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Menstrual and reproductive factors in relation to mammographic density: the Study of Women's Health Across the Nation (SWAN)

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Abstract

Menstrual and reproductive factors may increase breast cancer risk through a pathway that includes increased mammographic density. We assessed whether known or suspected menstrual and reproductive breast cancer risk factors were cross-sectionally associated with mammographic density, by measuring area of radiographic density and total breast area on mammograms from 801 participants in the Study of Women's Health Across the Nation (SWAN), a multi-ethnic cohort of pre- and early perimenopausal women. From multivariable linear regression, the following menstrual or reproductive factors were independently associated with percent mammographic density (area of dense breast/breast area): older age at menarche ($\beta = 10.3$, $P < 0.01$, for >13 vs. <12 years), premenstrual cravings and bloating ($\beta = -3.36$, P = 0.02), younger age at first full-term birth ($\beta = -8.12$, $P < 0.01$ for ≤23 years versus no births), greater number of births ($\beta = -6.80$, $P < 0.01$ for ≥3 births versus no births), and premenopausal status ($\beta = 3.78$, $P < 0.01$ versus early perimenopausal). Only number of births remained associated with percent density after adjustment for age, race/ethnicity, study site, body mass index (BMI), and smoking. In addition, stratified analyses revealed that the association with number of births was confined to women within the lowest BMI tertile ($\beta = -12.2$, $P < 0.01$ for ≥3 births versus no births). Our data support a mechanism for parity and breast cancer that involves mammographic density among pre- and early perimenopausal women that may be modified by body size.

Keywords

Age at first birth; Body size; Breast cancer risk factor; Mammographic density; Menarche; Menstrual factors; Parity; Perimenopause; Premenopausal; Reproductive factors

Introduction

It is hypothesized that breast cancer risk increases with greater cumulative exposure to estrogen [1] and related increase in rate of breast tissue aging [2]. Menstrual and reproductive factors that are associated with an increased risk of breast cancer because they may increase lifetime

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exposure to estrogen include: earlier age at menarche, shorter menstrual cycle length, and later age at menopause [3]. Women who have shorter menstrual cycles (i.e., <26 days) spend more time in the luteal phase [3], when estrogen and progesterone levels are high and when breast mitotic activity is at its peak, compared to women with longer cycle length [4]. Although not associated with breast cancer, presence of premenstrual symptoms may be associated with higher plasma estrogen levels [5].

Other reproductive breast cancer factors include greater number of births and early age at first full-term birth (FFTB) [3]. These factors are associated with reduced risk, because during pregnancy the breast differentiates from lobular type 1 to 4 [6]. These fully differentiated breast cells are less susceptible to carcinogens compared to undifferentiated cells, based on experimental data (Reviewed in [7]).

Mammographic density prior to menopause may be a surrogate for lifetime estrogen exposure [8]. Higher mammographic density is associated with an increased risk of breast cancer. Women with mammographic density in at least 60% of the breast have a four- to six-fold higher risk than those with little or no density [9]. Most established risk factors for breast cancer are hormone-related and others may act by modulating the activity of growth factors in breast tissue. The biological mechanism responsible for the relation between mammographic density and the risk of breast cancer has not been established. It has been proposed that mammographic density principally reflects proliferation of breast stroma [10]. The formation and maintenance of dense breast tissue may be the result of an interaction between breast stroma and epithelium, and dependent on the activity of growth factors and hormones such as estrogen, insulin, and prolactin [10,11].

Previous studies have evaluated menstrual and reproductive factors in relation to mammographic density. Parity, or having a full-term birth, is most consistently reported to be inversely associated with density [12,13], although stronger associations with greater number of births has only been reported for qualitative density measures, such as parenchymal patterns, and not with quantitative measures such as the percent of the breast occupied by dense tissue [14]. Less consistently, later age at FFTB has been directly associated with mammographic density [12,15], whereas little evidence has been reported for an association between age at menarche and density [12,16,17].

Although mammographic density appears to confer similar risk for breast cancer among white and non-white U.S. populations [18,19], few studies have examined menstrual and reproductive factors in relation to mammographic density in multi-ethnic U.S. populations. In addition, little data are available for the association of menstrual and reproductive factors with mammographic density during the very early stages of the menopausal transition [20,21], before its decline with menopause [22]. We evaluated the association between menstrual and reproductive risk factors and mammographic density in a community-based cohort of pre- and early perimenopausal Chinese, Japanese, African-American and non-Hispanic white women in the U.S.

