor status of the tumor. A recent systematic review (1) and meta-analysis (2) reported that parity and young age at first birth decrease the risk of estrogen receptor-progesterone receptor (ERPR) positive tumors, but do not impact the risk of ERPR-negative tumors. The meta-analysis also found that breastfeeding protects against both receptor positive and negative tumors (2). We have previously reported similar findings from the Women's Contraceptive and Reproductive Experiences (CARE) Study (3).

One area of uncertainty is whether age at first birth or breastfeeding modifies the effect of parity on the long term risk of ERPR-positive and ERPR-negative breast cancer. In the United States, mean age at first birth has continued to rise from 21.4 years in 1970 to 24.9 years in 2000 (4). It is not clear whether the protective effect of parity on ERPR-positive tumors is as strong in women who start their families later, at age 25 years or thereafter. Further, it is unknown what the combined effect of breastfeeding and parity is in this group of women with later first birth.

Since the immediate impact of a full-term pregnancy is a transient increase in breast cancer risk that may last as many as 10 to 15 years following the pregnancy (5,6) and older women have a higher proportion of ERPR-positive tumors than younger women (7), the long term effect of parity on the ERPR status of breast cancer may be optimally examined in women diagnosed with breast cancer at least 15 years after child-bearing age. Thus, in the present study, we investigated associations between

parity, age at first full-term pregnancy and breastfeeding on the risk of ERPR-positive and ERPR-negative breast cancer among women 55-64 years of age enrolled in the Women's CARE Study.

Methods

The Women's CARE Study is a population-based case-control study designed to examine risk factors for breast cancer among White and African-American women aged 35 to 64 years in five United States (US) regions (Atlanta, Seattle, Detroit, Philadelphia, and Los Angeles). Study methods have been described in detail previously (8).

Case patients

Case patients were US-born, English-speaking women first diagnosed with a primary invasive breast cancer between July 1994 and April 1998. Case patients were identified by the Surveillance, Epidemiology, and End Results (SEER) cancer registries in Atlanta, Seattle, Detroit and Los Angeles, or from hospitals in Philadelphia. African-American women and younger White women were oversampled to provide approximately equal numbers of women in each five-year age category from 35 to 64 years and to maximize the number of African-American participants. Of the 5,982 eligible case patients, 4,575 (76.5%), were interviewed (2,953 Whites and 1,622 African-Americans).

Control subjects

Control subjects were US-born, English-speaking women identified through random digit dialing (RDD); those eligible had no prior diagnosis of invasive or *in situ* breast

cancer. Control subjects were randomly selected from the pool of RDD screened women and were frequency matched to case patients by study region, race, and five-year age group. Approximately 82% of residential households called were successfully screened. Of the 5,956 eligible women selected as control subjects, 4,682 (78.6%) were interviewed (3,021 Whites and 1,611 African-Americans).

Data collection

All participants were interviewed in person by trained interviewers who used a structured questionnaire. Interview questions covered demographics, reproductive and breastfeeding history, medical history including body mass index (BMI) and use of postmenopausal hormones (PMH), family history of cancer and lifestyle factors. We established a reference date for each participant, the date of breast cancer diagnosis for case patients and the date on which the RDD screening questionnaire was administered by telephone for control subjects. Interview information was collected up to each woman's reference date.

ER and PR status of case patients was recorded by each study center. Overall, 3837 (83.9%) cases had ER and PR status data available (range: Detroit 72.2%, Seattle 93.6%).

Data analyses

We conducted all analyses in three different patient groups: i) all cases combined; ii) ERPR-positive cases; and iii) ERPR-negative cases. We restricted these analyses to women aged 55 years or older and excluded 7 women (3 cases and 4 controls) who did not provide complete information on pregnancy or breastfeeding history and one

case patient who had never menstruated. We considered any pregnancy lasting more than 26 weeks as a full-term pregnancy and excluded 84 women (41 cases and 43 controls) who had only experienced short-term pregnancies because they do not share the same risk profile as nulligravid or parous women (9), leaving 1457 case patients and 1455 control subjects for our analyses of all cases combined. This combined analysis was conducted to maximize our power to estimate the overall effect of parity and breastfeeding on all tumor types. Case patients without ER or PR status available (258 cases) or a borderline ER or PR status result (24 cases) were excluded from our analysis of associations by ERPR-status. We also excluded case patients with ER+PR- (165 cases), or ER-PR+ tumors (41 cases) from these analyses because these tumors may represent an intermediate risk group and there were too few to examine them separately (10); resulting in a total of 969 case patients for analyses according to ERPR status (708 ERPR-positive cases and 261 ERPR-negative cases).

