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Reproductive Factors and Risk of Premenopausal Breast Cancer by Age at Diagnosis: Are There Differences Before and After Age 40?

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Abstract

PURPOSE—We examined the relationship between reproductive factors and risk of premenopausal breast cancer among women less than age 40 compared with older premenopausal women.

METHODS—We documented 374 incident cases of breast cancer diagnosed before age 40 and 2,533 cases diagnosed at age 40 and older among premenopausal women in the Nurses' Health Study cohorts. Biennial questionnaires were used to determine age at menarche, age at first birth, parity, breastfeeding and other reproductive factors. Multivariate relative risks (RR) and 95% confidence intervals (CI) were calculated using Cox proportional hazards models within age at diagnosis groups.

RESULTS—Tumors in younger women were significantly more likely to be higher grade, larger size, and hormone receptor negative than were tumors in older premenopausal women ($p < 0.0001$). There was no significant heterogeneity according to age in associations between reproductive factors and risk of premenopausal breast cancer. First birth at age 30 or older increased breast cancer risk in both age groups (age <40 : RR: 1.10, 95% CI: 0.80, 1.50; age ≥ 40 : RR: 1.16, 95% CI: 1.02, 1.32; p -heterogeneity= 0.44). Risk of premenopausal breast cancer decreased with each additional year of age at menarche in both age groups (age <40 RR: 0.93, 95% CI: 0.87, 0.99; p -trend=0.02; age ≥ 40 RR: 0.94, 95% CI: 0.91, 0.97; p -trend= <0.0001). Among premenopausal parous women, breastfeeding was protective regardless of age at diagnosis (age <40 RR: 0.84, 95% CI 0.57, 1.22; age ≥ 40 : RR: 0.85, 95% CI 0.72, 0.99; p -heterogeneity=0.79).

CONCLUSIONS—In the largest prospective examination of reproductive risk factors and risk of breast cancer before and after age 40, we found that younger women were more likely to develop

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Conflict of Interest

The authors declare that they have no conflict of interest.

tumors with less favorable prognostic characteristics. However, associations between reproductive factors and risk of breast cancer were similar regardless of age at diagnosis of premenopausal breast cancer.

Keywords

breast cancer; age at diagnosis; young women; reproductive factors

Introduction

Breast cancer is the most commonly diagnosed cancer among women, with an estimated 232,340 new cases diagnosed in 2013 [1]. About 7% of those breast cancers were diagnosed among women less than 40 years of age [1, 2]. While incidence is relatively low, breast cancer represents about 40% of all cancers diagnosed among these young women. Breast cancer incidence rates among women younger than 40 years of age have been stable for the past three decades [3-5]. However, a recent report suggests that only the incidence of local and regional tumors has been stable among 20-39 year olds, while incidence of distant breast cancer increased 2% per year between 1978 and 2008 [6].

Owing to the low incidence rates among this age group, few reports address breast cancer in young women and many studies that have been conducted use a case-control design [7]. Much of the prospective data available on breast cancer in young women are from studies examining premenopausal breast cancer where authors did sub-analyses stratified by age to examine potential effect modification [8, 9]. Additionally, there is little consistency in the definition of young. Age cutoffs of 45, 40 and 35 can all be found in the literature [4, 10-15]. Studies have also used inconsistent comparison groups when comparing tumor characteristics in younger versus older women with breast cancer, and sometimes have been a mixture of pre- and postmenopausal women [16]. There are known clear distinctions in tumor characteristics and risk factors between pre and postmenopausal women therefore these comparisons may be of limited utility.

Some authors have suggested that breast cancer occurring in women before the age of 40 may be etiologically and clinically distinct from cancers occurring in older women [17-20]. At diagnosis, younger women tend to have larger tumors, a higher proportion of late stage, high grade, and are more likely to be estrogen receptor negative (ER-) [15, 21, 22]. There has been inconsistency in findings regarding human epidermal growth receptor 2 (HER-2) expression [23-26], though a recent paper showed that adolescent and young adult women in California had higher proportions of HER-2 positive tumors than did older women [27]. Differences in stage and tumor size are likely due, at least in part, to the fact that these women have not reached the recommended age for mammography, while differences in grade and estrogen receptor status may be more indicative of differences in etiology [28]. Tumors in women diagnosed at a young age share a pattern of gene expression which differentiates them from tumors diagnosed in older women, but there is conflicting evidence whether this difference is attributable to differences in tumor subtype distributions across age groups [29-31]. Several studies have demonstrated that young women have an increased risk of disease recurrence and death as compared to older women [32, 33], though it is difficult to disentangle the effects of age from those of tumor characteristics. Yet, several studies suggest that age is an independent prognostic factor, and this association may vary by tumor subtype and stage at diagnosis [34, 35]. Understanding risk factors for breast cancer among young women, particularly within subtypes, is critical.

