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Reproductive factors related to childbearing and mammographic breast density

Lusine Yaghjyan[1], **Graham A. Colditz**[2,3], **Bernard Rosner**[4], **Kimberly A. Bertrand**[5], and **Rulla M. Tamimi**[4]

[1]University of Florida, College of Public Health and Health Professions and College of Medicine, Department of Epidemiology, 2004 Mowry Rd., Gainesville, FL 32610, USA

[2]Washington University in St. Louis School of Medicine, Department of Surgery, 660 S. Euclid Ave., St. Louis, MO, 63110, USA

[3]Institute for Public Health, Washington University in St. Louis, St. Louis, MO USA

[4]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 181 Longwood Avenue, Boston, MA 02115, USA

[5]Slone Epidemiology Center at Boston University, 1010 Commonwealth Avenue, Boston, MA 02215, USA

Abstract

Purpose—We investigated the associations of reproductive factors related to childbearing with percent breast density, absolute dense and non-dense areas, by menopausal status.

Methods—This study included 4,110 cancer-free women within the Nurses' Health Study and Nurses' Health Study II cohorts. Percent breast density, absolute dense and non-dense areas were measured from digitized mammography film images with computerized techniques. All density measures were square root-transformed in all the analyses to improve normality. The data on reproductive variables and other breast cancer risk factors were obtained from biennial questionnaires, at the time of the mammogram date.

Results—As compared to nulliparous women, parous postmenopausal women had lower percent density (β= −0.60, 95% CI −0.84; −0.37), smaller absolute dense area (β= −0.66, 95% CI −1.03; −0.29), and greater non-dense area (β=0.72, 95% CI 0.27; 1.16). Among parous women, number of children was inversely associated with percent density in pre- (β per one child=−0.12, 95% CI −0.20; −0.05) and postmenopausal women (β per one child=−0.07, 95% CI −0.12; −0.02). The positive associations of breastfeeding with absolute dense and non-dense areas were limited to

Correspondence to: Dr. Lusine Yaghjyan, Assistant Professor, Department of Epidemiology, College of Public Health and Health Professions and College of Medicine, University of Florida, 2004 Mowry Road, Room 4216, Box 100231, Gainesville, FL 32610-0231; Phone: (352) 294-5940; Fax: (352) 273-5365; lyaghjyan@ufl.edu.

Compliance with ethical standards

This study was approved by the Institutional Review Board at the Brigham and Women's Hospital. Informed consent was obtained or implied by return of questionnaires.

Conflict of interest

The authors declare that they have no conflict of interest.

premenopausal women, while the positive association of the age at first child's birth with percent density and the inverse association with non-dense area were limited to postmenopausal women.

Conclusions—Women with greater number of children and younger age at first child's birth have more favorable breast density patterns that could explain subsequent breast cancer risk reduction.

Keywords

parity; breastfeeding; age at first child; breast density; risk prediction

Introduction

High mammographic breast density is a well-established and strong predictor of breast cancer risk [1–4]. Appearance of the breast on a mammogram is a reflection of the amount of fat, connective tissue, and epithelial tissue in the breast [3]. Light (non-radiolucent) areas on the mammogram represent the fibrous and glandular tissues ("radiographically dense"), whereas, the dark (radiolucent) areas are primarily fat. Women with breasts of 75% or greater percent density (proportion of the total breast area that appears dense on the mammogram) are at 4- to 6-fold greater risk of breast cancer compared to women with more fat tissues in the breasts [3, 5, 6]. Absolute dense area of the breast that represents fibroglandular tissue has been shown to be positively associated with breast cancer risk in both pre- and postmenopausal women [7–13], while findings for the association between non-dense area of the breast (representing adipose tissue) and breast cancer risk have been conflicting [7, 9, 14, 15].

Reproductive factors related to childbearing have been associated with the risk of breast cancer in the previous studies. Parity has been shown to decrease the risk of estrogen and progesterone receptor-positive breast tumors [16]. Breastfeeding, on the other hand, was shown to reduce the risk of both receptor-positive and receptor-negative tumors, suggesting that the mechanisms behind these effects could be different [17]. Younger age at first birth was associated with reduced breast cancer risk [18–20].

