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## Lactation and Incidence of Premenopausal Breast Cancer, A Longitudinal Study

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### Abstract

**Background**—Findings from observational studies suggest an inverse association between lactation and premenopausal breast cancer risk, but results are inconsistent, and data from large prospective cohort studies are lacking.

**Methods**—We used information from 60,075 parous women participating in the prospective cohort study of the Nurses' Health Study II from 1997 to 2005. Our primary outcome was incident premenopausal breast cancer.

**Results**—We ascertained 608 incident cases of premenopausal breast cancer during 357,556 person-years of follow-up. Women who had ever breastfed had a covariate-adjusted hazard ratio [HR] of 0.75 (95% confidence interval [CI] 0.56-1.00) for premenopausal breast cancer compared to women who had never breastfed. No linear trend was found with duration of total lactation ( $p=0.95$ ), exclusive lactation ( $p=0.74$ ), or lactation amenorrhea ( $p=0.88$ ). The association between lactation and premenopausal breast cancer was modified by family history of breast cancer ( $p$  for interaction =0.03). Among women with a first-degree relative with breast cancer, those who had ever breastfed had a covariate-adjusted HR of 0.41 (95% CI 0.22-0.75) for premenopausal breast cancer compared to women who had never breastfed, while no association was observed among women without a family history of breast cancer.

**Conclusion**—In this large, prospective cohort study of parous premenopausal women, having ever breastfed was inversely associated with incidence of breast cancer among women with a family history of breast cancer.

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## Introduction

Worldwide, more women develop breast cancer than any other malignancy. Established risk factors include early age at menarche, nulliparity, late age at first birth, and family history.

Some studies have suggested that breastfeeding reduces breast cancer risk, but evidence has been mixed. Observational studies relating lactation and breast cancer among postmenopausal women have largely failed to identify an association<sup>1, 2</sup>. Reports from case-control studies suggest a modest inverse association between breastfeeding and premenopausal breast cancer risk, but findings have been inconsistent and limited by the potential for recall bias<sup>3, 4</sup>. Longitudinal studies have produced conflicting results<sup>1, 2, 5-7</sup>. These discrepant findings have been attributed to differences in intensity of breastfeeding among study populations<sup>8</sup>. This hypothesis has not been tested, because prior prospective studies have not collected information on supplemental feeding or duration of amenorrhea.

To assess the relation between breastfeeding intensity and incidence of premenopausal breast cancer, we collected detailed information on lactation history, supplemental feeding, and lactation amenorrhea among participants in the Nurses' Health Study II, a large prospective study on women's health.

## Methods

### Study Population

The Nurses' Health Study II began in 1989, enrolling 116,608 women from 14 U.S. states. Participants were between 25 and 42 years of age at baseline, and 90 percent reported their primary ancestry as Caucasian. All participants were registered nurses; in 2001, the most common category of reported pre-tax household income was \$75,000 to 100,000 per year. Among participants who were married, more than half of their husbands had completed a 4-year college or graduate degree.

Each woman completed a detailed questionnaire on demographic, anthropometric, and lifestyle factors, with follow-up questionnaires every two years. For the current analyses, we restricted the study population to women who had reported at least one pregnancy in 1997, when breastfeeding was assessed in detail (Figure 1). Women who were nulliparous or missing data on parity in 1997 (n=41,882) or did not report breastfeeding history (n=841) were excluded at baseline. We further excluded women who were postmenopausal (N=6,962) or whose menopausal status was unknown (N=3,479), as well as those with prevalent breast cancer (N=505), carcinoma in situ (N=118), or other malignancies (N=2451), missing year of first birth (N=670) or missing height (N=89), leaving 60,075 NHS II participants for the current analyses.

### Assessment of Parity and Lactation History

At baseline in 1989 and on each biennial questionnaire, women reported the number of pregnancies lasting six months or more. In 1997, participants completed a detailed questionnaire on breastfeeding and use of medication to suppress lactation for each of their first four children. Women with more than four children reported total months of breastfeeding across all additional pregnancies. All durations were reported as categorical variables. For assessment of total duration, women were asked, "If you breastfed, at what month did you stop breastfeeding altogether?" For assessment of exclusive duration, women were asked, "at what month did you start giving formula or purchased milk at least once daily?" and "at what month did you start giving solid food at least once daily (baby food, cereal, table food, etc.)?" Exclusive duration was defined as the earlier of these two time points. For assessment of lactation amenorrhea, women were asked, "At what month after delivery did your menstrual

periods return?" If a woman conceived another pregnancy prior to resuming menses, duration of amenorrhea was coded as missing for the index birth. For each definition, contributions from all pregnancies were summed to determine lifetime duration. To assess use of medications to suppress lactation, women were asked "Did you use any medication to suppress lactation?" Options for response were "Pills for 1-2 days only," "Pills for >2 days", "Injection", or "No."

