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Menstrual and reproductive characteristics and breast density in young women

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Abstract

Purpose—Breast density is strongly related to breast cancer risk, but determinants of breast density in young women remain largely unknown.

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Conflict of interest The authors declare that they have no conflict of interest.

Methods—Associations of reproductive and menstrual characteristics with breast density measured by magnetic resonance imaging were evaluated in a cross-sectional study of 176 healthy women, 25–29 years old, using linear mixed effects models.

Results—Parity was significantly inversely associated with breast density. In multivariable adjusted models that included non-reproductive variables, mean percent dense breast volume (%DBV) decreased from 20.5 % in nulliparous women to 16.0 % in parous women, while mean absolute dense breast volume (ADBV) decreased from 85.3 to 62.5 cm^3. Breast density also was significantly inversely associated with the age women started using hormonal contraceptives, whereas it was significantly positively associated with duration of hormonal contraceptive use. In adjusted models, mean %DBV decreased from 21.7 % in women who started using hormones at 12–17 years of age to 14.7 % in those who started using hormones at 22–28 years of age, while mean ADBV decreased from 86.2 to 53.7 cm^3. The age at which women started using hormonal contraceptives and duration of hormone use were inversely correlated, and mean %DBV increased from 15.8 % in women who used hormones for not more than 2.0 years to 22.0 % in women who used hormones for more than 8 years, while mean ADBV increased from 61.9 to 90.4 cm^3 over this interval.

Conclusions—Breast density in young women is inversely associated with parity and the age women started using hormonal contraceptives but positively associated with duration of hormone use.

Keywords

Breast density; Parity; Breast feeding; Hormonal contraceptives; Menarche; Menstrual cycle

Introduction

The breast is comprised of adipose tissue and dense fibroglandular tissue and women with a high percent dense breast area (%DBA) or absolute dense breast area (ADBA) typically measured by mammography are at an increased risk of breast cancer. In a meta-analysis, risk was increased more than fourfold for women with the highest %DBA [1]. Percent dense breast volume (%DBV) and absolute dense breast volume (ADBV) measured by magnetic resonance imaging (MRI) and other three-dimensional modalities are similarly positively associated with breast cancer risk [2].

Breast cancer is a hormonally dependent cancer and a woman's menstrual and reproductive histories are associated with risk. Specifically, early age at menarche and late age at menopause increase risk, whereas parity and early age at first pregnancy decrease risk [3].

One potential mechanism by which menstrual and reproductive characteristics could influence breast cancer risk is by altering breast density. Most earlier studies estimated breast density as %DBA and ADBA from mammographic images and included older premenopausal and postmenopausal women. However, dense breast tissue is comprised of stroma and ductal epithelium, and menstrual and reproductive characteristics might be more likely to influence breast density before involution of the breasts at menopause.

Because of the sensitivity of the young breast to radiation, few studies have evaluated the association of menstrual and reproductive characteristics with breast density in girls and young women. Novotny and colleagues [4] measured breast density of 10–16-year-old girls by dual-energy X-ray absorptiometry (DXA) and found that Tanner breast stage and onset of menarche were significantly positively associated with %DBV. In contrast, in a study of young women aged 15–30 years by Boyd et al. [5], neither age at menarche nor current oral contraceptive use was associated with %DBV or ADBV measured by MRI. We used data

from the Dietary Intervention Study in Children Follow-Up Study (DISC06) to identify menstrual and reproductive correlates of breast density in young women 25–29 years old.

Methods

Design

DISC was a multicenter randomized controlled clinical trial sponsored by the National Heart, Lung, and Blood Institute (NHLBI) to test the safety and efficacy of a dietary intervention to reduce serum low-density lipoprotein cholesterol (LDL-C) in children with elevated LDL-C. The trial's design and results have been described previously [6–13]. Briefly, between 1988 and 1990, 663 healthy, prepubertal, 8–10-year-old children, including 301 girls, with elevated LDL-C were recruited into DISC at six clinical centers and randomized to a behavioral dietary intervention or usual care control group. Planned intervention continued until 1997 when the mean age of participants was 16.7 years. In 2006–2008 when participants were 25 to 29 years old, the DISC06 Follow-Up Study was conducted to evaluate the longer-term effects of the diet intervention on biomarkers associated with breast cancer risk in DISC female participants. Assent was obtained from DISC participants and informed consent was obtained from their parents/guardians prior to randomization. Informed consent was obtained from participants again prior to the DISC06 follow-up visit. The original DISC protocol was approved by an NHLBI-appointed independent data and safety monitoring committee and institutional review boards at all participating clinical centers and the data coordinating center.[1] The DISC06 Follow-Up Study protocol was approved by the institutional review boards at the Fox Chase Cancer Center, all participating clinical centers, and the data coordinating center.