Reproductive factors are the group of factors with the strongest and most consistent associations with breast cancer risk [36]. Known factors associated with premenopausal

breast cancer include: age at menarche, age at first birth and parity. Later age at menarche and earlier age at first birth are consistently associated with lower risk of breast cancer, though there are known differences by estrogen and progesterone hormone status [37-40]. Several studies have shown interaction between the effect of parity by age, such that at younger ages (and closer in time to the birth) parous women experience an increased risk of breast cancer, while at older ages parity is protective [14, 41-44]. Prior studies have included relatively few women age under 40 at diagnosis and it remains unclear if these differences in risk exist among young women, and if similar differences in associations exist for other reproductive factors including breastfeeding and interval between menarche and first live birth.

The purpose of this study was to examine the relationship between reproductive factors and breast cancer risk among women less than 40 years of age overall, and according to subtypes defined by estrogen and progesterone receptor status, in a large prospective cohort study. We also assessed whether associations differ between premenopausal women less than 40 years of age and those age 40 or older.

Materials and Methods

Study Population

The Nurses' Health Studies (NHS I and NHS II) are ongoing prospective cohort studies of female registered nurses across the United States.[45] In 1976, 121,700 female registered ages 30 to 55 years and of primarily Caucasian descent, were enrolled in NHS I. NHS II began in 1989 with 116,608 largely Caucasian female registered nurses ages of 25 and 42. Nurses have complete biennial mailed questionnaires that comprise items about their health status, medical history, and known or suspected risk factors for cancer. Institutional Review Board approval for this study was obtained from Partners Healthcare Human Research Committee.

For analyses of the risk of premenopausal breast cancer diagnosed before age 40, women were excluded if at baseline they were: age 40 or older (n=94,337), were not premenopausal (n=7,156), reported a previous cancer diagnosis (n=1,433) or were diagnosed with breast cancer before baseline (n=51). Women stopped contributing person-time at the first report of any of the following events: reached 40 years of age, onset of menopause, breast cancer diagnosis, diagnosis of any other cancer (excluding non-melanoma skin cancer), or death. Otherwise follow-up ended June 2009. There were 374 confirmed, incident invasive breast cancers diagnosed in premenopausal women less than 40 years of age.

For analyses of the risk of premenopausal breast cancer diagnosed at age 40 or older, women were excluded if at baseline they were: not premenopausal (n=39,217), had breast cancer diagnosed before baseline (n=95) or reported a previous other cancer diagnosis (n=1,861). Women started contributing person time in the first data cycle in which they were age 40 or older and stopped at the first report of any of the following events: onset of menopause, breast cancer diagnosis, diagnosis of any other cancer (excluding non-melanoma skin cancer), or death. Otherwise follow-up ended June 2009. There were 2,533 confirmed, incident invasive breast cancers diagnosed in premenopausal women age 40 or older.

Outcome Assessment

Incident breast cancer diagnoses on each biennial questionnaire are, with participant or next of kin permission, confirmed through medical record review. Pathology reports are also requested and information on tumor characteristics including grade, stage and hormone

receptor status is obtained. Deaths are reported through family members or identified through review of the National Death Index.

Exposure Assessment

At baseline, participants reported their number of births, age at each birth, and age at menarche, history of breast cancer or any other cancers, history of benign breast disease, height and weight, age at menarche, oral contraceptive (OC) use, family history of breast cancer, alcohol consumption, and menopausal status. In subsequent biennial questionnaires, they reported any new diagnoses of breast cancer, and updated information on baseline factors including births, OC use, benign breast disease, and menopausal status. Breastfeeding was assessed in 1986 in NHS and in 1993 and 1997 in NHSII. As there were no breast cancers diagnosed among women under age 40 after the 1986-1988 cycle in NHS, we have limited analyses of breastfeeding to NHSII. As the last information on parity for women in NHS was collected in 1996, we have carried this value forward for all subsequent time periods.

In analyses restricted to parous women, we examined the relationship between time since last birth, interval between menarche and first birth, age at first birth, number of births, and breastfeeding with risk of breast cancer. Interval between menarche and first birth is calculated as the age at first birth minus age at menarche. Time since last birth is calculated as the date of return of the most recent questionnaire minus the date of last reported birth. Information on age at first birth, parity, menopausal status was updated through biennial questionnaires, and person-time was reassigned using updated information every two years. Missing indicators were used for missing reproductive exposure data and covariate data was carried forward for up to two questionnaire cycles.

Statistical Analysis

The distribution of hormone receptor status, tumor size and grade, lymph node involvement and initial sign or symptom of cancer among women diagnosed under age 40 were compared with premenopausal women age 40 and older using chi-square tests (for categorical variables) and Mantel-Haenszel chi-square tests for trend (for ordinal variables). Cox proportional hazards regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for breast cancer associated with each established premenopausal breast cancer risk factor stratified by age at diagnosis (<40 and ≥40). Age and multivariate adjusted models are presented. Multivariate models are adjusted for age (continuous), BMI at age 18 (kg/m²), weight change since age 18 (kg) alcohol intake (g/day), height (meters), family history (first degree relative vs. none) and history of benign breast disease (yes/no).