Methods

Study population

This study was conducted among participants enrolled in the Study of Women's Health Across the Nation (SWAN), a community-based, longitudinal study designed to evaluate women though the menopausal transition [23]. To be eligible, women had to be between 42 and 52 years of age, to report having had a menstrual period and no use of exogenous hormones within the three months prior to recruitment, and to identify their primary race as African American (Boston, Chicago, Detroit, Pittsburgh), Japanese (Los Angeles), Chinese (Oakland), Hispanic

(Newark) or Caucasian (all sites). Approximately 50% of participants at each site were Caucasian and 50% were of another race/ethnicity. To identify women from the general population, three sites (Los Angeles, Pittsburgh, Newark) used random digit dialing–sampling. The other four sites (Boston, Chicago, Detroit, Oakland) selected randomly from lists of names from utility (Detroit) or healthcare organization membership (Oakland) listings or household addresses. Oversampling was conducted to obtain adequate numbers of non-white women at all sites.

Three SWAN sites, University of California Davis-Kaiser (Oakland), University of California Los Angeles (Los Angeles) and University of Pittsburgh (Pittsburgh), participated in the mammographic density ancillary study. Of the 1,248 women in follow-up at the three SWAN sites at the time of enrollment into the ancillary study (i.e., at the fifth or sixth annual follow-up visit), 85% agreed to participate. Of those who participated, 1,005 (95%) had at least one eligible mammogram for density assessment.

Mammographic density declines through the menopausal transition [22]. For this reason, women were included in these analyses if they were pre- or early perimenopausal at the time of their index mammogram in order to evaluate menstrual/reproductive factors at a time closest to that of peak breast density. Based on SWAN criteria [24], premenopausal status was defined as menses in the past three months, with no change over the past year in predictability of menstrual periods [25,26]. Early perimenopausal status was defined as menses in the past three months with some change in the predictability of menstrual periods over the past year. Assessments of menopausal status were made at the annual SWAN visit closest to the participant's index mammogram. Among women excluded because they were late perimenopausal or postmenopausal at the time of their index mammogram (N = 191), 33% were African American, 23% were Japanese, 19% were white, and 8% were Chinese. These differences by race/ethnicity distribution reflect differences in age at menopause by race/ethnicity previously reported in SWAN [27], and did not represent a potential source of bias in these analyses, since menstrual/reproductive characteristics did not appreciably vary by race/ethnicity (data not shown).

A total of 801 pre- or early perimenopausal women had an eligible mammogram available for these analyses (391 non-Hispanic white, 60 African American, 171 Japanese, and 179 Chinese). Both the core SWAN protocol and the protocol for the mammographic density ancillary study were approved by all institutions participating in this ancillary study, and all women provided signed, written informed consent for participation in the study.

Exposure assessment

Menstrual and reproductive factors—At baseline (1996–1997), in-person interviews obtained information on several menstrual and reproductive factors, including: age at menarche; usual menstrual characteristics within the past year including cycle length, days of flow, and flow amount; pregnancy history including age at FFTB, number of live births, and breast feeding duration for each birth. At baseline and at each annual follow-up visit starting in 1997, information was collected on gynecologic events, including menopausal status, and medication use, including hormones (e.g., birth control pills and/or injections, estrogen and/or progestin pills, injections, and/or patches).

To assess premenstrual symptoms at baseline, we asked: "During the last year, have you had any of the following during at least half of your menstrual periods or in the week before them (yes/no/don't know)?" We selected the following five symptom groupings, based on previously conducted principal components analysis [28]: (1) anxiety/jittery/nervous and mood changes, (2) abdominal cramps and back/joint/muscle pain, (3) increased appetite/craving and weight gain/bloating, (4) breast pain/tenderness, and (5) headaches.

Other factors—The SWAN protocol included annual measures of weight and height, measured with calibrated electronic or balance beam scales and stadiometer, and those data were used to calculate body mass index (BMI): kg/m^2. Covariate data collected during baseline interviews included date of birth, race/ethnicity, highest level of education, and family history of breast cancer. Data collected during annual interviews included smoking and annual household income.

