

Breast Cancer Risk and Hormone Receptor Status in Older Women by Parity, Age of First Birth, and Breastfeeding: A Case-Control Study

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Abstract

Background: Early age at first birth and multiparity reduce the risk of estrogen receptor-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 or ≥25 years) and breastfeeding (ever/never) modify the long-term effect of parity on risk of ERPR-positive and ERPR-negative cancer using 1,457 incident breast cancer cases and 1,455 controls ages ≥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 with nulligravida that was not observed for women who

started their families at an older age ($P_{\text{heterogeneity}} = 0.0007$). This protective effect was restricted to ERPR-positive breast cancer ($P_{\text{heterogeneity}} = 0.004$). 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 ($P_{\text{trend}} = 0.0001$) and among women who breastfed ($P_{\text{trend}} = 0.004$) 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. (Cancer Epidemiol Biomarkers Prev 2008;17(7):1723–30)

Introduction

Epidemiologic 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 affect the risk of ERPR-negative tumors. The meta-analysis also found that breast-

feeding protects against both receptor-positive and receptor-negative tumors (2). We have reported previously 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 increase from 21.4 years in 1970 to

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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.

Because the immediate effect 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 ages 55 to 64 years enrolled in the Women's CARE Study.

Materials and 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 ages 35 to 64 years in five United States regions (Atlanta, Seattle, Detroit, Philadelphia, and Los Angeles). Study methods have been described in detail previously (8).

Case Patients. Case patients were U.S.-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 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 5-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 U.S.-born, English-speaking women identified through random-digit dialing; those eligible had no prior diagnosis of invasive or *in situ* breast cancer. Control subjects were randomly selected from the pool of random-digit dialing screened women and were frequency matched to case patients by study region, race, and 5-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 and use of postmenopausal hormones, 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 random-digit dialing 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, 3,837 (83.9%) cases had ER and PR status data available (range, Detroit 72.2% and Seattle 93.6%).

Data Analyses. We conducted all analyses in three different patient groups: (a) all cases combined, (b) ERPR-positive cases, and (c) ERPR-negative cases. We restricted these analyses to women ages ≥ 55 years 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 >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 1,457 case patients and 1,455 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-positive/PR-negative (165 cases) or ER-negative/PR-positive (41 cases) tumors 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 1 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 χ^2 tests. Multivariable polytomous logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (95% CI) for breast cancer by ERPR status. In these analyses, we included categorical variables for age (55-59 or 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 body mass index [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 $<5\%$ 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 breastfeeding, 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 or ≥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 breastfeeding 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 epidemiologic 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 or ≥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 OR estimates for ERPR-positive and ERPR-negative breast cancers (13). We have reported previously 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 ages <25 or ≥25 years at first birth; $P > 0.15$); therefore, we present the results for the races combined.

All P values reported are two sided. Analyses were done using the SAS Statistical Package (version 9.0, SAS Institute) or EPILOG (Epicenter Software).

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 with nulligravida, whereas 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 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 ($P_{\text{trend}} = 0.0001$), although the test for heterogeneity by ERPR status was not statistically significant ($P = 0.06$).

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

Characteristics	Cases, <i>n</i> (%)		Controls, <i>n</i> (%)	
	ERPR-positive	ERPR-negative	<i>n</i> (%)	<i>P</i> *
Reference age (y)	708 (73.1)	261 (26.9)	1,455	
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 †				
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
No. 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 (y)				
≤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

* χ^2 test for differences in the distribution of characteristics by case/control status.

†Women with a history of short-term pregnancies <26 wk 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 or ≥25 years) among all women ages 55 to 64 years in the Women's CARE Study and by ERPR status