### Ascertainment of Breast Cancer

On each biennial questionnaire, participants were asked to report whether they had been newly diagnosed with breast cancer and when the diagnosis was made. Study staff routinely search the National Death Index for women who have not responded to questionnaires. Women diagnosed with breast cancer (or their next of kin) were asked for permission to review medical records and confirm the diagnosis. We confirmed self-reported breast cancer for more than 99% of women whose records were obtained. Because self-reports of breast cancer are very reliable in our cohort, we included in our analysis self-reported cases for which records could not be obtained (n=72, 12% of cases). Cases of carcinoma in situ were censored from the analysis. Our analysis was limited to incident cases of invasive breast cancer between 1997 and 2005.

### Measurement of Covariates

The following time-fixed covariates were included in our multivariate adjusted model: Age at menarche, weight at age 18, and current height and weight were reported on the enrollment survey in 1989. Birth weight of the participant was reported in 1991. Family history of breast cancer was assessed in 1989, 1997, and 2001, when each participant reported whether her mother, one or two sisters, or maternal or paternal grandmother had been diagnosed with breast cancer. Although family history was reported at multiple time points, we used the cumulative report of family history as of 2001 as a time-fixed covariate in our models, because genetic transmission of risk does not vary over time.

Time-varying covariate data were collected on multiple questionnaires. On each biennial questionnaire, women reported current weight, personal history of benign breast disease, menopausal status, and oral contraceptive use. Women reported alcohol consumption in 1991, 1995, 1999, and 2003. Physical activity data were collected in 1989, 1991, 1997, and 1999. Women reported number of hours per week engaged in a specified list of activities. These data were used to compute a total activity score based on metabolic equivalents (METs) per week of physical activity<sup>9</sup>. The most updated values of the time-varying covariates were used in the statistical analysis.

### Statistical Analysis

The relative risk of premenopausal breast cancer by lactation history was assessed with a Cox proportional hazards model. We evaluated proportionality of hazards by assessing the interactions between ever breastfeeding and both follow-up period and time since last birth. Women contributed person-years of follow-up from 1997 until reaching menopause, diagnosis of breast cancer, death, or study end date of June 2005. We excluded from follow-up participants whose menopausal status or parity was unknown until updated information was available. We censored participants if they reported a birth after 1997 to limit our analysis to prospectively reported lactation. To ensure such censoring did not bias our results, we performed a sensitivity analysis in which we retained participants who gave birth after 1997 without updating lactation history.

Because lactation duration was reported categorically, we modeled our primary analysis using categorical variables. We used midpoints of categories to assess linear trends. Two-sided p-

values are reported for trends, and 95% confidence intervals are reported for hazard ratio estimates.

All models are adjusted for age and follow-up time in months. In our covariate-adjusted analysis, we included only a priori risk factors breast cancer to avoid overfitting of the model. The following variables were included: height, body mass index, body mass index at age 18, and year of first birth (continuous); family history of first or second degree relative with breast cancer, history of benign breast disease, and use of medications to suppress lactation (dichotomous); and birth weight of participant, age at menarche, parity and age at first birth, physical activity, alcohol consumption, and oral contraceptive use (categorical). Menopausal status, BMI, oral contraceptive use, and history of benign breast disease were updated at two-year intervals.

To differentiate between the effects of parity and lactation, we conducted additional analyses restricted to women with only one child. Effect modification by family history of a first-degree relative with breast cancer, parity, and age at first birth were evaluated by adding a cross-product term and comparing regression models with a likelihood ratio test. All analyses were performed using SAS 9.1 software (Cary, NC).

### Ethics committee approval

The study was approved by the Institutional Review Boards of the Harvard School of Public Health and the Brigham and Women's Hospital, Boston, MA.