Mammographic density

Eligible mammograms were taken as part of routine medical care during the period from 2 years prior to baseline examination through 2 years after annual follow-up visit 06. If multiple mammograms were available for a given participant, then the mammogram closest to, either preceding or following, the baseline visit was selected.

Mammograms were sent periodically in batches to Martine Salane, an established expert in the techniques of measuring mammographic density [29]. She has been considered the standard expert against which computer-based methods have been evaluated [30]. Ms. Salane's measurements are therefore highly correlated with computer-assisted density measurements ($r = 0.90$) [31]. Unknown to Ms. Salane, 10% of the films were sent for re-review. The initial and repeat readings had excellent concordance (within-person Spearman correlation coefficient of percent density = 0.96; mean difference in percent density assessments = 2.2%).

Quantitative assessment was obtained by measuring the total area of the breast and the areas of dense breast with a compensating polar planimeter (LASICO, Los Angeles, CA) on the craniocaudal view of the right breast. Mammograms from the left breast were used for density assessments when a woman reported surgery in the right breast (e.g., biopsy, breast augmentation, reduction or reconstruction) or when films from the right breast were unavailable ($n = 81$). Percent density was calculated by dividing the area of dense breast by the total area of the breast times 100.

Statistical methods

The primary goal of these analyses was to assess whether menstrual and/or reproductive factors were related to percent mammographic density. Transformation was not needed to normalize the distribution of percent mammographic density. Statistical computing was conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Independent variables—The main independent variables of interest were menstrual/reproductive factors and included age at menarche (<12, 12, 13, >13 years), menstrual cycle length (≥26, <26 days), usual days of flow (1–2, 3–7, ≥8), flow amount (light to moderate, heavy, very heavy), premenstrual symptoms (yes, no for each group: anxiety/jittery/nervous and mood changes; abdominal cramps and back/joint/muscle pain; increased appetite/craving and weight gain/bloating; breast pain/tenderness; headaches), age at FFTB (nulliparous, ≤23, 24–27, 28–31, ≥32 years), number of births (nulliparous, 1–2, ≥3 births), breast feeding history among parous women (0, <12, ≥12 months), and menopausal status (pre-, early perimenopausal). For secondary analyses, we also created a variable for combined age at FFTB and number of births with the following eight categories: nulliparous, ≥1 births at ≥32 years, 1–2 births at 28–31 years, ≥3 births at 28–31 years, 1–2 births at 24–27 years, ≥3 births at 24–27 years, 1–2 births ≤23 years, and ≥3 births at ≤23 years.

Covariates—Covariates assessed as potential confounders were age, BMI, race/ethnicity, study site, education level, household income, smoking status, oral contraceptive use, other hormone use, and family history of breast cancer [11,32–34]. In addition, a combined variable race/ethnicity-study site was created, because each study site recruited a specific race/ethnic

group in addition to non-Hispanic whites. For example, Chinese women were recruited in Oakland, Japanese women in Los Angeles, and African-American women in Pittsburgh. Bivariate analyses were conducted to study mean mammographic density levels in relation to each covariate using ANOVA or simple linear regression, depending on variable type. Based on the bivariate analyses, the following covariates were included in all adjusted models: age, BMI, race/ethnicity-study site (non-Hispanic white-Oakland, Chinese-Oakland, non-Hispanic white-Los Angeles, Japanese-Los Angeles, non-Hispanic white-Pittsburgh, African American-Pittsburgh), and smoking status (never, former, current).

Modeling strategy—Independent variables (i.e., menstrual/reproductive factors) were evaluated in univariate and multivariable models adjusted for potential confounders. Factors univariately associated with percent density at the $P < 0.15$ level were further evaluated using stepwise regression to determine the set of menstrual/reproductive factors independently related to percent mammographic density. Finally, we examined whether the association between percent mammographic density and the main menstrual/reproductive variables varied by the following factors: age, BMI, race/ethnicity-study site, and/or smoking, by both stratified analyses, and fitness of interaction terms in adjusted models.