We recorded a woman's age at first full-term pregnancy as the date of completion of this pregnancy. We also refer to this as 'age at first birth'. Women who ever breastfed for at least one day were classified as having a positive history of breastfeeding.

We compared the distributions of reproductive and demographic characteristics by subject status (ERPR-positive case patients, ERPR-negative case patients and control subjects) using chi square tests. Multivariable polytomous logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer by ERPR-status. In these analyses, we included categorical variables for age (55-59, 60-64 years), race (African American/White), and study center (5 sites). We also adjusted for first degree family history of breast cancer (breast cancer in a mother

or sister: no, yes, unknown or adopted), age at menarche (≤11, 12, 13, ≥14 years), and education (up to high school, technical school/some college, college graduate). Other potential confounders including BMI (weight (kg)/height $(m)^2$), duration of hormone therapy (estrogen or estrogen plus progestin, never, <6 months use, ≥6 months use) and recent use of hormone therapy (never, within 6 months of reference date, ≥6 months ago) altered point estimates by less than 5% and were not included in the model. In analyses limited to parous women, we also adjusted for age at first full-term pregnancy (≤19, 20-24, 25-29, ≥30 years), ever/never breast feeding and number of full-term pregnancies (1, 2, 3, 4+) where appropriate.

We assessed the relationship between a full-term pregnancy and risk of breast cancer overall, and then assessed associations between parity, age at first full-term pregnancy, breastfeeding and breast cancer risk, stratified by age at first full-term pregnancy (< 25 years, ≥25 years) and breastfeeding history (ever, never) for all women included in this analysis and then among women with ERPR-positive breast cancer and ERPR-negative breast cancers. We evaluated a model that assessed the three-way interaction of number of births by breast feeding status by age at first birth on breast cancer risk. We do not present the results of this three-way interaction by ERPR tumor status due to the small numbers of ERPR-negative tumors available. The age at first full-term pregnancy cut-points used for stratification were based on previous epidemiological studies which showed reduced risk among women whose first pregnancy occurred before age 25 years (11,12).

We tested for effect modification by age at first full-term pregnancy (</≥25 years) and breastfeeding history (ever/never) by testing for heterogeneity of the parity estimates

across categories of these effect modifiers as follows: We used a likelihood ratio test to compare the fit of a model with a binary variable or a trend variable for parity versus the fit of a model where the parity variable was allowed to vary according to the categories of the effect modifier.

We fitted multivariable unconditional polytomous logistic regression models to evaluate differences in odds ratio estimates for ERPR-positive and ERPR-negative breast cancers (13). We have previously reported findings from the Women's CARE Study that parity and breastfeeding had similar effects on breast cancer risk in White and African American women (9). We also found no apparent differences in the effect of parity and lactation on risk of ERPR-positive and ERPR-negative tumors by race (tests for heterogeneity of parity trends by race for risk of ERPR-positive or ERPR-negative tumors for women aged <25 years or ≥25 years at first birth, P>0.15) and therefore we present the results for the races combined.

All *P*-values reported are two-sided. Analyses were performed using the SAS® statistical package (Version 9.0, SAS institute, Cary, NC, USA) or EPILOG (Epicenter Software, Pasadena, CA).

Results

The distribution of women classified by race, parity status, number of full-term pregnancies and age at first full-term pregnancy varied between ERPR-positive cases, ERPR-negative cases and control subjects (Table 1).

Women who reported having at least one full-term pregnancy before age 25 years were at 36% reduced risk of breast cancer compared to nulligravida, while no such effect was seen for women with a first birth after age 25 years (Table 2). Further, the statistically significant decreasing risk of breast cancer with increasing number of births was only seen in women who with a first birth before age 25 years (*P* for heterogeneity of parity trends by age at first full-term pregnancy = 0.001). The protective effect of a first birth before age 25 years was restricted to ERPR-positive breast cancer (Table 2, OR=0.59, 95% CI=0.42-0.82, test for heterogeneity by ERPR status = 0.004). Similarly, the protective effect of multiparity among women with a first birth before age 25 years was also restricted to ERPR-positive breast cancers (*P* for trend = 0.0001), although the test for heterogeneity by ERPR status was not statistically significant (*P*= 0.06).