## Results

Of the 60,075 premenopausal, parous women who were eligible our analysis, 87% had ever breastfed. Longer lifetime durations of breastfeeding were associated with higher parity and lower oral contraceptive use (Table 1). Duration of breastfeeding was inversely associated with history of benign breast disease. In addition, women who breastfed for longer durations were thinner both at age 18 and during study follow-up than women who breastfed for shorter durations.

Use of medication to suppress lactation was common in our cohort, with 72.2% of never-breastfeeders reporting suppression. Women who had never breastfed and had suppressed lactation were younger at their first birth and had more children than women who neither breastfed nor suppressed lactation.

A total of 608 cases of incident premenopausal breast cancer were diagnosed during 357,556 person-years of follow-up, with a mean age at diagnosis of 46.2 years. We found a lower incidence of premenopausal breast cancer among women who had ever breastfed (covariate-adjusted hazard ratio (HR) 0.75, 95% confidence interval (CI) 0.56-1.00) than among women who had never breastfed; however, we found no association with duration of lactation (Table 2,  $p$  for linear trend = 0.95).

To test for proportionality of hazards, we used interaction terms between ever-breastfeeding and both time since last birth and follow-up period. We found no evidence of effect modification in our models (ever breastfed and time since last birth interaction  $p = 0.57$ ; ever breastfed and follow-up period interaction  $p=0.93$ ).

The association between lactation and incident breast cancer appeared to be stronger among women with only one birth. In this subgroup, ever having breastfed was associated with a covariate-adjusted HR of 0.50 (95% CI 0.28-0.91) compared with never having breastfed; however, the difference in association between women with only one birth and those with two

births or more was not statistically significant ( $p$  for one child and ever breastfed interaction = 0.26). We found no association in this subgroup with duration of lactation (Table 3,  $p$  for linear trend = 0.50).

We further examined the associations between exclusive breastfeeding (Table 4), lactation amenorrhea (Table 5), and breast cancer incidence. Compared with women who breastfed but never exclusively, women who breastfed exclusively for more than 18 months had a covariate-adjusted risk of incident premenopausal breast cancer of 0.86 (95% CI 0.54-1.39,  $p$  for linear trend = 0.74). There was also no association between duration of lactation amenorrhea and incident disease. (HR for > 24 months vs. < 3 months amenorrhea: 0.92, 95% CI 0.58-1.44,  $p$  for linear trend 0.88).

The association between breastfeeding and breast cancer incidence was modified by family history of a first-degree relative with breast cancer ( $p$  = 0.03, Table 6). Among women with a first degree relative with breast cancer, ever having breastfed was associated with lower breast cancer incidence (covariate-adjusted HR 0.41; 95% CI 0.22-0.75) than never having breastfed. Among women without a first-degree family history, having ever breastfed was not associated with breast cancer incidence.

In analyses limited to women with only one birth, we found a stronger association between ever having breastfed and incident disease among women with a family history of at least one first or second degree relative with breast cancer than among women without a family history ( $p$  for interaction = 0.04; family history covariate-adjusted HR: 0.10, 95% CI 0.02-0.47; no family history covariate-adjusted HR 0.79, 95% CI 0.36-1.72, for ever-having breastfed compared with never-having breastfed).

We further investigated whether the relation between breastfeeding and incident breast cancer differed by reproductive history. We found no significant interactions between having ever breastfed and parity (likelihood ratio test  $p$  = 0.72) or age at first birth (likelihood ratio test  $p$ =0.88). To test whether breastfeeding the first of several children is associated with a difference in risk, we compared women who had or had not breastfed their first child. We found no association between incident premenopausal breast cancer and having ever breastfed the first child (covariate-adjusted HR 0.87, 95% CI 0.63-1.20, compared with not having breastfed the first child). We similarly found no association between duration of breastfeeding for the first child and incident disease ( $p$  for trend=0.61).

Use of medication to suppress lactation modified the association between breastfeeding and incident breast cancer. We found a lower incidence of breast cancer among women who had never breastfed but had suppressed lactation than among those who had neither breastfed nor suppressed (age-adjusted HR 0.58, 95% CI 0.37-0.90). This association was attenuated in the covariate-adjusted model (HR 0.65, 95% CI 0.42-1.02). Among women who had breastfed, cancer incidence was similar regardless of use of suppression (covariate-adjusted HR for suppressors who had breastfed: 0.60, 95% CI 0.38-0.96; HR for never-suppressors who had breastfed: 0.60, 95% CI 0.41-0.88) compared with women who had neither breastfed nor suppressed.