Results

Our cohort of 801 women had a mean age of 47 years, a mean BMI of 26 kg/m^2, and almost half were non-Hispanic white (Table 1). Percent mammographic density was nearly normally distributed (skewness = −0.1; kurtosis = 0.9), with a mean of 44.5 (standard deviation = 20.5) and a median of 45.9 (interquartile range = 29.2). BMI had a strong inverse association with percent mammographic density: density increased by 2% for each one kg/m^2 decrease in BMI. Mean percent mammographic density differed by race, was lower among older women, current smokers, and among women who previously used oral contraceptives (Table 1). Percent density was similar for women with and without a family history of breast cancer.

Results of the unadjusted linear regression models showed that age at menarche was positively associated with mammographic density; those with age at menarche greater than 13 years had 11% higher percent density compared to women with age at menarche less than 12 years (Table 2). Three premenstrual symptom groupings were associated with lower percent density: anxiety/mood changes, cramps/back pain, and cravings/bloating. Nulliparous women had a greater mean percent density (mean = 46.6, SD = 23.0), than parous women (mean = 44.0, SD = 19.8, ANOVA $P = 0.15$). Both younger age at FFTB and greater number of births were inversely associated with percent density in unadjusted models. Premenopausal women had higher density, compared to women in early perimenopause. After adjustment for potential confounders, nearly all menstrual/reproductive factor associations were attenuated and lost statistical significance. Associations with shorter menstrual cycle length and premenstrual groupings for breast pain and headaches were somewhat stronger in adjusted models.

When examined together in a single multivariable model, the following menstrual and reproductive variables remained as important predictors of mammographic density: age at menarche, premenstrual cravings and bloating, number of births, and menopausal status (Table 3). This model explained 7.0% of the variation in percent mammographic density. Secondary analyses showed that age at FFTB ($\beta = -8.12$, $P < 0.01$ for ≤23 years versus no births), and the combined variable for age at FFTB and number of births ($\beta = -9.19$, $P < 0.01$ for ≤23 years and ≥3 births versus no births) were also important predictors, in separate models with age at menarche, premenstrual cravings and bloating, and menopausal status. These models explained 8.0% and 8.2% of the variation in percent mammographic density, respectively. Menstrual and reproductive factors were not strongly correlated with each other; the strongest correlation was between premenstrual cravings and bloating and age at menarche ($r = -0.13$). In addition, no

evidence for collinearity was found in these models; variance inflation factors were less than 1.7.

With adjustment for covariates, associations with percent mammographic density remained for age at menarche (positive), number of births (negative) and premenopausal status (positive), however, only number of births remained statistically significant (Table 3). In secondary analyses, we observed that age at FFTB ($\beta = -4.59$, $P = 0.12$ for ≤23 years versus no births) and the combined variable for age at FFTB and number of births ($\beta = -4.09$, $P = 0.13$ for ≤23 years and ≥3 births versus no births) were both inversely associated with density, in separate models with age at menarche, premenstrual cravings and bloating, and menopausal status.

The adjusted menstrual/reproductive factor model presented in Table 3 explained 39.4% of the variance in percent mammographic density. Without BMI, the factor most strongly associated with percent mammographic density in these data, the variance explained by the adjusted base model was 11.8%. To be certain that BMI was not masking associations with additional menstrual or reproductive variables, we used stepwise regression after forcing BMI in the model, but did not identify additional factors associated with percent mammographic density.

Analyses stratified by BMI tertiles revealed modification of menstrual/reproductive factor associations for density (Table 4), although no interaction terms with BMI were statistically significant. For example, the inverse association with greater number of births was confined to women within the lowest BMI tertile, or with a BMI less than 21.3 kg/m^2 (P for interaction = 0.11) The same trend, although a somewhat weaker association was seen with younger age at FFTB (≤23 years versus no births) for density, among the lowest tertile ($\beta = -8.85$, $P = 0.02$), mid-tertile ($\beta = -1.05$, $P = 0.96$), and highest tertile ($\beta = -2.19$, $P = 0.50$) (P for interaction = 0.12). In contrast, the positive association with premenopausal status was strongest among the heaviest women (P for interaction = 0.23) (Table 4). Somewhat stronger associations were observed with age at menarche and number of births among early perimenopausal women, and among ever smokers, compared to premenopausal and never smokers (data not shown). Age (<, ≥ median) or race/ethnicity-study site did not appear to modify the associations between mammographic density and individual reproductive variables (age at menarche, premenstrual cravings and bloating, age at FFTB, number of births, or menopausal status).