A few studies examined associations of these reproductive risk factors with mammographic breast density. Parity and younger age at first birth have been inversely associated with breast density in previous reports [21, 22]. A recent study found a positive association between duration of breastfeeding and breast density (measured as percent fibroglandular volume assessed using single-energy X-ray absorptiometry) [23]. To date, the effects of these reproductive variables on breast density remain poorly understood.

Previous studies suggested that a longer period between menarche and first pregnancy is associated with increased breast cancer risk in pre- and postmenopausal women [24–27]. During this period the breast remains susceptible to carcinogenic influences until it undergoes final differentiation with permanent protective alterations in gene expression patterns during the first full-term pregnancy [28–31]. Whether the length of this interval could influence adult breast density is unknown.

We aimed to assess the associations of several reproductive variables (breastfeeding, parity, age at first and last birth, and duration of the time between menarche and first birth) with percent density, absolute dense and non-dense areas in pre- and postmenopausal women using prospective data in cancer-free women from the Nurses' Health Study and Nurses' Health Study II.

Materials and Methods

Study population

Women included in this study were selected from participants of the nested case-control study within Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII) cohorts. These prospective cohorts followed registered nurses in the United States who were 30–55 years (NHS) or 25–42 years old (NHSII) at enrollment. After administration of the initial questionnaire, the information on breast cancer risk factors and any diagnoses of cancer or other diseases was updated through biennial questionnaires [3, 32].

A nested case-control approach was originally used as an efficient design to examine the association between endogenous hormones, breast density, and breast cancer risk [3]. Using incidence density sampling, women without cancer history (other than non-melanoma skin cancer) at the time of the case's cancer diagnosis (controls) were matched 1:1 or 1:2 with women diagnosed with in situ or invasive breast cancer (cases) on age at the time of blood collection, menopausal status and postmenopausal hormone use (current vs. not current) at blood draw, and day/time of blood draw; for NHS II, additional matching included race/ethnicity and day in the luteal phase [33]. Our analysis was restricted to controls from this nested case-control study. We attempted to obtain mammograms closest to the time of blood collection from 6,361 controls. From these women, 5,028 women provided consent (79%) and of those, 4,342 women (86%) had a usable mammogram for density estimation. The final population included 4,110 women (82% of women providing consent). This study was approved by the Institutional Review Board at the Brigham and Women's Hospital. Informed consent was obtained or implied by return of questionnaires.

Reproductive variables

The data on age at menarche, parity, age at first and last birth, and breastfeeding were available from baseline and biennial questionnaires, completed closest to the date of the mammogram. Age at first birth was categorized as <24, 24–29, and ≥30 years. Parity was defined both as a binary variable (nulliparous, parous) as well as categorical (1, 2, 3, and ≥4 children). Parity and age at first birth were also modeled as continuous variables. Lifetime duration of breastfeeding (sum of breastfeeding duration across all births) was classified as none to <1, 1–6, >6–12, >12–18, >18–24, >24–36, and >36 months. Age at last birth and the time interval between menarche and first birth were modeled as continuous variables.

Assessment of mammographic breast density

To quantify mammographic density, the craniocaudal views of both breasts for all mammograms in the NHS and for the first two batches of mammograms in the NHSII were digitized at 261 μm per pixel with a Lumisys 85 laser film scanner (Lumisys, Sunnyvale,

California). The third batch of NHSII mammograms was digitized using a VIDAR CAD PRO Advantage scanner (VIDAR Systems Corporation; Herndon, VA) and comparable resolution of 150 dots per inch and 12 bit depth). The Cumulus software (University of Toronto, Toronto, Canada) was used for computer-assisted determination of the absolute dense area, non-dense area, and percent mammographic density [3, 34]. During this assessment, the observer was blinded to the participant's case-control status. As reported previously, the measure of breast density from NHS mammograms was highly reproducible (within-person intraclass correlation coefficient=0.93) [3]. All NHSII images were read by a single reader in three batches of mammograms approximately two-three years apart. Although within batch reproducibility was high (interclass correlation coefficient≥0.90) [7], density measures varied across the NHSII batches. The density measures from the second and third batches of NHSII mammograms were therefore adjusted to account for the batch effect, as previously described [35].