Finally, we tested whether censoring participants with an additional birth during follow-up affected our results. Inclusion of these subjects did not materially alter the observed relation between having ever breastfed and incident breast cancer risk (covariate-adjusted HR 0.77, 95% CI 0.58-1.01).

## Discussion

We found an inverse association between having ever breastfed and incidence of premenopausal breast cancer in a large, prospective cohort study of parous women. The inverse association was restricted to women with a first-degree family history of breast cancer. We found no relation between incident premenopausal breast cancer and duration or intensity of breastfeeding.

Our study has several strengths. Information on lactation was collected prior to diagnosis of breast cancer, preventing recall bias. Moreover, detailed data allowed us to test whether duration of exclusive breastfeeding or lactation amenorrhea were related to breast cancer incidence. Other prospective cohort studies were limited to lifetime duration of lactation<sup>2, 5</sup> or total duration per child<sup>1, 6, 7</sup>. Finally, the size of our study permitted us to examine whether family history modified the association between lactation and incident disease.

Our findings must be interpreted within the context of the study design. Our cohort is comprised entirely of registered nurses, 90 percent of whom are of self-reported Caucasian ancestry, limiting the generalizability of our results to more heterogeneous populations. Observational studies are subject to confounding, and studies of breastfeeding are particularly challenging in this regard. Nevertheless, when we adjusted for established risk factors for breast cancer in our analysis, the association between ever breastfeeding and incident disease was strengthened, making residual confounding by known risk factors unlikely to explain the observed association. As in any observational study, we cannot exclude the possibility that unmeasured confounding explains the observed difference in incident disease, but such a confounder would have to be strongly associated with both breast feeding and breast cancer risk in order to produce an association of this magnitude. Measurement error is also a concern, particularly for recall of breastfeeding history. However, in a validation study, Kark et al<sup>10</sup> found that maternally reported breastfeeding duration 20 years after the index birth correlates well with pediatric records (Pearson  $r=0.82$ ), suggesting that measurement error is unlikely to have materially affected our results.

Several authors have examined the association between lactation and incident premenopausal breast cancer in cohort studies, with differing results. Two authors have reported an inverse association between lactation and risk of premenopausal or early-onset breast cancer<sup>6, 7</sup>, whereas two others found no association<sup>1, 2</sup>. These conflicting results may reflect differences in age at diagnosis among study populations. In studies that suggest a protective association, subjects were considerably younger. This is consistent with multiple cohort studies that have found no association between lactation and post-menopausal breast cancer<sup>1, 2, 5</sup>. Alternatively, it may be that only very long durations of lactation confer protection for older women<sup>11</sup>.

Our study is the first to examine prospectively duration of exclusive breastfeeding, lactation amenorrhea, and incident breast cancer, and we found no association. Our results suggest that, at the durations of breastfeeding found in our population, anovulation does not mediate observed associations between lactation and breast cancer risk. Others have suggested that failed breastfeeding may be a marker for abnormal breast tissue, conferring an increased risk of cancer<sup>12</sup>. We did not assess reasons for weaning, but for each birth, we asked participants, "Did you breastfeed at least 1 month?" Options for response were "Yes," "No, not at all," and "No, less than 1 month." If failed milk production were a marker for breast cancer risk, we would expect to see an increased risk of breast cancer among women who breastfed for less than one month, compared with those who never breastfed. Nevertheless, in our analysis, we found no association between breastfeeding for less than one month and incident breast cancer, compared with never having breastfed.

We found a reduced risk among women who never breastfed and used medication to suppress lactation. Use of suppression in our study population reflects secular trends in obstetrical care in the United States, with use declining from the 1970s to late 1980s<sup>13-15</sup>. No other prospective studies have assessed use of suppressive medication, and results from case-control studies have been mixed<sup>16-20</sup>. We speculate that breast cancer incidence may be higher among women who neither breastfed nor used suppressive medication because of disordered involution. During involution, a highly coordinated process of apoptosis, remodeling, and inflammation returns mammary tissue to its pre-pregnant state<sup>21</sup>. In physiologic weaning, this process occurs over weeks or months. By contrast, if a woman does not breastfeed, she experiences abrupt engorgement, and mammary tissue may become progressively inflamed. We hypothesize that both breastfeeding and use of suppressive medications prevent this inflammation, thereby preventing disordered involution. It is also possible that systematic differences among women who did or did not suppress lactation explain the observed association. Further studies are needed to test these hypotheses.