Discussion

Reproductive and menstrual factors, such as younger age at menarche, nulliparity, later age at FFTB, and shorter menstrual cycle length are associated with increased breast cancer risk [3]. We hypothesized that these and other menstrual/reproductive factors would be associated with percent mammographic density in the same direction as they are related to breast cancer risk or, if not an established risk factor, in the same direction that they are hypothesized to be related to estrogen levels. Using cross-sectional data from a cohort of mid-life women, we observed that the following menstrual/reproductive factors were associated with percent mammographic density: older age at menarche (positive), premenopausal status (positive), premenstrual cravings and bloating (inverse), greater number of births (inverse), and younger age at first FFTB (inverse). With the exception of age at menarche, the associations were in the direction we had hypothesized.

Our observed positive association between older age at menarche and density suggests that the mechanism by which age at menarche increases risk of breast cancer does not operate through a pathway involving mammographic density. This hypothesis was further supported by an inverse association between age at menarche and mean non-dense breast area ($P < 0.01$), but not with mean dense breast area ($P = 0.8$) during post hoc analyses. A similar trend was observed in a previous study evaluating reproductive factors in relation to dense and non-dense

breast area, with the hypothesis that factors associated with dense breast area were more etiologically relevant [35]. Most previous studies reported no association between age at menarche and percent density [12,15–17,35,36].

Our main finding for reduced percent density with greater number of births support most previous findings [12,16,17,35,36]. In our data, this association was most pronounced among thinner women, although the interaction term for number of births and BMI was not statistically significant. Modification by BMI has been previously reported in at least one study of mammographic density [37]. Using a statewide mammography registry, Titus-Ernstoff et al. reported stronger inverse associations between greater number of births and density among women with lower BMI [37]. Similar modification by BMI has been observed in breast cancer studies, where stronger associations with reproductive factors were reported among thinner women [38,39]. Therefore, it is possible that the hypothesized beneficial effects of parity on cumulative estrogen levels are most evident in terms of reducing breast cancer risk, only when the effects of BMI on circulating sex hormone levels are absent [40,41]. An alternative hypothesis is that BMI may be in the causal pathway, for example between number of births and mammographic density [42]. Unfortunately, with these cross-sectional data we were unable to determine whether BMI was in the pathway or a true confounder and/or effect modifier.

To our knowledge, this is the first study to evaluate whether premenstrual symptoms were associated with mammographic density. We hypothesized that women who experienced premenstrual symptoms would have greater mammographic density, because it has been suggested that increased levels of circulating sex steroids were related to premenstrual symptoms (Reviewed in [43]). However, we observed lower percent density among women with the premenstrual groupings: anxiety and mood changes; cramps and back pain; and cravings and bloating. In our data, these premenstrual symptoms were not important predictors of mammographic density, since after adjustment for potential confounders, the association with each premenstrual grouping was attenuated and lost statistical significance.

The high quality of both exposure and outcome data in our study are its primary strengths. Self-reported and measured data in SWAN were collected in-person by trained interviewers who followed a specified protocol [23]. In addition, SWAN was specifically designed to measure outcomes in relation to the menopausal transition, so careful assessment of menopausal status was made allowing us to assess modification of menstrual/reproductive factor associations with mammographic density by pre- and early perimenopausal status. We cannot exclude the possibility of misclassification due to recall bias, but think it is unlikely that accuracy of recall would vary by mammographic density. Further, our protocol using planimeter assessment of mammographic density from a single expert was highly reproducible and accurate, and made without knowledge of reproductive risk factors.

In conclusion, our data support a pathway between number of births and breast cancer that involves mammographic density among pre- and early perimenopausal women. An alternative hypothesis for why other menstrual and reproductive factors were not related to mammographic density, despite their associations with breast cancer risk is that perhaps the breast has no long-term hormonal “memory” that results in a permanent increase in mammographic density, such that the increased breast cancer risk due to menstrual and reproductive factors may instead be mediated by biologic effects not captured by mammographic density.