Percent breast density was measured as percentage of the total area occupied by epithelial/stromal tissue (absolute dense area) divided by the total breast area. Because breast densities of the right and left breast for an individual woman are strongly correlated [34], the average density of both breasts was used in this analysis.

Covariate information

Information on breast cancer risk factors was obtained from the biennial questionnaires closest to the date of the mammogram. Women were considered to be postmenopausal if they reported: 1) no menstrual periods within the 12 months before blood collection with natural menopause, 2) bilateral oophorectomy, or 3) hysterectomy with one or both ovaries retained, and were 54 years or older for ever smokers or 56 years or older for never smokers [36, 37].

Statistical analysis

We used multivariate linear regression to examine the associations of parity, age at first and last birth, breastfeeding, and interval between menarche and first birth with percent density, absolute dense and non-dense areas. Because density measures were non-normally distributed, we used square root-transformed density values in all the regression analyses to improve normality. The analyses were performed separately in pre- and postmenopausal women. The risk estimates were adjusted for age, body mass index (BMI), race, a family history of breast cancer, a history of benign breast disease, alcohol use, age at menarche, and in postmenopausal women, for postmenopausal hormone use. Additionally, in the analysis of the association of breastfeeding and age at last birth with density, the estimates were adjusted for parity and age at first birth. In the analysis of the associations of parity and age at first birth, the risk estimates were mutually adjusted for these two variables. In the analysis for the interval between menarche and first birth, the estimates were adjusted for parity.

The analyses of all reproductive variables except nulliparity were limited to parous women only. Parity and age at first birth were modeled both as continuous and categorical and breastfeeding was modeled as categorical. The lowest category for parity (1 child), age at

first birth (<24 years), and breastfeeding (0-<1 month) were used as the reference. To assess the overall trend for each of the categorical reproductive variables, we used respective medians within each category. Age at last birth and duration of the interval between menarche and first birth were modeled as continuous variables.

Differences in the associations of reproductive variables with breast density by menopausal status were evaluated with two-way interactions and using Wald Chi-square test. To test interactions of menopausal status with nulliparity, we modeled both of these variables as nominal. To test interactions of breastfeeding with menopausal status, we used respective medians within each of the breastfeeding categories to model the interaction. Other reproductive factors were modeled as continuous variables to test their interactions with menopausal status. Statistical significance in all the analyses was assessed at 0.05 level. Finally, as distribution of percent density in premenopausal women approximated normal distribution, we examined the association of untransformed percent density with reproductive variables in premenopausal women to assess the magnitude of these associations that might be clinically relevant. The analyses were performed using SAS software (version 9.2, SAS Institute, Cary, NC, USA).

Results

In this study of 4,110 cancer-free women, the average age at the mammogram was 53 years (range 30–84). A majority of the women were postmenopausal at the mammogram (2,250 or 54.7%) and of those, 44.5% were using postmenopausal hormones at the time of the mammogram. The majority of women were parous (86.6% for premenopausal and 91.1%, for postmenopausal). The majority of parous women had at least two children (83.6% for premenopausal and 91.0% for postmenopausal) and breastfed for at least one month (76.2% for premenopausal and 60.0% for postmenopausal). The average age at first birth was 26 years (range 15–45) for premenopausal women and 25 years (range 15–40) for postmenopausal women. Age-adjusted characteristics of pre- and postmenopausal women in the study by nulliparous status are presented in Table 1.

Associations of reproductive variables with density measures in premenopausal women

Among premenopausal women, nulliparity was not associated with any of the density measures (Table 2). Although longer duration of breastfeeding was not associated with percent density (p-trend=0.52), longer duration was associated with larger areas of both absolute dense (β=0.10 per 6 months increase in breastfeeding duration, p-trend=0.01) and non-dense breast tissue (β=0.09 per 6 months increase in breastfeeding duration, p-trend=0.03) (Table 2). Among parous women, a greater number of children was associated with lower percent density (β per child=−0.12, 95% CI −0.20; −0.05) and larger area of non-dense tissue (β=0.20, 95% CI 0.07; 0.34). Associations of the other reproductive variables with density measures in premenopausal women were not significant.