We found a 59% reduction in incidence of premenopausal breast cancer with having ever breastfed among women with a first-degree relative with breast cancer. No other prospective study to our knowledge has examined whether family history modifies the association between breastfeeding and breast cancer risk. Authors of several case-control studies<sup>22-24</sup> have noted stronger inverse associations among women with than without a family history, but formal tests of interaction were not always significant. Others have observed no interaction between lactation, family history, and incident disease<sup>25</sup>. Authors have also examined whether BRCA1 or 2 mutation carriage modifies the effect of lactation on disease risk, with mixed results<sup>26-28</sup>. Future studies of interactions between breastfeeding history, family history, and genotypes associated with breast cancer risk will be needed to confirm these associations and explore underlying mechanisms.

In conclusion, we found an inverse association between having ever breastfed and the incidence of premenopausal breast cancer in a large prospective cohort of parous women. This association was restricted to women with a first-degree family history of breast cancer. The observed 59% reduction in risk compares favorably with hormonal treatments such as tamoxifen for women at high risk for breast cancer. Moreover, breastfeeding is associated with multiple other health benefits for both mother and child<sup>29</sup>. These data suggest that women with a family history of breast cancer should be strongly encouraged to breastfeed.

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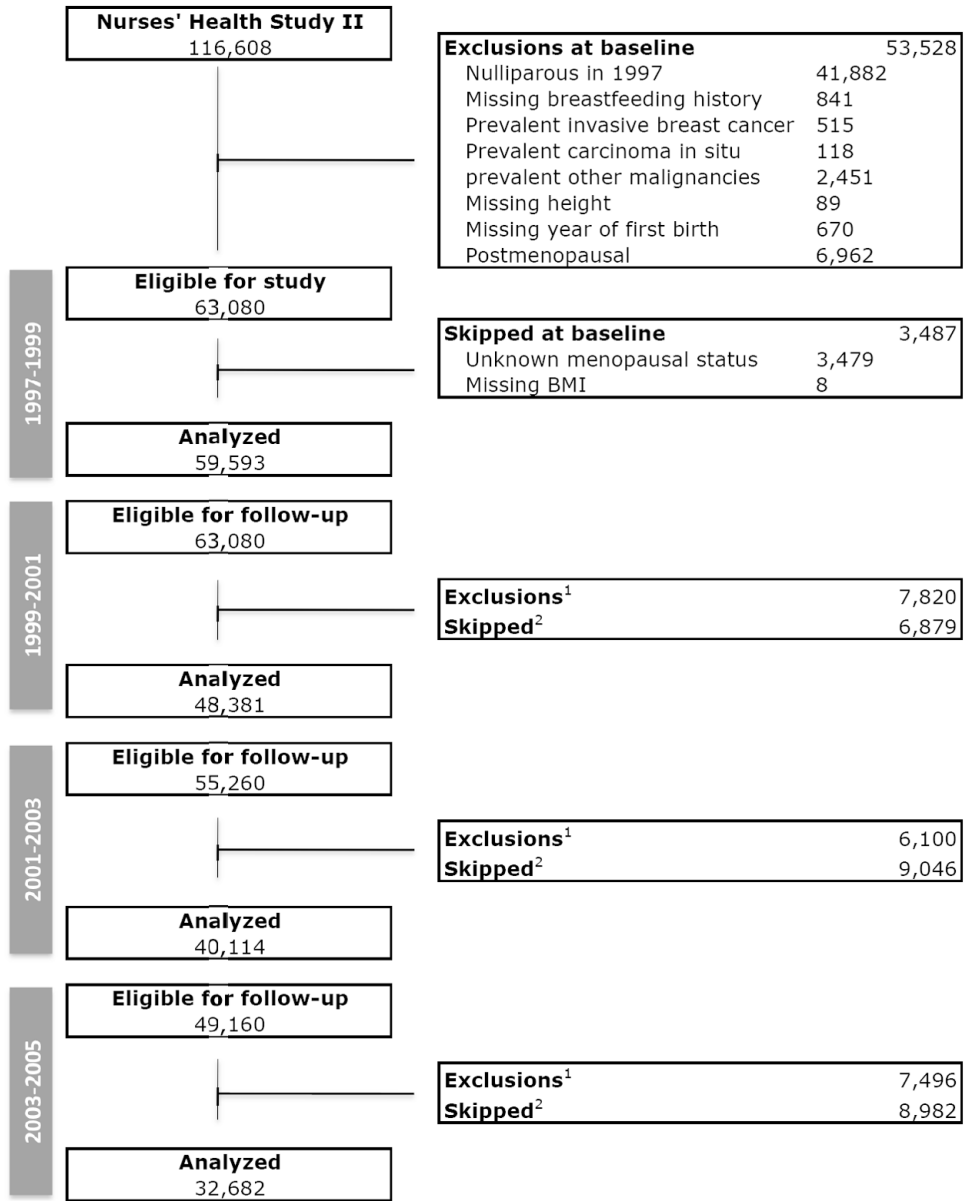
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1. We excluded from follow-up participants who reported another birth, became post-menopausal, were diagnosed with incident invasive breast cancer or carcinoma in situ, or died.
2. We excluded from the current follow-up cycle women with unknown menopausal status or missing body mass index or parity.