We tested for heterogeneity by age at diagnosis using likelihood ratio tests by comparing models with and without interaction terms for continuous exposures and a binary indicator of age. To evaluate the consistency of risk estimates among hormone receptor types defined by estrogen and progesterone receptor status jointly (ER-PR- or ER+PR+) we performed a competing risks analysis allowing estimates to vary for all reproductive exposure variables [46-48]. Likelihood ratio tests were used to compare a model with different slopes for each hormone receptor status with a model with a common slope. Chi-square tests are used to obtain 2-sided *P* values for all likelihood ratio statistics.

Results

The distribution of traditional premenopausal breast cancer risk factors at baseline according to age group is shown in table 1. Women younger than age 40 were more likely to be

nulliparous (25% vs. 9%), and current OC users (15% vs. 6%) and were less likely to be currently obese (9% vs. 11%) and to have had their first menstrual cycle at age 14 or older (18% vs. 20%) than were women age 40 and older. The distribution of BMI at age 18 was similar between groups. Women younger than 40 were more likely to report a current BMI less than 20 (17%) than were women age 40 and older (10%).

Mean age at diagnosis was 36.8 years among women diagnosed with breast cancer before age 40 and 48.2 years for women diagnosed age 40 or older (table 2). Younger women were more likely to be diagnosed with hormone receptor negative, higher grade and larger tumors compared to older premenopausal women. For example, 30% of tumors were estrogen and progesterone receptor negative (ER-PR-) among women diagnosed before age 40, while 19% were for women 40 or older ($p < 0.0001$). Younger women were somewhat more likely to be diagnosed at a later stage, with 19% diagnosed at stage III compared to 15% of women age 40 or older at diagnosis ($p = 0.03$).

Associations with age at menarche and breast cancer risk were similar in both age groups (table 3). Women experiencing menarche at age 14 or older were 24% less likely to develop breast cancer before age 40 (RR: 0.76, 95% CI: 0.55, 1.04; p -trend=0.02) and were 11% less likely to develop breast cancer at age 40 or older (RR: 0.89, 95% CI: 0.79, 1.00); p -trend < 0.0001). Women with an age at first birth of age 30 or older were at a higher risk of premenopausal breast cancer compared to nulliparous women in both age groups (Age < 40 : RR: 1.10, 95% CI: 0.80, 1.50; Age 40: RR: 1.16, 95% CI: 1.03, 1.30; p -heterogeneity=0.32). In each age group, women with three or more births had a lower breast cancer risk compared to nulliparous women (Age < 40 : RR: 0.78, 95% CI: 0.56, 1.08; Age 40: RR: 0.84, 95% CI: 0.73, 0.97). When stratified by breastfeeding in both age groups, we observed no protective association of parity among women that never breastfed (Age < 40 : RR: 1.14, 95% CI: 0.71, 1.83; Age 40: RR: 0.93, 95% CI: 0.75, 1.14). Premenopausal women age 40 or older with two or more children who ever breastfed (RR: 0.84, 95% CI: 0.70, 0.94) or had a last birth 10 or more years ago (RR: 0.81, 95% CI: 0.70, 0.94) were at a reduced risk of breast cancer. Such associations were not observed among those younger than 40.

Among parous women, long duration between menarche and first birth was associated with an increased risk of breast cancer among premenopausal women age 40 or older at diagnosis (table 4). Among older women, having 15 or more years between menarche and first birth was associated with a 21% increased risk of breast cancer (RR: 1.21, 95% CI: 1.04, 1.42) compared to those with less than five years. That same interval was associated with a non-statistically significant increase in risk (RR: 1.17, 95% CI: 0.75, 1.80) among younger women. Among premenopausal women age 40 or older, parous women were at decreased risk of premenopausal breast cancer relative to nulliparous women. Older parous women with 10 years or more since last pregnancy were at lower risk of breast cancer (RR: 0.94, 95% CI: 0.78, 1.14) compared to those with 4-10 years since last pregnancy, though the estimate was not significant after multivariate adjustment. Parous women who had ever breastfed were at reduced risk of breast cancer in both age at diagnosis groups (Age < 40 : RR: 0.84, 95% CI: 0.57, 1.22; Age 40: RR: 0.85, 95% CI: 0.72, 0.99). We did not observe a significant trend for breastfeeding duration in either age group although the suggested direction of associations were similar.

Among women younger than 40, earlier age at menarche was associated with an increased risk of breast cancer in both ER+PR+ and ER-PR- tumors, though results were not statistically significant for the latter (table 5). For ER+PR+ tumors, women with an age at menarche of age 14 or older were 50% less likely to be diagnosed with breast cancer than those with an age of menarche of under 12 (RR: 0.50, 95% CI: 0.28, 0.90). While the observed associations between age at first birth and age at menarche were similar across

hormone receptor groups among young women, there was a significant heterogeneity for parity (ER+PR+: RR: 0.97, 95% CI: 0.59, 1.60; ER-PR-: RR: 1.79, 95% CI: 0.92, 3.50; p -heterogeneity=0.048). We observed no differences in risk patterns by ERPR status among women age 40 or older.