In a secondary analysis with untransformed percent density in premenopausal women, having four or more children was associated with 5% decrease in percent density. On average, parous premenopausal women had 2.5% lower percent density as compared to

nulliparous women. The magnitude of the associations of percent density with other reproductive variables did not exceed 2%.

Associations of reproductive variables with density measures in postmenopausal women

In postmenopausal women, parous women had lower percent density (β= −0.60, 95% CI −0.84; −0.37), smaller absolute dense area (β= −0.66, 95% CI −1.03; −0.29), and larger non-dense area (β=0.72; 95% CI 0.27; 1.16) as compared to nulliparous women (Table 2). These associations were stronger than in premenopausal women (p-interaction<0.001, 0.04, and 0.01, respectively). Among parous women, older age at first birth was positively associated with percent density (β=0.03, 95% CI 0.01; 0.05) and inversely associated with non-dense area (β= −0.10, 95% CI −0.13; −0.06). Among parous women, a greater number of children was associated with lower percent density (β= −0.07, 95% CI −0.12; −0.02) and smaller absolute dense (β= −0.14, 95% CI −0.21; −0.06) and non-dense area (β= −0.10, 95% CI −0.20; −0.01). Older age at last birth was associated with smaller non-dense area (β= −0.08; 95% CI −0.12; −0.04, p-interaction with menopausal status<0.01). Finally, a longer interval between menarche and first birth was positively associated with percent density (β=0.03, 95% CI 0.01; 0.05, p-interaction with menopausal status=0.03) and inversely associated with non-dense area (β= −0.07, 95% CI −0.11; −0.04, p-interaction with menopausal status=0.01) (Table 2). Interactions of other reproductive factors with menopausal status did not reach statistical significance (p-interaction>0.05 for all).

Discussion

In this study of 4,110 cancer-free women, nulliparity, number of children, age at first and last birth, duration of breastfeeding, and duration of the interval between menarche and first birth were associated with breast density measures and these associations varied in pre- and postmenopausal women. The positive associations of breastfeeding with absolute dense and non-dense area were limited to premenopausal women, while the positive association of the age at first birth with percent density and inverse association with non-dense area, the inverse association of the age at last birth with non-dense area and the positive association of interval between menarche and first birth with percent density and inverse association with non-dense area were limited to postmenopausal women.

Our results on the association of parity and the age at first birth with percent breast density are consistent with previous reports. Modugno et al. found lower percent density in parous women as compared to nulliparous women among 239 postmenopausal women (age 70–92) (23.7 versus 34.7%, p=0.005), but did not find associations with the age at first birth and breastfeeding [38]. An inverse association of parity with woman’s life-long history of percent density was previously reported in the Fernald Community Cohort [22]. Nulliparity and an older age at first birth were associated with increased percent density in both premenopausal and postmenopausal women in a study of 1,900 women by Vachon et al. [21]. Changes in the cellular processes in the breast tissue during pregnancy have been suggested as possible mechanisms behind protective effect of pregnancy on breast cancer risk [39]. Pregnancy results in reduction in the number of stem cells which are responsible for life-long decrease in the mammary stem cell numbers in parous women, and thus a

decrease in the pool of potentially transformable susceptible epithelial cells [16]. This theory is supported by emerging findings on the decrease in stem cell marker expression with increasing parity [40]. Tissue-specific stem cells serve as the source of the mature, functional cell types of a given tissue, have the capacity for self-renewal, and have ability to regenerate its "home" tissue in its entirety [41–46]. Reduction in the number of these stem cells might explain the decrease in breast density in parous women. On the other hand, an older age at the first birth leaves the undifferentiated breast tissue more susceptible to influences of exogenous and endogenous hormonal effects some of which have potential to increase epithelial proliferation and subsequently breast density [28, 29]. Whether this mechanism could explain increase in breast density with an older age at the first child's birth yet need to be explored.

We examine, for the first time, the associations of several reproductive variables related to childbearing with absolute dense and non-dense area. Our findings suggest that among both pre- and postmenopausal women, parity is inversely associated with both percent density and absolute dense area. In contrast, parity is positively associated with non-dense area among premenopausal women and inversely associated with non-dense area among postmenopausal women, which could explain the differences in the strength of associations with percent density by menopausal status.