No association was observed between giving birth for the first time at age 25 years or older and a woman's overall risk of breast cancer compared to nulligravida (Table 2). However, women with a late age at first birth had a higher risk of ERPR-negative tumors than nulligravida (OR=2.07, 95% CI=1.03-4.16). Among parous women with a late age at first birth, risk of both ERPR-positive and ERPR-negative tumors increased with each additional birth although neither result was statistically significant (Table 2).

Parous women who had breastfed had a non-significant lower risk of ERPR-positive tumors (OR=0.84, 95% CI=0.68-1.03) and ERPR-negative tumors (OR=0.84, 95% CI=0.63-1.12) than parous women who had not breastfed (Table 3). This association was statistically significant for women whose first birth was at age 25 years or older

(OR=0.62, 95% CI=0.43-0.89), but not for those who had their first birth at a younger age (OR=0.90, 95% CI=0.75-1.08) (Table 3); however, age at first birth did not significantly modify the effect of breastfeeding on parous women's breast cancer risk (test for heterogeneity *P*=0.43, data not shown).

When we stratified parous women into those who had breastfed and those who had not, and adjusted for the effect of multiparity, we found that among women who never breastfed those who gave birth at a later age had greater risk of all breast cancers than those with a first birth before the age of 20 years (trend test *P*= 0.01, Table 3). This trend was not observed among women who breastfed (trend test *P*=0.74), although this apparent effect modification by breastfeeding was not statistically significant (*P* for heterogeneity by breastfeeding = 0.32). This pattern was stronger for ERPR-positive cancers (trend test *P*=0.003), but again, the test for effect modification by breast feeding was not statistically significant (*P*=0.06). Multiparity reduced the risk of breast cancer among women who reported having breastfed (trend test *P*=0.007), but did not reduce risk among those who never breastfed (trend test *P*=0.58); this apparent effect modification by breastfeeding was not statistically significant (*P*=0.33), and was only observed for ERPR-positive tumors. Multiparity did not reduce the risk of ERPR negative cancers, even among those who breastfed.

Because of the possibility that breastfeeding modifies the effects of multiparity and age at first birth, we assessed whether breastfeeding modified the effects of multiparity in women with a late first birth. We therefore stratified our analyses by age at first birth (under age 25/age 25 years or later) as well as breastfeeding status. In order to directly assess the differences in effects according to age at first birth, we

used the common reference group of women who had never been pregnant. Due to the small numbers of women in some of these subgroups, we collapsed the categories for number of births to 0, 1, 2 and 3 or more for these analyses.

Breastfeeding did not modify the protective effect of multiparity in women who had their first birth before age 25 years (Table 4). Comparing this group of women to nulligravid women, multiparity was associated with a reduced risk of breast cancer for women who breastfed and for those who never breastfed (trend test $P = 0.002$ and 0.0001, respectively).

Repeating these analyses in women who began their families at or after 25 years, again comparing them to nulligavid women, we observed that women who did not breastfeed had a statistically significant higher risk of breast cancer if they had more than two children (Table 4). This effect was statistically significant for both ERPR-positive and ERPR-negative tumors although patient numbers were small in these subgroups (data not shown). Further, the test for trend for increasing risk of breast cancer with each additional birth among women who gave birth at a late age and did not breastfeed did not reach statistical significance (P=0.06, Table 4).

Discussion

To our knowledge, this is the first study to examine the combined effects of parity, breastfeeding, and age at first birth on ERPR-positive and ERPR-negative breast cancer. We have previously reported findings from the Women's CARE Study among women aged 35-64 years, indicating that early age at first birth and multiparity reduce the risk of ERPR-positive tumors but not ERPR-negative tumors, while breastfeeding

reduces the risk of both tumor subtypes (3). In the present analysis, which was restricted to women aged 55 to 64 years, multiparity reduced the long term risk of breast cancer for women who experienced their first birth before age 25 years, but offered no protection for women with a later age at first birth. Further, the protective effect of multiparity in women who started their families early was confined to ERPR-positive tumors, while women whose first birth was at age 25 years or later were at an increased risk of ERPR-negative tumors. In addition we found some evidence that breastfeeding may modify the effects of multiparity and age at first birth, specifically that women who were older at first birth, had three or more children, and had not breastfed had an elevated risk of breast cancer, that was not observed in women who breastfed. However, these analyses were limited by small numbers.