Parity status	All women			
	Age at first <25 y		Age at first ≥25 y	
	n (case/control)	OR (95% CI)	n (case/control)	OR (95% CI)
Nulliparous*	140/107	1.00	140/107	1.00
≥1 full-term pregnancy	970/1076	0.64 (0.48-0.84)	347/272	0.97 (0.71-1.31)
$P_{\text{heterogeneity ERPR-positive vs ERPR-negative}}$		0.004		0.06
$P_{\text{heterogeneity <25 vs ≥25 y}}$		0.00007		
No. full-term pregnancy				
1	93/68	1.00	90/79	1.00
2	247/227	0.84 (0.58-1.22)	142/123	0.88 (0.58-1.33)
3	246/292	0.63 (0.44-0.91)	83/53	1.35 (0.77-2.04)
≥4	384/489	0.57 (0.40-0.81)	32/17	1.56 (0.78-3.15)
P_{trend}		0.0001		0.13
$P_{\text{heterogeneity ERPR-positive vs ERPR-negative}}$		0.06		0.75
$P_{\text{heterogeneity <25 vs ≥25 y}}$	0.001			

NOTE: All unconditional logistic regression models include categories of age, race, study site, education, age at menarche, and first-degree family history of breast cancer.

*These models used all nulligravida as the reference group.

†In addition to factors listed in (1), models include categories of age at first full-term pregnancy.

No association was observed between giving birth for the first time at age ≥25 years and a woman's overall risk of breast cancer compared with 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 nonsignificant 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, 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 ($P_{\text{heterogeneity}} = 0.43$; 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 age 20 years ($P_{\text{trend}} = 0.01$; Table 3). This trend was not observed among women who breastfed ($P_{\text{trend}} = 0.74$), although this apparent effect modification by breastfeeding was not statistically significant ($P_{\text{heterogeneity by breastfeeding}} = 0.32$). This pattern was stronger for ERPR-positive cancers ($P_{\text{trend}} = 0.003$); but again, the test for effect modification by breastfeeding was not statistically significant ($P = 0.06$). Multiparity reduced the risk of breast cancer among women who reported having breastfed ($P_{\text{trend}} = 0.007$) but did not reduce risk among those who never breastfed ($P_{\text{trend}} = 0.58$); 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 (<25 or ≥25 years) as well as breastfeeding status. 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 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 with nulligravid women, multiparity was associated with a reduced risk of breast cancer for women who breastfed and for those who never breastfed ($P_{\text{trend}} = 0.002$ and 0.0001, respectively).

Repeating these analyses in women who began their families at or after 25 years, again comparing them with nulligravid 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 reported previously findings from the Women's CARE Study among women ages 35 to 64 years, indicating that early age at first birth and multiparity

Table 2. Associations between parity status and breast cancer stratified by age at first full-term pregnancy (<25 or ≥25 years) among all women ages 55 to 64 years in the Women's CARE Study and by ERPR status (Cont'd)

ERPR positive				ERPR negative			
Age at first <25 y		Age at first ≥25 y		Age at first <25 y		Age at first ≥25 y	
<i>n</i> (cases)	OR (95% CI)	<i>n</i> (cases)	OR (95% CI)	<i>n</i> (cases)	OR (95% CI)	<i>n</i> (cases)	OR (95% CI)
72	1.00	72	1.00	11	1.00	11	1.00
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)
	0.00001				0.23		
41	1.00	45	1.00	11	1.00	14	1.00
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)
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)
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)
	0.0001		0.15		0.26		0.13
	0.002				0.04		

reduce the risk of ERPR-positive tumors but not ERPR-negative tumors, whereas breastfeeding reduces the risk of both tumor subtypes (3). In the present analysis, which was restricted to women ages 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, whereas women whose first birth was at age ≥25 years 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, which 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 eight 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 ($P_{\text{interaction}} = 0.07$; ref. 15). Although our analysis included fewer breast cancer cases, it was restricted to women ages 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 >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 ages 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 ages 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; 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 suggested previously that the mechanisms by which breastfeeding protects against breast cancer must be different from those of parity and age at first birth because breastfeeding