Participants

All female DISC participants were invited to participate in the DISC06 Follow-Up Study and 260 (86.4 %) of the 301 females originally randomized took part. Women who were pregnant or breastfeeding at or within 12 weeks before the visit ($n = 30$) and those who had breast implants or breast reduction surgery ($n = 16$) were not eligible for inclusion in the current analysis leaving a total of 214 women. Thirty-eight otherwise eligible women were excluded because they had technically unacceptable or missing breast MRI or whole-body dual-energy X-ray absorptiometry (DXA) images leaving a total of 176 participants for inclusion in analyses.

Data collection

For the follow-up study, each female participant attended a single visit at one of the 6 DISC clinics between 2006 and 2008. Visits were scheduled to take place in the luteal phase of the menstrual cycle whenever possible, and 85 % of visits took place within 14 days of onset of next menses. All data for a participant were collected on the same day except 24-h dietary recalls, which were collected over 2 weeks following the visit. Additionally, if a participant had not fasted, blood collection was rescheduled for the following day whenever possible. Data were collected by staff masked to treatment assignment. A centralized data collection training session was held before initiation of data collection to train and certify individuals responsible for data collection.

Participants completed several questionnaires on demographic characteristics; medical, reproductive, and menstrual histories; medication use; and health habits. Height, weight, and

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waist circumference were measured and body composition was assessed by whole-body DXA as previously described [13].

Breast density was measured using non-contrast MRI. Equipment standards were consistent with American College of Radiology guidelines for breast MRI and required that imaging be performed using a whole-body 1.5 Tesla or higher field strength MRI scanner and dedicated breast imaging radiofrequency coil. A standard image acquisition protocol was prescribed consisting of a three-dimensional T1-weighted fast gradient echo pulse sequence performed both with and without fat suppression and in both the transaxial and coronal orientations. All scanning was performed using a 32–40 cm field-of-view for bilateral coverage.

To insure accuracy and uniformity of data acquisition at the different clinical centers, MRI technologists at the sites were individually trained (by C. Klifa) to recognize and correct failures due to incomplete fat suppression, motion artifacts, and inadequate breast coverage. In addition, acceptable image quality on 3 volunteers was required for site certification. Participant scans that were inaccurate due to artifacts, motion or technique were excluded (n = 21).

All MRI image data were processed at UCSF by the same investigator (C. Klifa) using customized software to identify the chest wall–breast tissue boundary and skin surface, and to separate breast fibroglandular and fatty tissue using a segmentation method based on fuzzy C-means (FCM) clustering [14]. FCM segmentation was performed using fat-suppressed images; non-fat-suppressed images were used when incorrect or failed segmentation occurred due to poor fat suppression. In problematic cases that could not be segmented with automated FCM methods, manual delineation was used. Total volumes of fibroglandular tissue were measured by the absolute dense breast volume (ADBV) separately for each breast. Percent dense breast volume (%DBV) was then measured as the ratio of ADBV to total volume of the breast (ADBV plus absolute non-dense breast volume (ANDBV)). Results for the two breasts were averaged to provide single measures of %DBV, ADBV, and ANDBV for each participant.