The evidence that young age at first birth and multiparity independently reduce the risk of breast cancer is substantial (14). A meta-analysis of 8 Nordic observational studies (5,568 cases) that included women of all ages has provided some evidence that multiparity has a protective effect for women who start their families at a young age, but a harmful effect for women who start their families at age 35 years and older (test for interaction, P=0.07) (15). Although our analysis included fewer breast cancer cases, it was restricted to women aged 55 to 64 years to allow us to examine the long term effects of parity and age at first birth. All breast cancers included in our analysis among women with a late age at first birth occurred more than 15 years after the last reported full-term pregnancy. We also used a lower cut-point for classifying late age at first birth (≥25 years), which may explain why we were able to show a statistically significant interaction.

Our finding that the protective effect of age at first birth and multiparity are confined to ERPR-positive cancers is consistent with a recent systematic review (1) and with a meta-analysis (2) of data from many studies (including the Women's CARE Study). However, neither review found an association between late age at first birth and increased risk of ERPR-negative tumors. Several studies have reported that women with a late age at first birth (30-35 years) have a higher overall risk of breast cancer than nulliparous women (16-18). Our findings provide some support for these conclusions among women who never breastfed as discussed below.

Results from a large prospective population-based cohort study (23,890 breast cancer cases) suggest a time delay in the protective effect of pregnancy of up to 27 years that anticipates women who begin their families at a late age will eventually attain a lower long-term risk of breast cancer than nulliparous women (19). Our results further suggest that the long-term protective effect of parity may apply to ERPR-positive tumors, but not ERPR-negative tumors.

We found that a history of breastfeeding reduces the risk of breast cancer for women aged 55 to 64 years. Moreover, multiparity was associated with an increased risk of breast cancer in women with a late age at first full-term pregnancy who had not breastfed. The meta-analysis conducted by the Collaborative Group on Hormonal Risk Factors established that breastfeeding has a protective effect against breast cancer independent of the protective effect of multiparity (14). This effect was similar when women were stratified by categories of age, menopausal status or age at first birth. Our finding that breastfeeding may have a stronger protective effect in women

aged 55 to 64 years who began their families at a later age was not addressed in the Collaborative effort. Our finding has several interpretations. Firstly, we examined many associations in our analyses, and therefore this observation could have been due to chance. Another possible explanation is that the protective effect of breastfeeding is time-limited. Analysis of all women who participated in the CARE study (9), and results from another case-control study (20) showed that the effect of breastfeeding was stronger in younger women and decreased over time. Our finding is consistent with these results if we assume that women with an early age at first birth are more likely to complete their families, and therefore their breastfeeding years, earlier than women who begin their families at a later age. A third explanation for our finding is that a true synergy exists between these factors, and that somehow lactation inhibits the harmful hormonal effects of late pregnancies on both tumor subtypes. We and others have previously suggested that the mechanisms by which breastfeeding protects against breast cancer must be different from those of parity and age at first birth since breast feeding protects against both ERPR-positive and ERPR-negative tumors, while parity and age at first birth only protect against ERPR-positive cancers. Breastfeeding may protect against breast cancer through hormonal mechanisms (delayed ovulation, increased breast differentiation or changing the hormonal environment of the breast); or directly, by excretion of carcinogenic agents (4,21,22).

Given that women are increasingly starting their families at a later age, it is important to confirm this finding on the long-term effects of breastfeeding and how it may modify the effects of parity on risk of ERPR-positive and ERPR-negative tumors in this group of women. In our study, 54% of parous cases and 59% of parous controls reported ever breastfeeding. This proportion is similar or slightly higher than that

reported by nine previous studies from the United States (14). The National Survey of Family Growth reported a breastfeeding rate of 55% in 1995, rising up to 67% for babies born between 1997-2000 (4). Encouragingly, women aged 30 years or over at the time of birth reported the highest breastfeeding rate in this survey (77.5%), however rates varied substantially by race with Non-Hispanic blacks reporting the lowest rates of breastfeeding (47%).