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Table 1

Study population characteristics by mean percent mammographic density (N = 801)

Characteristics[a]	%N[b]	Mean percent mammographic density	SD[c]	P-value[d]
Age (years)				
40–44	26	47.4	20.8	
45–49	56	43.9	20.4	
50–55	17	41.7	19.7	0.02
BMI, kg/m[b]				
< 18.5	2	64.3	19.3	
18.5–24.9	55	52.3	17.3	
25.0–29.9	24	40.4	17.1	
≥30	19	24.8	17.2	< 0.01
Race/ethnicity				
Non-Hispanic white	49	42.1	21.4	
African American	8	34.0	21.1	
Chinese	22	52.1	18.6	
Japanese	21	45.6	17.0	<0.01
Highest education level				
High school graduate or less	16	44.1	20.3	
Some college	30	42.3	20.3	
College graduate or more	54	45.8	20.5	0.11
Household annual income				
< $50,000	26	42.2	20.6	
$50–74,000	46	45.8	18.8	
≥$75,000	29	43.7	22.8	0.12
Smoking status				
Never	68	46.6	20.0	
Former	23	40.9	20.2	
Current	9	38.4	21.1	<0.01
Ever used oral contraceptives				
No	26	47.7	19.1	
Yes	73	43.2	20.8	<0.01
Family history of breast cancer				
None	71	44.6	20.2	
≥1 first degree relative	10	47.5	18.9	
≥1 second degree relative	19	42.2	21.9	0.16

[a] Data was from baseline (race/ethnicity, education, and oral contraceptive use) or from the closest annual follow-up visit closest to the woman's index mammogram (age, BMI, household income, smoking status, and menopausal status)

[b] Percentages may not add up to 100, due to rounding

[c] SD = standard deviation

[d] ANOVA *P*-values

Table 2

Results from individual linear regression models for each menstrual and reproductive factor in relation to percent mammographic density

Characteristic	%N[a]	Univariate models		Adjusted models	
		Beta estimate (SE)[b]	*P*-value	Beta estimate(SE)[c]	*P*-value
Age at menarche, years			<0.01		0.13
< 12 (reference)	21	0.00		0.00	
12	29	2.47 (2.05)		−0.24 (1.69)	
13	29	7.99 (2.04)		1.95 (1.70)	
> 13	21	11.1 (2.20)		3.32 (1.85)	
Usual cycle length, days			0.76		0.27
≥26 (reference)	72	0.00		0.00	
< 26	22	−0.54 (1.75)		−1.58 (1.44)	
Usual days of flow			0.21		0.91
1–2	3	−4.51 (4.42)		−0.17 (3.60)	
3–7 (reference)	93	0.00		0.00	
≥8	4	5.04 (3.59)		1.21 (2.89)	
Usual flow amount			0.10		0.75
Light to moderate (reference)	46	0.00		0.00	
Heavy	39	−1.83 (1.57)		−0.75 (1.27)	
Very heavy	15	−4.48 (2.16)		−1.15 (1.75)	
Premenstrual symptoms					
Had anxiety and mood changes	37	−3.89 (1.50)	0.01	−1.59 (1.23)	0.20
Had cramps and back pain	34	−3.30 (1.54)	0.03	−0.66 (1.27)	0.61
Had craving and bloating	44	−4.51 (1.45)	<0.01	−0.92 (1.22)	0.45
Had breast pain	63	0.71 (1.49)	0.64	1.91 (1.21)	0.12
Had headaches	23	0.36 (1.73)	0.84	2.14 (1.40)	0.13
Number of births			0.02		0.05
0 (reference)	18	0.00		0.00	
1–2	58	−1.47 (1.92)		−2.47 (1.55)	
≥3	23	−5.74 (2.24)		−4.52 (1.82)	
Age at FFTB (years)			<0.01		0.19
Nulliparous (reference)	19	0.00		0.00	

Characteristic	%N[a]	Univariate models		Adjusted models	
		Beta estimate (SE)[b]	*P*-value	Beta estimate(SE)[c]	*P*-value
≥32	19	0.43 (2.32)		−2.51 (1.87)	
28–31	21	−0.13 (2.27)		−2.05 (1.86)	
24–27	20	−3.70 (2.30)		−3.88 (1.88)	
≤23	20	−7.81 (2.29)		−4.12 (1.91)	
Breastfeeding history among parous women (months)			0.56		0.37
0 (reference)	16	0.00		0.00	
< 12	34	2.22 (2.14)		0.23 (1.80)	
≥12	32	1.04 (2.17)		−1.70 (1.86)	
Menopausal status			<0.01		0.18
Early perimenopausal	54	0.00		0.00	
Premenopausal	46	4.27 (1.44)		1.63 (1.21)	