**Figure 1.** Consort diagram for Lactation and Incidence of Premenopausal Breast Cancer, A Longitudinal Study.

**Table 1**

Age-standardized\* characteristics of parous women in the Nurses' Health Study II in 1997, by lifetime duration of lactation.

	Never	<1 months	>1 to 12 months	>12 to 24 months	>24 to 36 months	>36 months
<b>Person-years</b>	44,341	19,919	123,631	87,546	48,522	33,597
Age in 1997, mean	43.1	41.7	41.6	41.8	42.1	42.2
Height, in	64.8	64.9	64.8	64.9	64.9	64.9
BMI†, kg/m2	26.5	27.2	26.2	25.6	25.3	25.3
BMI at age 18, kg/m2	21.2	21.5	21.1	20.8	20.7	20.8
<b>Breast disease history</b>						
First or second degree relative with breast cancer, %	21.2	22.0	21.9	22.6	23.4	23.8
First degree relative with breast cancer, %	9.0	8.9	8.6	9.2	9.3	9.7
Benign breast disease, %	16.9	17.2	17.0	16.7	16.5	13.7
<b>Childhood risk factors</b>						
Birth weight < 5.5 lbs, %	7.4	6.8	6.1	6.0	5.5	5.5
Age at menarche, mean	12.4	12.3	12.4	12.5	12.5	12.5
<b>Parity, %</b>						
One	27.9	26.3	24.6	9.5	0.0	0.0
Two	52.9	52.0	54.7	53.5	51.8	11.5
Three	15.7	17.8	17.8	30.6	35.8	48.6
Four or more	3.6	3.9	2.9	6.3	12.4	39.9
<b>Pregnancy history</b>						
Age at first birth, mean	25.6	26.9	27.2	27.0	26.8	25.9
Year of first birth, median	1980	1984	1984	1983	1983	1982
Used medication to suppress lactation, %	72.2	38.8	15.3	5.5	3.4	2.2
<b>Oral contraceptive use</b>						
Never	10.2	9.7	9.8	12.4	15.5	21.4
Past	74.2	75.7	75.3	73.7	72.0	68.5
Current	8.8	8.3	9.1	8.1	7.3	5.2
Missing	6.8	6.3	5.7	5.9	5.2	4.9
<b>Activity mets/wk</b>	127.5	123.5	118.9	114.5	110.2	114.5
<b>Alcohol consumption</b>						
None, %	36.4	37.5	31.6	32.8	35.6	42.2

	Never	< 1 months	> 1 to 12 months	> 12 to 24 months	> 24 to 36 months	> 36 months
Alcohol g/d, among drinkers	5.9	6.0	6.3	6.3	6.1	5.6

\* Data presented are directly standardized in years to the age distribution of the Nurses' Health Study II, with the exception of mean age in 1997.

† Body Mass Index

**Table 2**

Hazard ratio of incident premenopausal breast cancer by duration of lactation among 60,075 parous women in the Nurses' Health Study II from 1997 to 2005.