Strengths of our study include the restriction of the study population to women aged 55-64 years which allowed us to examine the long term effects of parity, after any short-term increase in risk that would immediately follow a term pregnancy. Despite the large size of the Women's CARE Study, our analyses were limited by the small number of cases in some categories after stratification by age at first full-term pregnancy and breastfeeding status. In particular, we had few cases with an older age at first term pregnancy and no history of breastfeeding (N=182) and estimates of the effect of multiparity in this group of women are surrounded by wide confidence intervals. These small numbers did not allow us to examine whether these associations varied by tumor ERPR-status.

We had no data on ERPR status for 17.9% of case patients. Chu et al (2002) reported a similar proportion of patients with unknown ERPR status in their study of 123,732 breast cancer cases from 11 SEER sites between 1992-1998 (7). Cases with data on ERPR status had fewer children (χ^2 P=0.01), later age at first birth (P=0.0001), and breastfed longer (P=0.03) than those without data on ERPR status (3), but it is not clear if and how the lack of receptor information on these patients could have altered our results.

Another limitation is that our analyses involved many comparisons in subgroups of women stratified by age at first birth, breast feeding status and ERPR tumor status; therefore it is possible that our results represent false positive findings and confirmation from other (larger) observational studies is essential.

Similar to other studies investigating the independent effects of parity and breastfeeding, we classified women according to whether they reported ever versus never breastfeeding (14). This included 7% of case patients and 6% of control subjects aged 55 to 64 years who breastfed for less than 2 weeks. We have previously reported that longer breastfeeding duration is associated with reduced risk of ERPR-positive and ERPR-negative tumors in the Women's CARE Study with modest reductions observed for women who breastfed for less than 2 weeks (3). However, the modifiying effects of breastfeeding we describe here were similar when we excluded those who breastfed for less than 2 weeks.

ERPR status of tumors was determined by different laboratories at each study site. This may have introduced some measurement error due to variations in laboratory methods and conditions. However, any differences in measurement would be expected to be random and result in non-differential bias which may have obscured the associations we report here.

In conclusion, this study suggests that the effect of parity on a woman's long-term risk of ERPR-positive and ERPR-negative breast cancer is modified by age at first birth and possibly by breastfeeding. In women with a late first term pregnancy, our

finding that breast feeding offers broad protection against breast cancer may be used to promote the benefits of breast feeding in this group of women.

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Table 1: Distribution of demographic and reproductive characteristics of 969 case patients with ERPR-positive and ERPR-negative breast cancer and control subjects aged 55-64 years in the Women's CARE Study

	Cases *N* (%)		Controls *N* (%)	
Characteristic	**ERPR-positive**	**ERPR-negative**	***N* (%)**	***P*[1]**
	708 (73.1)	261 (26.9)	1455	
Reference age (years)				
55-59	349 (49.3)	148 (56.7)	772 (53.1)	
60-64	359 (50.7)	113 (43.3)	683 (46.9)	0.09
Race				
White	542 (76.6)	143 (54.8)	961 (66.1)	
African American	166 (23.5)	118 (45.2)	494 (34.0)	0.0001
Parity status[2]				
Nulligravid	72 (10.2)	11 (4.2)	107 (7.4)	
At least one full-term pregnancy	636 (89.8)	250 (95.8)	1348 (92.7)	0.005
Number of full-term pregnancies				
1	86 (13.5)	25 (10.0)	147 (10.9)	
2	215 (33.8)	69 (27.6)	350 (26.0)	
3	157 (24.7)	68 (27.2)	345 (25.6)	
4+	178 (28.0)	88 (35.2)	506 (37.5)	0.0004
Age at first full-term pregnancy (years)				
≤ 19	165 (25.9)	93 (37.2)	454 (33.7)	
20-24	278 (43.7)	104 (41.6)	622 (46.1)	
25-29	142 (22.3)	37 (14.8)	190 (14.1)	
>30+	51 (8.02)	16 (6.4)	82 (6.1)	0.0001
Ever breastfed				
No	291(45.8)	113 (45.2)	555 (41.2)	
Yes	345 (54.3)	137 (54.8)	793 (58.8)	0.12

ERPR= estrogen receptor-progesterone receptor

1. *P*-value: X^2 test for differences in the distribution of characteristics by case/control status; 2. Women with a history of short-term pregnancies <26weeks but no full-term pregnancies excluded (20 ERPR-positive cases, 6 ERPR-negative cases and 43 controls).