Discussion

We examined types of tumors diagnosed, and relationships between age at menarche, age at first birth and parity, and birth timing characteristics and risk of premenopausal breast cancer before and after age 40. Younger premenopausal women were diagnosed with more hormone receptor negative, larger size and, higher grade tumors as compared to older premenopausal women. We did not observe evidence of differing associations for the reproductive factors we studied according to age at diagnosis. The associations with age at first birth, parity and age at menarche and premenopausal breast cancer risk were similar across age at diagnosis groups. We further investigated whether the associations of these factors varied by hormone receptor type. Among women in both age groups increasing parity appeared protective for ER+PR+ tumors, while it was associated with increased risk for ER-PR- tumors.

In our study, we expected parity and shorter times since last birth to be associated with increased risk of breast cancer among younger women. However, we did not observe any increased risk associated with parity or time since last birth women among women you than 40. Given the small number of breast cancers diagnosed among women prior to age 40, it is possible that we lacked the power to observe any possible increased risk, though our results suggest a protective association (RR: 0.82, 95% CI: 0.59,1.14). More in line with our hypothesis, for time since last birth, we observed that women with 2-4 years since last pregnancy had a non-statistically significant 73% increase in risk of premenopausal breast cancer (RR: 1.73, 95% CI: 0.93, 2.00). Second, in prior studies ‘older’ women included postmenopausal women, while our study is restricted to premenopausal women and therefore has a narrower range of ages included. The ‘older’ women in our study may not be old enough, or far enough removed from childbearing, to fully observe the expected association. Third, the increased risk of breast cancer is observed largely with first pregnancy and is strongest in women having their first child after age 35. Given that our analysis of young women was restricted to women younger than 40, there was limited opportunity for births after age 35 and , overall there were relatively few births age 35 or older in these two cohorts (NHS I, 3.5%; NHS II, 3.6%). Lastly, given the known differences in association between reproductive factors and breast cancer subtypes, our results may be influenced by differences in hormone receptor status between women diagnosed before and after age 40.

Our finding that for both age groups, parity was inversely associated with risk of ER+PR+ tumors, but positively associated with risk of ER-PR- tumors is consistent with some prior literature [49, 50]. However, several studies have found that parity is not associated with risk of ER- breast cancer [51-53]. Some reports show breastfeeding to be more strongly associated with a reduced risk of ER- tumors than ER+ tumors [49, 54-56] and that breastfeeding may eliminate any increased breast cancer risk associated with parity [49, 54, 56]. We did not observe this in our study. Breastfeeding was similarly associated with reduced risk of breast cancer for ER+PR+ and ER-PR- tumors across age at diagnosis strata. Our examination of cross-classified breastfeeding and parity was limited by small case numbers, particularly among women diagnosed before age 40. There was, however, a suggestion of increased risk of ER-PR- tumors before age 40 for women with two or more children that never breastfed.

With 374 cases diagnosed among women before age 40, we had limited statistical power for several analyses, resulting in wide confidence intervals and non-significant p-values. For example, we were unable to examine whether the association between family history and breast cancer differed by age at diagnosis because only 28 cases under age 40 reported a family history. Additional follow-up in these cohorts will not yield additional incident cases in our under 40 group, as by the study cutoff date, all women in both cohorts were older than age 40. Nevertheless, to our knowledge, this analysis represents the largest prospective examination of the relationship between reproductive factors and premenopausal breast cancer in women younger than 40 and the first comparison to premenopausal women age 40 or older.

We were unable to examine the role of genetic mutations such as BRCA 1 and 2 in this analysis. Women diagnosed before age 40 are more likely to have a family history of breast cancer (in first or second degree relatives) and are more likely than older women to have BRCA 1 and/or 2 mutations. In this analysis, we used family history as a proxy for genetic susceptibility [57]. Research suggests that the role of genetics in breast cancer etiology increases with younger age at diagnosis and more extensive family history [58]. While these genetic mutations are of relatively more importance in younger compared to older women, their absolute contribution to risk remains low. For example, in a population-based study, only 4.9% of cases were found to have BRCA 1 and/or 2 mutations [59]. Thus, we believe that this is unlikely to have biased our results.

Breast cancer in women younger than 40 is most common among African-American women [60-62], of whom there are very few in this sample. Our results may not be generalizable to African-American women since their subtype distribution may differ from what we observed in our cohorts [54, 63-65], and the higher rates of breast cancer before age 40 in African-American women appear to be driven by subtype-specific differences [66]. Also, because we lacked sufficient data on HER-2 among the young cases that were generally diagnosed early in the follow-up period of both cohorts, we were unable to determine the distribution of triple negative tumors or other subtypes.

This study is one of the first to prospectively examine the relationship of reproductive factors with risk of premenopausal breast cancer risk according to age. We found little evidence of differing associations between age at first birth, parity and age at menarche and risk of premenopausal breast cancer among women diagnosed before and after age 40.