	Cases <sup>a</sup>	Person-years	Age-adjusted HR (95%CI)	Cov-adjusted <sup>b</sup> HR (95%CI)
Never breastfed	92	44,341	1.00 (ref)	1.00 (ref)
Ever Breastfed	516	313,215	0.87 (0.69 - 1.08)	0.75 (0.56 - 1.00)
Breastfed < 1 month	39	19,919	1.04 (0.71 - 1.51)	0.93 (0.63 - 1.38)
>1 to 3	30	20,294	0.80 (0.53 - 1.21)	0.72 (0.46 - 1.11)
>3 to 6	38	33,414	0.62 (0.43 - 0.91)	0.54 (0.36 - 0.82)
>6 to 12	121	69,923	0.91 (0.69 - 1.19)	0.78 (0.56 - 1.08)
>12 to 24	142	87,546	0.84 (0.65 - 1.10)	0.71 (0.51 - 1.00)
>24 to 36	100	48,522	1.07 (0.80 - 1.43)	0.92 (0.64 - 1.32)
>36	46	33,597	0.71 (0.50 - 1.01)	0.63 (0.40 - 0.99)
P for trend			0.88	0.95

<sup>a</sup> Incident cases of invasive breast cancer

<sup>b</sup> Hazard ratio and 95% confidence interval adjusted for age, height, current BMI, BMI at age 18, personal history of benign breast disease, first or second degree relative with a history of breast cancer, year of first birth, birth weight of participant, age at menarche, parity and age at first birth, use of medications to suppress lactation, use of oral contraceptives, consumption of alcohol, and physical activity.

**Table 3**

Hazard ratio of incident premenopausal breast cancer by duration of lactation, among 10,164 women with only one child in the Nurses' Health Study II from 1997 to 2005.

	Cases <sup>a</sup>	Person-years	Age-adjusted HR (95%CI)	Cov-adjusted <sup>b</sup> HR (95%CI)
Never breastfed	32	12,371	1.00 (ref)	1.00 (ref)
Ever Breastfed	80	43,786	0.67 (0.44 - 1.03)	0.50 (0.28 - 0.91)
Breastfed < 1 month	12	5,216	0.95 (0.48 - 1.87)	0.74 (0.34 - 1.59)
1 to 2	10	4,814	0.77 (0.37 - 1.58)	0.59 (0.26 - 1.35)
3 to 5	14	11,457	0.46 (0.24 - 0.88)	0.33 (0.16 - 0.71)
6 to 8	12	8,161	0.61 (0.31 - 1.20)	0.43 (0.19 - 0.96)
9 to 11	13	5,776	0.71 (0.37 - 1.37)	0.51 (0.23 - 1.13)
12 to 18	11	5,428	0.72 (0.35 - 1.44)	0.53 (0.23 - 1.21)
19+	8	2,934	0.85 (0.38 - 1.88)	0.55 (0.22 - 1.40)
P for trend			0.49	0.50

<sup>a</sup> Incident cases of invasive breast cancer

<sup>b</sup> Hazard ratio and 95% confidence interval adjusted for age, height, current BMI, BMI at age 18, personal history of benign breast disease, first or second degree relative with a history of breast cancer, year of first birth, birth weight of participant, age at menarche, age at first birth, use of medications to suppress lactation, use of oral contraceptives, consumption of alcohol, and physical activity.

**Table 4**

Hazard ratio of incident premenopausal breast cancer by duration of exclusive lactation among 52,080 parous women who had ever breastfed in the Nurses' Health Study II from 1997 to 2005.

Exclusive lactation (months)	Cases <sup>a</sup>	Person-years	Age-adjusted HR (95%CI)	Cov-adjusted <sup>b</sup> HR (95%CI)
Breastfed, never exclusively <sup>c</sup>	144	90,720	1.00 (ref)	1.00 (ref)
>0 to 3	60	38,801	0.94 (0.70 - 1.28)	0.94 (0.69 - 1.28)
>3 to 6	78	46,430	1.08 (0.82 - 1.42)	1.08 (0.82 - 1.43)
>6 to 12	141	81,339	1.08 (0.86 - 1.37)	1.07 (0.84 - 1.36)
>12 to 18	70	38,917	1.11 (0.83 - 1.48)	1.09 (0.80 - 1.48)
>18	23	16,991	0.83 (0.53 - 1.29)	0.86 (0.54 - 1.39)
p for trend			0.74	0.74

<sup>a</sup> Incident cases of invasive breast cancer

<sup>b</sup> Hazard ratio and 95% confidence interval adjusted for age, height, current BMI, BMI at age 18, personal history of benign breast disease, first or second degree relative with a history of breast cancer, year of first birth, birth weight of participant, age at menarche, parity and age at first birth, use of medications to suppress lactation, use of oral contraceptives, consumption of alcohol, and physical activity.