We found a positive association of breastfeeding with both absolute dense and non-dense areas in premenopausal women. There were no associations in postmenopausal women suggesting that the effects of breastfeeding on breast tissue are likely temporary. In a previous study by Prebil et al., duration of breastfeeding was positively associated with fibro-glandular volume among 2440 parous women (β for square root-transformed fibro-glandular volume= 0.01, 95% CI 0.003; 0.02) [23]. Studies on breast tissue remodeling after lactation in humans are very limited, but animal reports suggest that with discontinuation of lactation, the breast tissue undergoes postpartum involution and remodeling as the result of apoptosis, regression of alveoli, and adipocyte repopulation [47, 48]. This mechanism, if confirmed in human studies, could potentially explain the increase in non-dense area in women with longer duration of breastfeeding as after longer duration a larger area of epithelium will undergo remodeling and replacement with adipose tissue (non-dense tissue on the mammogram).

To our knowledge, this is the largest study to date that simultaneously explored associations of several reproductive variables with percent density, absolute dense, and non-dense areas in pre- and postmenopausal women. The analysis used data from the Nurses' Health Study and Nurses' Health Study II, established cohorts with more than 30 years of follow-up, ascertainment of disease status, and comprehensive information on breast cancer risk factors and breast density. Our study has a few limitations. The examined associations are based on the density measures from a single mammogram which might not be reflective of the woman's life-long density pattern. Despite the prospective nature of the cohort, the recall bias for selected reproductive variables especially in postmenopausal women is possible. For example, previous studies had conflicting findings on the accuracy of recall for age at menarche [49–51] which could potentially influence the results for associations of the interval between menarche and first birth with density measures. Some reports suggest that

recall bias for breastfeeding in older women can affect the estimated associations between breastfeeding and health outcomes [52] and its influence on the null results among postmenopausal women in our study population should be acknowledged.

In conclusion, we investigated the associations of several reproductive variables related to childbearing with percent density, absolute dense and non-dense areas. Our findings suggest that nulliparous women are more likely to have high-risk breast density patterns as compared to parous women. Parous women with greater number of children and younger age at first birth have more favorable breast density patterns (lower percent density, smaller absolute dense area, and larger non-dense area) that could explain subsequent breast cancer risk reduction. The biological mechanisms underlying the associations of reproductive factors with density patterns yet need to be elucidated.

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Table 1

Age-adjusted characteristics of the study population at the time of the mammogram

	Premenopausal		Postmenopausal	
Characteristic	**Nulliparous (n=248)**	**Parous (n=1600)**	**Nulliparous (n=198)**	**Parous (n=2034)**
Mean (SD)				
Percent mammographic density	40.7 (19.6)	39.2 (19.0)	31.1 (19.9)	25.3 (17.5)
Dense area (cm^2)	88.2 (51.7)	80.6 (51.2)	61.0 (44.5)	47.9 (39.6)
Non-dense area (cm^2)	147.7 (94.8)	134.8 (79.5)	158.3 (102.6)	156.3 (90.7)
Age (years)[a]	44.7 (4.2)	46.3 (4.4)	55.3 (8.5)	58.4 (7.7)
Age at menarche (years)	12.3 (1.4)	12.5 (1.4)	12.3 (1.3)	12.5 (1.4)
Age at menopause (years)	NA	NA	45.9 (6.8)	47.7 (5.9)
Body Mass Index (kg/m^2)	25.9 (6.5)	25.5 (5.3)	27.3 (6.8)	26.2 (5.2)
Alcohol Use (grams)	6.4 (9.6)	4.3 (7.5)	6.0 (7.7)	5.0 (8.7)
Parity	NA	2.5 (1.0)	NA	3.1 (1.5)
Age at first birth (years)	NA	26.1 (4.2)	NA	25.1 (3.5)
Percentages				
Family history of breast cancer	9	9	12	12
Benign breast disease	17	16	21	23
Never used PMH	NA	NA	30	35
Past PMH use	NA	NA	19	20
Current PMH use	NA	NA	50	44
Breastfeeding 0–<1 month	NA	23	NA	39
Breastfeeding 1–6 months	NA	16	NA	25
Breastfeeding >6–12 months	NA	16	NA	12
Breastfeeding >12–18 months	NA	13	NA	10
Breastfeeding >18–24 months	NA	11	NA	5
Breastfeeding >24–36 months	NA	12	NA	5
Breastfeeding >36 months	NA	9	NA	3

Abbreviations: SD= standard deviation, PMH= postmenopausal hormone, NA-not applicable

Note: Values are means (SD) and percentages and are standardized to the age distribution of the study population.