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Table 1

Distribution of risk factors among premenopausal women by age, Nurses' Health Study I and II, at baseline in 1976 and 1989

	Age < 40 N=135,151 (%)	Age 40 N=61,348 (%)
Age at menarche (yrs)		
< 12	33,009 (24)	13,792 (23)
12	40,565 (30)	16,283 (27)
13	37,972 (28)	18,749 (31)
14+	23,605 (18)	12,524 (20)
Oral contraceptive use		
Never	28,010 (21)	28,734 (47)
Past, <5 years	60,745 (45)	19,319 (32)
Past, 5 years	26,567 (20)	9,765 (16)
Current	19,829 (15)	3,530 (6)
Parity		
Nulliparous	33,299 (25)	5,252 (9)
1	22,535 (17)	5,339 (9)
2	44,590 (33)	16,582 (28)
3	33,962 (25)	33,148 (54)
Age at first birth		
<25	46,096 (46)	28,542 (52)
25-29	43,179 (43)	19,750 (36)
30	11,788 (12)	6,769 (12)
BMI (current) (kg/m2)		
<20	22,360 (17)	6,105 (10)
20-22.4	46,693 (35)	18,434 (30)
22.5 – 24.9	30,499 (23)	16,132 (26)
25-29.9	23,084 (17)	13,765 (22)
30+	12,515 (9)	6,912 (11)
BMI (at age 18) (kg/m2)		
<19	26,142 (19)	10,099 (17)
19-20.4	41,587 (21)	21,122 (34)
20.5 – 21.9	30,040 (22)	13,237 (22)
22-24.9	24,437 (18)	11,279 (18)
25+	12,945 (10)	5,611 (9)
Family history (mother/ sister)		
No	128,053 (95)	57,074 (93)
Yes	7,098 (5)	4,274 (7)
Benign breast disease		
No Reported BBD	121,771 (90)	50,517 (82)

	Age < 40 N=135,151 (%)	Age 40 N=61,348 (%)
BBD Reported	13,380 (10)	10,831 (18)
Alcohol intake (grams/day)		
None	54,106 (40)	27,545 (45)
<7.5	60,664 (45)	21,298 (35)
7.5-14.9	13,654 (7)	7,189 (12)
15-29.9	4,029 (3)	3,052 (5)
30	1,811 (1)	2,112 (4)

Note: numbers may not add to column totals due to missing data and percentages may not add to 100 due to rounding

Table 2

Distribution of Tumor Characteristics among Premenopausal Women Diagnosed with Breast Cancer, Nurses' Health Study I and II, 1976-2009

	Age at diagnosis < 40 N=374 (%)	Age at diagnosis ≥ 40 N=2,533 (%)	P-VALUE
Age at diagnosis [mean(SD)]	36.8 (2.6)	48.2 (3.8)	
Estrogen Receptor Status (ER)			
Positive	169 (63)	1519 (76)	<0.0001
Negative	100 (37)	475 (24)	
Progesterone Receptor Status (PR)			
Positive	152 (60)	1390 (72)	<0.0001
Negative	103 (40)	543 (28)	
Joint Hormone Receptor Status			
ER+PR+	130 (53)	1288 (68)	<0.0001
ER+PR–	27 (11)	167 (9)	
ER–/PR+	17 (7)	82 (4)	
ER–/PR–	74 (30)	358 (19)	
Tumor Size			
0.1 to 1.0 cm	62 (19)	527 (24)	0.0001
1.1 to < 2.0 cm	110 (34)	802 (37)	
2.0 to < 4.0 cm	97 (30)	640 (30)	
4+ cm	55 (17)	198 (9)	
Lymph Node Involvement			
No nodes involved	209 (61)	1328 (61)	0.33
1-3 nodes	69 (20)	516 (24)	
4-9 nodes	55 (16)	226 (10)	
10+ nodes or metastatic	13 (4)	98 (5)	
Tumor Grade			
Primarily well-differentiated	16 (8)	261 (18)	<0.0001
Moderately differentiated	85 (41)	624 (42)	
Poorly differentiated	109 (52)	596 (40)	
Initial Sign or Symptom			
Self-exam	92 (72)	765 (52)	<0.0001
Health professional exam	11 (9)	124 (8)	
Husband or other non-health prof.	2 (2)	29 (2)	
Routine Mammography	22 (17)	553 (38)	
Stage at diagnosis			
I	163 (44)	1160 (49)	0.03
II	132 (36)	812 (35)	
III	71 (19)	355 (15)	
IV	4 (1)	26 (1)	

Note: numbers may not add to column totals due to missing data and percentages may not add to 100 due to rounding

Table 3

Relative Risk of Premenopausal Breast Cancer by Reproductive Factors According to Age at Diagnosis, Nurses' Health Study I & II, 1976-2009