<sup>c</sup> Women who breastfed and introduced daily solid food or formula at 0-2 months of age for all births, and therefore never breastfed exclusively.

**Table 5**

Hazard ratio of incident premenopausal breast cancer by duration of lactation amenorrhea among 51,738 parous women who had ever breastfed in the Nurses' Health Study II from 1997 to 2005.

Lactation amenorrhea (months)	Cases <sup>a</sup>	Person-years	Age-adjusted HR (95%CI)	Cov-adjusted <sup>b</sup> HR (95%CI)
0 to 3	112	65,585	1.00 (ref)	1.00 (ref)
>3 to 6	73	46,756	0.92 (0.68 - 1.24)	0.90 (0.67 - 1.22)
>6 to 12	160	97,089	0.98 (0.77 - 1.25)	0.94 (0.73 - 1.21)
>12 to 24	136	78,791	1.04 (0.81 - 1.33)	1.01 (0.76 - 1.34)
>24	33	23,082	0.87 (0.59 - 1.29)	0.92 (0.58 - 1.44)
P for trend			0.96	0.88

<sup>a</sup>Incident cases of invasive breast cancer

<sup>b</sup>Hazard ratio and 95% confidence interval adjusted for age, height, current BMI, BMI at age 18, personal history of benign breast disease, first or second degree relative with a history of breast cancer, year of first birth, birth weight of participant, age at menarche, parity and age at first birth, use of medications to suppress lactation, use of oral contraceptives, consumption of alcohol, and physical activity.



**Table 6**

Hazard ratio of incident premenopausal breast cancer by duration of lactation, stratified by family history of a first degree relative with breast cancer, among 60,075 parous women in the Nurses' Health Study II from 1997 to 2005 (p for interaction = 0.03).

Lactation history	No family history of breast cancer				With family history of breast cancer			
	Cases <sup>a</sup>	Person-years	Age-adjusted HR (95%CI)	Cov-adjusted <sup>b</sup> HR (95%CI)	Cases <sup>a</sup>	Person-years	Age-adjusted HR (95%CI)	Cov-adjusted <sup>b</sup> HR (95%CI)
Never	68	39,377	1.00 (ref)	1.00 (ref)	24	4,965	1.00 (ref)	1.00 (ref)
Ever	429	278,545	0.97 (0.75 - 1.25)	0.89 (0.64 - 1.22)	87	34,670	0.55 (0.34 - 0.88)	0.41 (0.22 - 0.75)
Breastfed < 1 month	33	17,780	1.16 (0.76 - 1.76)	1.08 (0.70 - 1.67)	6	2,139	0.67 (0.26 - 1.70)	0.54 (0.21 - 1.43)
>1 to 3	24	18,305	0.85 (0.53 - 1.35)	0.82 (0.50 - 1.33)	6	1,989	0.71 (0.28 - 1.80)	0.51 (0.19 - 1.36)
>3 to 6	33	30,109	0.71 (0.47 - 1.08)	0.66 (0.42 - 1.05)	5	3,304	0.33 (0.12 - 0.88)	0.23 (0.08 - 0.66)
>6 to 12	96	62,313	0.96 (0.70 - 1.32)	0.90 (0.62 - 1.30)	25	7,610	0.68 (0.37 - 1.23)	0.48 (0.24 - 0.98)
>12 to 24	119	77,511	0.96 (0.71 - 1.29)	0.88 (0.60 - 1.28)	23	10,035	0.51 (0.28 - 0.94)	0.35 (0.17 - 0.74)
>24 to 36	88	42,940	1.28 (0.93 - 1.77)	1.16 (0.77 - 1.75)	12	5,582	0.49 (0.24 - 1.00)	0.33 (0.14 - 0.79)
>36	36	29,586	0.76 (0.50 - 1.14)	0.68 (0.41 - 1.12)	10	4,011	0.53 (0.25 - 1.13)	0.42 (0.16 - 1.09)
P for trend			0.52	0.73			0.09	0.16

<sup>a</sup>Incident cases of invasive breast cancer

<sup>b</sup>Hazard ratio and 95% confidence interval adjusted for age, height, current BMI, BMI at age 18, personal history of benign breast disease, year of first birth, birth weight of participant, age at menarche, parity and age at first birth, use of medications to suppress lactation, use of oral contraceptives, consumption of alcohol, and physical activity.