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

	All parous women			
	Never breastfed		Ever breastfed	
	<i>n</i> (case/control)	OR (95% CI)	<i>n</i> (case/control)	OR (95% CI)
All parous women	600/555	1.00	717/793	0.87 (0.74-1.02)*
Age at first <25 y	418/427	1.00	552/649	0.90 (0.75-1.08)
Age at first ≥25 y	182/128	1.00	165/144	0.62 (0.43-0.89)
Age first full-term pregnancy (y)				
<20	139/161	1.00	265/293	1.00
20-24	279/266	1.21 (0.90-1.64)	287/356	0.87 (0.67-1.13)
25-29	128/83	1.86 (1.25-2.78)	118/107	1.12 (0.77-1.63)
≥30	54/45	1.47 (0.88-2.45)	47/37	1.05 (0.62-1.79)
<i>P</i> _{trend}		0.01		0.74
<i>P</i> _{heterogeneity ERPR-positive vs ERPR-negative}		0.46		0.71
<i>P</i> _{heterogeneity ever vs never breastfed}				0.32
No. full-term pregnancies				
1	113/95	1.00	70/52	1.00
2	194/167	1.02 (0.71-1.47)	195/183	0.82 (0.53-1.25)
3	153/134	1.02 (0.69-1.50)	176/211	0.66 (0.42-1.01)
≥4	140/159	0.90 (0.61-1.35)	276/347	0.61 (0.40-0.93)
<i>P</i> _{trend}		0.58		0.007
<i>P</i> _{heterogeneity ERPR-positive vs ERPR-negative}		0.11		0.35
<i>P</i> _{heterogeneity ever vs never breastfed}				0.33

NOTE: Unconditional logistic regression used to calculate OR and 95% 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.

*OR of ever breastfeeding compared with parous women who have never breastfed.

protects against both ERPR-positive and ERPR-negative tumors, whereas 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

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

All women	Never breastfed		Ever breastfed	
	<i>n</i> (case/control)	OR (95% CI)	<i>n</i> (case/control)	OR (95% CI)
No. full-term pregnancies*				
Age at first full-term pregnancy <25 y				
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)
<i>P</i> _{trend}	0.002		0.0001	
<i>P</i> _{heterogeneity of trend ever vs never breastfed†}		0.68		
Age at first full-term pregnancy ≥25 y				
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)
<i>P</i> _{trend}	0.06		0.24	
<i>P</i> _{heterogeneity ever vs never breastfed†}		0.04		

NOTE: Unconditional logistic regression used to calculate OR and 95% CI; models include categories of age, race, study site, education, age at menarche, and family history of breast cancer.

*These models used all nulligravida as the reference group.

†Test for heterogeneity of parity trend effect by breastfeeding status among parous women.

Table 3. Associations between age at first full-term pregnancy, number of full-term pregnancies, and breast cancer risk, stratified by breastfeeding status (ever/never), among parous women ages 55 to 64 years in the Women's CARE Study and by ERPR status (Cont'd)

ERPR positive				ERPR negative			
Never breastfed		Ever breastfed		Never breastfed		Ever breastfed	
<i>n</i> (cases)	OR (95% CI)	<i>n</i> (cases)	OR (95% CI)	<i>n</i> (cases)	OR (95% CI)	<i>n</i> (cases)	OR (95% CI)
291	1.00	345/793	0.84 (0.68-1.03)	113	1.00	137	0.84 (0.63-1.12)
190	1.00	253/649	0.91 (0.71-1.15)	85	1.00	112	0.82 (0.60-1.14)
101	1.00	92/144	0.57 (0.37-0.87)	28	1.00	25	0.65 (0.33-1.27)
55	1.00	110/293	1.00	32	1.00	61	1.00
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)
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	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)
	0.003		0.81		0.20		0.99
			0.06				0.66
55	1.00	31	1.00	15	1.00	10	1.00
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)
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)
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)
	0.41		0.004		0.32		0.32
			0.61				0.29

by nine previous studies from the United States (14). The National Survey of Family Growth reported a breastfeeding rate of 55% in 1995, increasing up to 67% for babies born between 1997 and 2000 (4). Encouragingly, women ages ≥ 30 years 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 ages 55 to 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 95% CI. 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. reported a similar proportion of patients with unknown ERPR status in their study of 123,732 breast cancer cases from 11 Surveillance, Epidemiology, and End Results sites between 1992 and 1998 (7). Cases with data on ERPR status had fewer children ($\chi^2 P = 0.01$), 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, breastfeeding 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 ages 55 to 64 years who breastfed for < 2 weeks. We have reported previously 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 < 2 weeks (3). However, the modifying effects of breastfeeding we describe here were similar when we excluded those who breastfed for < 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 nondifferential 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 breastfeeding offers broad protection against breast cancer may be used to promote the benefits of breastfeeding in this group of women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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