	AGE AT DIAGNOSIS <40 (N=374)				AGE AT DIAGNOSIS 40 (N=2,533)				^b p-value
	Person-years	Cases	Age adjusted RR	Multivariable Adjusted RR ^a	Person-years	Cases	Age adjusted RR	Multivariable Adjusted RR ^a	
Age at menarche									
<12	197,256	101	1.00 (0.77, 1.30)	1.02 (0.78, 1.33)	310,492	631	1.08 (0.97, 1.20)	1.12 (1.02, 1.28)	0.16
12	249,662	125	1.00 (reference)	1.00 (reference)	386,640	724	1.00 (reference)	1.00 (reference)	
13	230,633	91	0.78 (0.60, 1.02)	0.78 (0.59, 1.02)	391,871	748	1.01 (0.91, 1.12)	1.00 (0.89, 1.01)	
14	148,303	57	0.77 (0.56, 1.06)	0.76 (0.55, 1.04)	242,893	430	0.93 (0.83, 1.05)	0.89 (0.79, 1.00)	
			p-trend: 0.04	p-trend: 0.02			p-trend: 0.001	p-trend: <0.0001	
Age at first birth									
<25	247,423	104	0.83 (0.64, 1.08)	0.83 (0.64, 1.07)	513,084	874	0.86 (0.77, 0.95)	0.87 (0.78, 0.95)	0.44
25-29	290,173	138	1.00	1.00	451,852	875	1.00 (REF)	1.00	
30	179,667	57	1.10 (0.80, 1.45)	1.10 (0.80, 1.50)	200,001	436	1.15 (1.02, 1.29)	1.16 (1.03, 1.30)	
			p-trend: 0.15	p-trend: 0.17			p-trend: <0.0001	p-trend: <0.0001	
Parity									
Nulliparous	181,205	74	1.00 (reference)	1.00 (reference)	157,229	325	1.00 (reference)	1.00 (reference)	0.32
1	130,728	60	1.03 (0.73, 1.45)	0.96 (0.66, 1.39)	140,894	297	1.04 (0.88, 1.23)	0.94 (0.79, 1.12)	
2	294,618	151	1.07 (0.80, 1.43)	1.07 (0.79, 1.43)	466,810	929	0.97 (0.85, 1.12)	0.95 (0.83, 1.09)	
3	216,201	88	0.78 (0.56, 1.08)	0.82 (0.59, 1.14)	633,082	857	0.81 (0.70, 0.93)	0.84 (0.73, 0.97)	
			p-trend: 0.35	p-trend: 0.46			p-trend: 0.01	p-trend: 0.05	
Parity & breastfeeding^c									
Nulliparous	169,589	69	1.00 (reference)	1.00 (reference)	131,474	258	1.00 (reference)	1.00 (reference)	0.19
1 child, never breastfed	24,403	12	1.12 (0.61, 2.08)	1.09 (0.59, 2.03)	29,581	61	1.03 (0.79, 1.36)	1.05 (0.80, 1.40)	
1 child, ever breastfed	71,119	29	0.94 (0.61, 1.45)	0.93 (0.60, 1.45)	64,679	120	0.94 (0.75, 1.16)	0.94 (0.76, 1.17)	
2 children, never breastfed	43,339	24	1.15 (0.72, 1.83)	1.14 (0.71, 1.83)	80,308	147	0.90 (0.74, 1.11)	0.93 (0.75, 1.14)	
2 children, ever breastfed	278,280	118	0.91 (0.67, 1.23)	0.92 (0.67, 1.26)	415,699	675	0.83 (0.72, 0.96)	0.84 (0.73, 0.97)	

	AGE AT DIAGNOSIS <40 (N=374)				AGE AT DIAGNOSIS 40 (N=2,533)				<i>p</i> -value ^b
	Person-years	Cases	Age adjusted RR ^a	Multivariable Adjusted RR ^a	Person-years	Cases	Age adjusted RR	Multivariable Adjusted RR ^a	
Parity & time since last birth^c									
Nulliparous	169,589	69	1.00 (reference)	1.00 (reference)	131,474	258	1.00 (reference)	1.00 (reference)	0.11
1 child, <10 years	86,188	42	1.14 (0.78, 1.68)	1.14 (0.77, 1.68)	27,191	38	0.98 (0.69, 1.38)	0.98 (0.70, 1.39)	
1 child, 10 years	21,638	7	0.69 (0.32, 1.52)	0.68 (0.31, 1.48)	74,712	152	0.93 (0.76, 1.14)	0.95 (0.77, 1.16)	
2 children, <10 years	302,237	133	0.93 (0.69, 1.25)	0.95 (0.70, 1.28)	160,905	232	1.04 (0.86, 1.25)	1.07 (0.89, 1.29)	
2 children, 10 years	49,725	21	0.94 (0.57, 1.56)	0.94 (0.56, 1.56)	356,760	633	0.80 (0.69, 0.92)	0.81 (0.70, 0.94)	