[a]Value is not age adjusted

Table 2

Associations of reproductive variables related to childbearing with breast density measures [a]

	Premenopausal (n=1,860)				Postmenopausal (n=2,250)			
Reproductive variable	**N**	**Average Percent density**	**Average Dense area**	**Average Non-dense area**	**N**	**Average Percent density**	**Average Dense area**	**Average Non-dense area**
Nulliparity [b]								
Nulliparous	241	ref	ref	ref	195	ref	ref	ref
Parous	1557	−0.17 (−0.36; 0.02)	−0.11 (−0.46; 0.23)	0.20 (−0.16; 0.56)	2010	−0.60 (−0.84; −0.37)	−0.66 (−1.03; −0.29)	0.72 (0.27; 1.16)
Breast Feeding duration, months [c]								
0–< 1	347	ref	ref	ref	789	ref	ref	ref
1–6	247	−0.22 (−0.46; 0.01)	−0.34 (−0.75; 0.07)	0.12 (−0.32; 0.55)	498	−0.01 (−0.18; 0.17)	−0.08 (−0.36; 0.19)	−0.11 (−0.44; 0.22)
> 6–12	246	0.15 (−0.09; 0.38)	0.36 (−0.05; 0.78)	0.07 (−0.37; 0.50)	233	0.10 (−0.13; 0.33)	0.19 (−0.17; 0.55)	0.02 (0.41; 0.46)
>12–18	197	0.05 (−0.20; 0.31)	0.42 (−0.04; 0.87)	0.41 (−0.07; 0.88)	206	0.07 (−0.17; 0.31)	−0.05 (−0.42; 0.33)	−0.03 (−0.49; 0.43)
>18–24	160	0.02 (−0.25; 0.30)	0.29 (−0.19; 0.78)	0.31 (−0.20; 0.82)	104	−0.07 (−0.39; 0.26)	0.10 (−0.41; 0.61)	0.32 (−0.30; 0.93)
>24–36	187	−0.09 (−0.35; 0.18)	0.16 (−0.31; 0.64)	0.47 (−0.03; 0.97)	104	0.18 (−0.15; 0.51)	0.19 (−0.33; 0.70)	−0.17 (−0.79; 0.46)
>36	142	0.10 (−0.21; 0.41)	0.61 (0.06; 1.15)	0.49 (−0.09; 1.06)	52	−0.11 (−0.56; 0.33)	0.22 (−0.48; 0.92)	1.24 (0.39; 2.08)
p-trend[d]	1526	0.52	0.01	0.03	1986	0.69	0.32	0.08
Parity [e]								
1	211	ref	ref	ref	180	ref	ref	ref
2	699	−0.05 (−0.27; 0.17)	−0.01 (−0.41; 0.38)	−0.01 (−0.43; 0.40)	599	−0.02 (−0.28; 0.25)	−0.16 (−0.58; 0.25)	−0.41 − (−0.92; 0.09)
3	432	−0.13 (−0.38; 0.12)	−0.24 (−0.67; 0.20)	0.07 (−0.39; 0.53)	566	−0.18 (−0.46; 0.10)	−0.24 (−0.68; 0.19)	−0.16 (−0.68; 0.36)
≥4	212	−0.37 (−0.66; −0.09)	−0.34 (−0.85; 0.17)	0.57 (0.03; 1.10)	664	−0.27 (−0.55; 0.01)	−0.59 (−1.03; −0.14)	−0.55 (−1.09; −0.02)
p-trend	1554	0.01	0.07	0.03	2009	0.01	<0.01	0.13
Parity (continuous) [e]	1554	−0.12 (−0.20; −0.05)	−0.13 (−0.26; 0.00)	0.20 (0.07; 0.34)	2009	−0.07 (−0.12; −0.02)	−0.14 (−0.21; −0.06)	−0.10 − (−0.20; −0.01)
Age at first birth, years [f]								
<24	436	ref	ref	ref	723	ref	ref	ref
24–29	848	0.15 (−0.02; 0.31)	0.16 (−0.14; 0.46)	−0.04 (−0.35; 0.27)	1069	0.14 (−0.01; 0.29)	0.01 (−0.22; 0.25)	−0.45 (−0.73; −0.17)
≥30	270	0.12 (−0.11; 0.36)	0.05 (−0.37; 0.46)	−0.19 (−0.63; 0.24)	217	0.28 (0.03; 0.53)	0.07 (−0.32; 0.46)	−0.82 (−1.29; −0.34)
p-trend [c]	1554	0.28	0.78	0.39	2009	0.02	0.75	<0.001