Table 2: Associations between parity status and breast cancer stratified by age at first full-term pregnancy (< 25/ ≥ 25 years) among all women aged 55-64 years in the Women's CARE Study, and by ERPR status[1]

	All women				ERPR-positive				ERPR-negative			
	Age at first < 25 yrs		Age at first ≥ 25 yrs		Age at first < 25 yrs		Age at first ≥ 25 yrs		Age at first < 25 yrs		Age at first ≥ 25 yrs	
Parity status	N (case/ control)	OR (95% CI)	N (case/ control)	OR (95% CI)	N (cases)	OR (95% CI)	N (cases)	OR (95% CI)	N (cases)	OR (95% CI)	N (cases)	OR (95% CI)
Nulliparous[2]	140/107	1.00	140/107	1.00	72	1.00	72	1.00	11	1.00	11	1.00
1+ full-term pregnancy	970/1076	0.64 (0.48-0.84)	347/272	0.97 (0.71-1.31)	443	0.59 (0.42-0.82)	193	1.05 (0.73-1.51)	197	1.62 (0.84-3.11)	53	2.07 (1.03-4.16)
P heterogeneity ERPR-positive vs ERPR-negative						0.004		0.06				
P heterogeneity <25 yr vs ≥ 25 yr				0.00007				0.00001				0.23
No. full-term pregnancy												
1	93/68	1.00	90/79	1.00	41	1.00	45	1.00	11	1.00	14	1.00
2	247/227	0.84 (0.58-1.22)	142/123	0.88 (0.58.1.33)	132	0.93 (0.59-1.47)	83	1.04 (0.64-1.69)	48	1.61 (0.78-3.31)	21	0.93 (0.43-2.01)
3	246/292	0.63 (0.44-0.91)	83/53	1.35 (0.77-2.04)	109	0.56 (0.35-0.88)	48	1.36 (0.77-2.41)	58	1.50 (0.74-3.04)	10	1.09 (0.43-2.73)
4+	384/489	0.57 (0.40-0.81)	32/17	1.56 (0.78-3.15)	161	0.51 (0.33-0.80)	17	1.63 (0.73-3.63)	80	1.10 (0.55-2.19)	8	2.76 (0.94-8.07)
P trend		0.0001		0.13		0.0001 .		0.15		0.26		0.13
P heterogeneity of trend ERPR-positive vs ERPR-negative						0.06		0.75				
P heterogeneity of trend <25 yr vs ≥ 25 yr[3]				0.001				0.002				0.04

CI= confidence interval; ERPR=estrogen receptor-progesterone receptor; OR=odds ratio

1. All unconditional logistic regression models include categories of age, race, study site, education, age at menarche and first degree family history of breast cancer; 2. These models used all nulligravida as the referent group; 3. In addition to factors listed in (1), models include categories of age at first full-term pregnancy.

Table 3: Associations between age at first full-term pregnancy, number of full-term pregnancies and breast cancer risk, stratified by breast feeding status (ever/never), among parous women aged 55-64 years in the Women's CARE Study, and by ERPR status[1]