RR= relative risk; CI = confidence interval

^a adjusted for the following covariates: age, history of benign breast disease, mother or sister with breast cancer, current alcohol consumption, adult height, oral contraceptive use, BMI at age 18, weight change since age 18, age at first birth, age at menarche, and parity

^b *p*-value heterogeneity for age at diagnosis

^c NHSII only

Table 4

Relationship of Birth Characteristics to Risk of Premenopausal Breast Cancer According to Age at Diagnosis among Parous Premenopausal Women, Nurses' Health Study I & II, 1976-2009

	AGE AT DIAGNOSIS < 40 (N=299)				AGE AT DIAGNOSIS 40 (N=2,146)				^b p-value
	Person-years	Cases	Age adjusted RR	Multivariable Adjusted RR ^a	Person-years	Cases	Age adjusted RR	Multivariable Adjusted RR ^a	
Parity									
1	129,948	60	1.00 (reference)	1.00 (reference)	139,835	292	1.00 (reference)	1.00 (reference)	0.78
2	293,262	151	1.05 (0.77, 1.42)	1.12 (0.81, 1.55)	462,314	901	0.93 (0.81, 1.06)	1.00 (0.87, 1.14)	
3	215,626	88	0.77 (0.54, 1.08)	0.87 (0.60, 1.27)	550,807	953	0.79 (0.69, 0.91)	0.91 (0.79, 1.06)	
			p-trend:0.01	p-trend:0.35			p-trend:0.0001	p-trend:0.11	
Time from menarche to first birth									
<5 years	11,685	7	1.47 (0.68, 3.16)	1.36 (0.52, 3.58)	18,229	20	0.63 (0.40, 0.98)	0.70 (0.43, 1.12)	0.74
5-10 years	131,875	41	0.63 (0.45, 0.89)	0.63 (0.41, 0.97)	278,150	445	0.89 (0.80, 1.00)	0.94 (0.82, 1.07)	
10-15 years	317,065	152	1.00 (reference)	1.00 (reference)	563,236	1030	1.00 (reference)	1.00 (reference)	
15 years	178,211	99	1.20 (0.92, 1.56)	1.17 (0.75, 1.80)	293,344	651	1.29 (1.16, 1.43)	1.21 (1.04, 1.42)	
			p-trend:0.05	p-trend:0.11			p-trend: <0.0001	p-trend: 0.03	
Time since last birth^c									
< 2 years	86,996	27	0.78 (0.49, 1.25)	0.81 (0.44, 1.40)	38,005	14	1.21 (0.70, 2.09)	1.07 (0.62, 1.85)	0.48
2-4 years	145,576	82	1.35 (0.97, 1.88)	1.73 (0.93, 2.00)	30,572	57	1.23 (0.91, 1.65)	1.14 (0.84, 1.54)	
4-10 years	146,576	66	1.00 (reference)	1.00 (reference)	119,518	199	1.00 (reference)	1.00 (reference)	
10 years	71,363	28	1.02 (0.65, 1.60)	0.94 (0.55, 1.62)	431,473	785	0.83 (0.70, 0.98)	0.94 (0.78, 1.14)	
			p-trend:0.91	p-trend:0.99			p-trend: 0.0005	p-trend:0.07	
Breastfeeding^c									
Never (< 1 month)	68,742	36	1.00 (reference)	1.00 (reference)	109,889	208	1.00 (reference)	1.00 (reference)	0.79
Ever	349,429	147	0.80 (0.55, 1.15)	0.84 (0.57, 1.22)	480,377	795	0.90 (0.77, 1.05)	0.85 (0.72, 0.99)	
Breastfeeding (months)^c									
<1	68,742	36	1.00 (reference)	1.00 (reference)	109,889	208	1.00 (reference)	1.00 (reference)	0.63
1-12	162,355	61	0.73 (0.48, 1.10)	0.73 (0.48, 1.10)	192,332	319	0.91 (0.76, 1.09)	0.86 (0.69, 1.03)	

	AGE AT DIAGNOSIS < 40 (N=299)				AGE AT DIAGNOSIS 40 (N=2,146)			<i>p</i> -value ^b
	Person-years	Cases	Age adjusted RR	Multivariable Adjusted RR ^a	Person-years	Cases	Age adjusted RR	Multivariable Adjusted RR ^a
12-24	105,462	59	1.06 (0.70, 1.61)	1.13 (0.73, 1.73)	148,335	246	0.90 (0.75, 1.08)	0.83 (0.68, 1.01)
24	81,612	27	0.62 (0.37, 1.02)	0.68 (0.40, 1.17)	139,700	230	0.89 (0.73, 1.07)	0.84 (0.68, 1.03)
			p-trend:0.63	p-trend: 0.84			p-trend: 0.19	p-trend: 0.09

RR= relative risk; CI = confidence interval

^a adjusted for the following covariates: age, history of benign breast disease, mother or sister with breast cancer, current alcohol consumption, adult height, oral contraceptive use, BMI at age 18, weight change since age 18, age at first birth (except time from menarche to first birth), age at menarche (except time from menarche to first birth)