[a] Percentages may not add up to 100, due to rounding. Missing values were present for: age at menarche (n = 4), cycle length (n = 47), days of flow (n = 1), premenstrual symptoms (n = 11), number of births (n = 1), and age at FFTB (n = 1)

[b] Parameter estimates for each factor modeled individually, in separate models. SE = standard error

[c] Parameter estimates for each factor modeled individually, in separate models, and adjusted for age, BMI, race/ethnicity-study site, and smoking. SE = standard error

Table 3

Stepwise regression results for percent mammographic density in relation to menstrual and reproductive characteristics

Characteristic	Stepwise regression model		Adjusted for covariates	
	Beta estimate (SE)[a]	*P*-value	Beta estimate (SE)[b]	*P*-value
Age at menarche, years		<0.01		0.09
< 12 (reference)	0.00		0.00	
12	1.78 (2.04)		−0.53 (1.70)	
13	7.35 (2.03)		1.97 (1.71)	
> 13	10.3 (2.19)		3.32 (1.85)	
Premenstrual craving and bloating	−3.36 (1.44)	0.02	−0.70 (1.23)	0.57
Number of births		<0.01		0.02
0 (reference)	0.00		0.00	
1–2	−1.94 (1.88)		−2.70 (1.56)	
≥3	−6.80 (2.20)		−5.16 (1.83)	
Menopausal status		<0.01		0.18
Early perimenopausal (reference)	0.00		0.00	
Premenopausal	3.78 (1.42)		1.63 (1.22)	

[a] Parameter estimates from a single multivariable model with variables for age at menarche, premenstrual craving and bloating, number of births, and menopausal status. SE = standard error

[b] Parameter estimates from a single multivariable model with the variables listed above, in addition to age, BMI, race/ethnicity-study site, and smoking

Table 4

Results from a single linear regression model for percent mammographic density by BMI

Characteristic	First tertile BMI[a]			Second tertile BMI			Third tertile BMI		
	N (%)	Beta estimate (SE)[b]	*P*-value	*N* (%)	Beta estimate (SE)[b]	*P*-value	*N* (%)	Beta estimate (SE)[b]	*P*-value
Age at menarche, years			0.80			0.36			0.31
< 12 (reference)	31 (12)	0.00		60 (23)	0.00		71 (27)	0.00	
12	69 (26)	1.73 (3.55)		66 (25)	1.40 (2.96)		89 (34)	−2.77 (2.64)	
13	92 (35)	2.69 (3.51)		79 (30)	0.83 (2.87)		63 (24)	0.48 (2.81)	
> 13	71 (27)	3.38 (3.61)		57 (22)	5.15 (3.16)		37 (14)	2.87 (3.29)	
Premenstrual craving and bloating			0.95			0.80			0.55
No	176 (67)	0.00		137 (52)	0.00		131 (50)	0.00	
Yes	87 (33)	0.15 (2.37)		125 (48)	−0.54 (2.16)		129 (50)	−1.22 (2.06)	
Number of births			<0.01			0.99			0.31
0 (reference)	50 (19)	0.00		48 (18)	0.00		49 (19)	0.00	
1–2	167 (64)	−7.61 (2.69)		154 (59)	−0.31 (2.79)		134 (52)	−0.29 (2.71)	
≥3	46 (17)	−12.2 (3.36)		60 (23)	−0.33 (3.22)		77 (30)	−3.73 (3.12)	
Menopausal status			0.91			0.31			0.17
Early perimenopausaln (reference)	133 (51)	0.00		141 (54)	0.00		153 (59)	0.00	
Premenopausal	130 (49)	0.23 (2.13)		121 (46)	2.14 (2.09)		107 (41)	3.06 (2.25)	

[a] BMI tertiles were: <21.3, 21.3–25.8, and >25.8 kg/m^2

[b] Parameter estimates from a single multivariable model with variables for age at menarche, premenstrual craving and bloating, number of births, and menopausal status, age, BMI, race/ethnicity-study site, and smoking. SE = standard error