	All parous women				ERPR-positive				ERPR-negative			
	Never breastfed		Ever breastfed		Never breastfed		Ever breastfed		Never breastfed		Ever breastfed	
	N (case/ control)	OR (95% CI)	N (case/ control)	OR (95% CI)	N (cases)	OR (95% CI)	N (cases)	OR (95% CI)	N (cases)	OR (95% CI)	N (cases)	OR (95% CI)
All parous women	600/555	1.00	717/793	0.87 (0.74-1.02)[2]	291	1.00	345/793	0.84 (0.68-1.03)	113	1.00	137	0.84 (0.63-1.12)
Age at first < 25 years	418/427	1.00	552/649	0.90 (0.75-1.08)	190	1.00	253/649	0.91 (0.71-1.15)	85	1.00	112	0.82 (0.60-1.14)
Age at first ≥ 25 years	182/128	1.00	165/144	0.62 (0.43-0.89)	101	1.00	92/144	0.57 (0.37-0.87)	28	1.00	25	0.65 (0.33-1.27)
Age first full-term pregnancy (yrs)												
<20	139/161	1.00	265/293	1.00	55	1.00	110/293	1.00	32	1.00	61	1.00
20-24	279/266	1.21 (0.90-1.64)	287/356	0.87 (0.67-1.13)	135	1.34 (0.63-1.64)	143/356	0.86 (0.61-1.20)	53	1.12 (0.33-1.35)	51	0.79 (0.50-1.25)
25-29	128/83	1.86 (1.25-2.78)	118/107	1.12 (0.77-1.63)	71	2.32 (0.83-2.53)	71/107	1.25 (0.79-1.97)	19	1.41 (0.37-2.08)	18	1.03 (0.52-2.04)
30+	54/45	1.47 (0.88-2.45)	47/37	1.05 (0.62-1.79)	30	1.97 (0.82-4.11)	21/37	0.86 (0.44-1.69)	9	1.44 (0.69-6.15)	7	1.10 (0.41-2.92)
P trend		0.01		0.74		0.003		0.81		0.20		0.99
P heterogeneity of trend ERPR-positive vs ERPR-negative						0.46		0.71				
P heterogeneity ever vs never breastfed				0.32				0.06				0.66
No. full-term pregnancies												
1	113/95	1.00	70/52	1.00	55	1.00	31	1.00	15	1.00	10	1.00
2	194/167	1.02 (0.71-1.47)	195/183	0.82 (0.53-1.25)	104	1.12 (0.72-1.75)	111	0.95 (0.56-1.61)	33	1.56 (0.77-3.14)	36	1.23 (0.56-2.71)
3	153/134	1.02 (0.69-1.50)	176/211	0.66 (0.42-1.01)	75	1.06 (0.65-1.74)	82	0.62 (0.36-1.07)	36	2.21 (1.06-4.61)	32	0.94 (0.42-2.11)
4+	140/159	0.90 (0.61-1.35)	276/347	0.61 (0.40-0.93)	57	0.85 (0.50-1.44)	121	0.58 (0.34-0.99)	29	1.50 (0.69-3.25)	59	0.89 (0.41-1.93)
P trend		0.58		0.007		0.41		0.004		0.32		0.32
P heterogeneity of trend ERPR-positive vs ERPR-negative						0.11		0.35				
P heterogeneity of trend ever vs never breastfed				0.33				0.61				0.29

CI=confidence interval; ERPR=estrogen receptor-progesterone receptor; OR=odds ratio.

1. Unconditional logistic regression used to calculate odds ratios (OR) and 95% confidence intervals (CI); models include categories of age, race, study site, education, age at menarche, family history of breast cancer, age at first full-term pregnancy and number of full-term pregnancies; 2. OR of ever breastfeeding as compared to parous women who have never breastfed.

Table 4: Associations between number of full-term pregnancies and breast cancer risk , stratified by age at first full-term pregnancy (</≥25 years) and breastfeeding status (ever/never), for all women aged 55-64 years in the Women's CARE Study cases[1]

All women	**Never breastfed**		**Ever breastfed**	
No. full-term pregnancies[2]	N (case/control)	OR (95% CI)	N (case/control)	OR (95% CI)
Age at first full-term pregnancy < 25 years				
0	140/107	1.00	140/107	1.00
1	55/40	0.97 (0.59-1.59)	38/28	0.92 (0.52-1.62)
2	127/114	0.81 (0.56-1.18)	120/113	0.76 (0.53-1.10)
3+	236/273	0.62 (0.44-0.86)	394/508	0.54 (0.40-0.73)
P trend		0.002		0.0001
P heterogeneity of trend ever vs never breastfed[3]				0.68
Age at first full-term pregnancy ≥ 25 years				
0	140/107	1.00	140/107	1.00
1	58/55	0.89 (0.56-1.41)	32/24	1.00 (0.55-1.84)
2	67/53	0.99 (0.63-1.54)	75/70	0.77 (0.49-1.20)
3+	57/20	2.19 (1.22-3.96)	58/50	0.80 (0.50-1.29)
P trend		0.06		0.24
P heterogeneity of trend ever vs never breastfed[3]				0.04

CI=confidence interval; OR=odds ratio

1. Unconditional logistic regression used to calculate odds ratios (OR) and 95% confidence intervals (CI); models include categories of age, race, study site, education, age at menarche, family history of breast cancer; 2. These models used all nulligravida as the referent group; 3.Test for heterogeneity of parity trend effect by breastfeeding status among parous women.