^b *p*-value heterogeneity for age at diagnosis

^c NHS II only

Table 5

Relative Risk of Premenopausal Breast Cancer by Reproductive Factors and According to Age at Diagnosis and Hormone Receptor Status, Nurses' Health Study I & II, 1976-2009

	AGE AT DIAGNOSIS <40					AGE AT DIAGNOSIS 40				
	Cases	ER+/PR+ RR (95% CI) ^d (n=118)	Cases	ER-/PR- RR (95% CI) ^d (n=71)	p-value ^b	Cases	ER+/PR+ RR (95% CI) ^d (n=1,246)	Cases	ER-/PR- RR (95% CI) ^d (n=347)	p-value ^b
Age at menarche										
< 12	25	0.61 (0.38, 0.99)	21	1.14 (0.63, 2.06)	0.22	333	1.21 (1.04, 1.41)	89	1.23 (0.91, 1.65)	0.47
12	49	1.00 (reference)	24	1.00 (reference)		354	1.00 (reference)	91	1.00 (reference)	
13	29	0.64 (0.40, 1.02)	16	0.72 (0.38, 1.37)		340	0.94 (0.81, 1.09)	104	1.12 (0.84, 1.48)	
14+	15	0.50 (0.28, 0.90)	10	0.70 (0.33, 1.49)		219	0.95 (0.80, 1.13)	63	1.06 (0.77, 1.47)	
		p-trend: 0.45		p-trend:0.27			p-trend: 0.0008		p-trend:0.52	
Age at first birth										
<25	33	1.09 (0.68, 1.75)	17	0.73 (0.40, 1.35)	0.27	417	0.83 (0.73, 0.96)	136	1.03 (0.80, 1.32)	0.31
25-29	39	1.00	31	1.00 (reference)		431	1.00 (reference)	115	1.00 (reference)	
30+	18	1.15 (0.65, 2.03)	10	0.77(0.37, 1.59)		216	1.15 (0.97, 1.36)	57	1.12 (0.81, 1.55)	
		p-trend:0.70		p-trend: 0.64			p-trend:<0.0001		p-trend: 0.28	
Parity										
Nulliparous	268	1.00 (reference)	13	1.00 (reference)	0.048	175	1.00 (reference)	33	1.00 (reference)	0.32
1	16	0.80 (0.41, 1.54)	12	1.41 (0.60, 3.28)		146	0.82 (0.65, 1.04)	44	1.42 (0.89, 2.29)	
2	46	0.97 (0.59, 1.60)	37	1.79 (0.92, 3.50)		483	0.89 (0.74, 1.06)	129	1.28 (0.86, 1.89)	
3	28	0.78 (0.45, 1.36)	9	0.63 (0.26, 1.53)		434	0.76 (0.63, 0.91)	134	1.12 (0.75, 1.68)	
		p-trend:0.49		p-trend: 0.06			p-trend:0.04		p-trend: 0.01	
Breastfeeding ^c										
Never (< 1 month)	14	1.00 (reference)	10	1.00 (reference)	0.98	127	1.00 (reference)	31	1.00 (reference)	0.86
Ever	55	0.79 (0.43, 1.44)	35	0.79 (0.38, 1.64)		478	0.81 (0.66, 0.99)	123	0.72 (0.32, 1.61)	
Parity & breastfeeding ^c										
Nulliparous	29	1.00 (reference)	12	1.00 (reference)	0.90	144	1.00 (reference)	28	1.00 (reference)	0.65
1 child, never breastfed	3	0.66 (0.20, 2.18)	2	1.13 (0.25, 5.12)		32	0.98 (0.70, 1.39)	10	1.60 (0.77, 3.31)	
1 child, ever breastfed	9	0.68 (0.32, 1.44)	8	1.67 (0.67, 4.18)		63	0.95 (0.77, 1.16)	19	1.36 (0.76, 2.45)	

	AGE AT DIAGNOSIS <40				AGE AT DIAGNOSIS 40				<i>b</i> <i>p</i> -value
	Cases	ER+/PR+ RR (95% CI) ^a (n=118)	Cases	ER-/PR- RR (95% CI) ^a (n=71)	<i>b</i> <i>p</i> -value	Cases	ER+/PR+ RR (95% CI) ^a (n=1,246)	ER-/PR- RR (95% CI) ^a (n=347)	
2 children, never breastfed	11	1.19 (0.58, 2.43)	8	2.35 (0.93, 5.97)		92	1.07 (0.89, 1.29)	1.17 (0.65, 2.10)	
2 children, ever breastfed	46	0.81 (0.50, 1.32)	27	1.30 (0.34, 2.66)		390	0.81 (0.70, 0.94)	1.10 (0.45, 2.29)	

RR= relative risk; CI = confidence interval

^a adjusted for the following covariates: age, history of benign breast disease, mother or sister with breast cancer, current alcohol consumption, adult height, BMI at age 18, weight change since age 18

^b *p*-value for heterogeneity for ER/PR status within age at diagnosis groups

^c NHSII only