	Premenopausal (n=1,860)				Postmenopausal (n=2,250)			
Reproductive variable	**N**	**Average Percent density**	**Average Dense area**	**Average Non-dense area**	**N**	**Average Percent density**	**Average Dense area**	**Average Non-dense area**
Age at first birth (continuous, years) [f]	1554	0.01 (−0.01; 0.02)	−0.00 (−0.03; 0.03)	−0.01 (−0.04; 0.02)	2009	0.03 (0.01; 0.05)	0.01 (−0.02; 0.04)	−0.10 (−0.13; −0.06)
Age at last birth, years [c]	1554	0.01 (−0.02; 0.03)	−0.01 (−0.06; 0.03)	−0.02 (−0.06; 0.03)	2009	0.00 (−0.02; 0.02)	−0.03 (−0.07; 0.00)	−0.08 (−0.12; −0.04)
Time between menarche and age at first birth, years [g]	1554	−0.00 (−0.02; 0.02)	−0.00 (−0.04; 0.03)	0.00 (−0.03; 0.04)	2009	0.03 (0.01; 0.05)	0.02 (−0.01; 0.05)	−0.07 (−0.11; −0.04)

[a] All density measures are square root-transformed

[b] Adjusted for age (continuous), BMI (continuous), race (White, other), age at menarche (<12, 12, 13, >13), a family history of breast cancer (Yes/No), a history of benign breast disease (Yes/No), NHS cohort (NHSI, NHSII), and alcohol use (none, >0–<5, ≥5 g/day); for postmenopausal women additionally adjusted for postmenopausal hormone use (none, past, current, past/unknown current)

[c] Among parous women; adjusted for age (continuous), BMI (continuous), race (White, other), age at menarche (<12, 12, 13, >13), parity, age at first birth, a family history of breast cancer (Yes/No), a history of benign breast disease (Yes/No), NHS cohort(NHSI, NHSII), and alcohol use (none, >0–<5, ≥5 g/day); for postmenopausal women additionally adjusted for postmenopausal hormone use (none, past, current, past/unknown current)

[d] P values were calculated using medians within respective categories

[e] Among parous women; adjusted for age (continuous), BMI (continuous), race (White, other), age at first birth, age at menarche (<12, 12, 13, >13), a family history of breast cancer (Yes/No), a history of benign breast disease (Yes/No), NHS cohort(NHSI, NHSII), and alcohol use (none, >0–<5, ≥5 g/day); for postmenopausal women additionally adjusted for postmenopausal hormone use (none, past, current, past/unknown current)

[f] Among parous women; adjusted for age (continuous), BMI (continuous), race (White, other), parity, age at menarche (<12, 12, 13, >13), a family history of breast cancer (Yes/No), a history of benign breast disease (Yes/No), NHS cohort(NHSI, NHSII), and alcohol use (none, >0–<5, ≥5 g/day); for postmenopausal women additionally adjusted for postmenopausal hormone use (none, past, current, past/unknown current)

[g] Among parous women; adjusted for age (continuous), BMI (continuous), race (White, other), parity, a family history of breast cancer (Yes/No), a history of benign breast disease (Yes/No), NHS cohort(NHSI, NHSII), and alcohol use (none, >0–<5, ≥5 g/day); for postmenopausal women additionally adjusted for postmenopausal hormone use (none, past, current, past/unknown current)