Statistical analysis

%DBV, ADBV, and ANDBV were transformed to natural logarithms to improve normality. Linear mixed effects models were fit by maximum likelihood with robust standard errors separately for %DBV, ADBV, and ANDBV to evaluate associations with menstrual and reproductive characteristics. Clinic was included in all models as a random effect; all other variables were included as fixed effects. Adjusted models included terms for race (white, non-white), education (attended college), current smoker (yes, no), whole-body percent fat measured by DXA and BMI at 8–10 years of age expressed as a z-score relative to CDC 2000 Growth Charts. [15] Menstrual and reproductive characteristics significantly associated with %DBV or ADBV in multivariable adjusted models were included in fully adjusted models that also included non-reproductive variables identified above. Tests for interaction were performed by including cross-products terms in fully adjusted models that also included terms for main effects. Mean values reported for all breast density measures are geometric means. All tests of statistical significance are two sided. All analyses were conducted using STATA 12.0 (College Station, TX) and SAS 9.2 (Cary, NC).

Results

Participant characteristics are shown in Table 1. Their mean age was 27.2 years (range 24.9–29.7 years), and the majority were white. The women were well educated with 66.5 % having a college degree. Most (73.3 %) had never completed a full-term pregnancy. At the time of the visit, 58.5 % of the women were using hormonal contraceptives and 35.2 % had

used them formerly. Among current and former hormone users, the mean duration of use was 5.6 ± 3.5 years. Almost one-quarter of participants smoked cigarettes at the time of the visit with an average of 8.3 ± 7.5 cigarettes per day. Participants' mean BMI was 25.0 ± 4.9 kg/m^2; 25.6 % were overweight (25 ≤ BMI < 30) and another 16.5 % were obese (BMI ≥ 30). The participants' mean percent fat mass measured by DXA was 35.4 ± 8.8 %.

Thirty-eight eligible women who were excluded from analysis because they were missing or had technically unacceptable MRI breast density or DXA whole-body percent fat measures did not differ significantly from women included in analysis on descriptive characteristics included in Table 1.

Associations of menstrual and reproductive characteristics with %DBV, ADBV, and ANDBV are shown in Tables 2, 3, 4. Parity was significantly inversely associated with %DBV and ADBV in unadjusted and multivariable adjusted analysis. Adjusted for non-reproductive variables, %DBV decreased from a mean of 20.5 %for women who had never completed a full-term pregnancy to 16.1 %for women who completed one pregnancy and 15.9 % for women who completed more than one pregnancy (trend-p = 0.03). Mean ADBV similarly decreased from 85.3 cm^3 for women who had never completed a full-term pregnancy to 62.8 and 62.1 cm^3, respectively, for women who completed one and more than one pregnancy (trend-p < 0.001). In contrast, in unadjusted analysis, parity was significantly positively associated with ANDBV. However, ANDBV and percent body fat were strongly positively correlated (r = 0.81; p < 0.0001), and after adjusting for percent fat and other non-reproductive variables, the association was no longer significant.

Use of hormonal contraceptives categorized as never, former or ever was not associated with %DBV, ADBV, or ANDBV. However, the age women started using hormonal contraceptives and duration of hormone use were significantly associated with %DBV and ADBV such that women who started using hormones at a younger age and who used them for a longer duration had higher breast density. In adjusted analyses, mean %DBV decreased from 21.7 % for women who started using hormonal contraceptives when 12–17 years to 14.7 % for those who started when 22–28 years, while mean ADBV decreased from 86.2 to 53.7 cm^3 over this age range (both trend-p < 0.001). For duration of use, in adjusted analysis, mean %DBV increased from 15.8 % for women who used hormonal contraceptives for not more than 2.0 years to 22.0 % for those who used hormonal contraceptives for more than 8 years, while mean ADBV increased from 61.9 to 90.4 cm^3 over this interval (both trend-p < 0.01). The age women started using hormonal contraceptives and duration of hormone use were inversely correlated (r = −0.71; p < 0.0001). Results of analysis mutually adjusted for duration of hormonal contraceptive use and the age women started using hormones as well as non-reproductive variables suggested that these two measures of hormone use were independently associated with %DBV and ADBV. However, with further adjustment for parity, only the age women started using hormonal contraceptives remained significantly associated with %DBV and ADBV (both trend-p < 0.02).

Results shown in Tables 2, 3, and 4 adjusted for reproductive variables are from models that included terms for parity and the age women started using hormonal contraceptives in addition to non-reproductive variables. Similar results were obtained when the age women started using hormones was replaced in models with duration of use.

Tests for interaction did not indicate that associations of menstrual and reproductive characteristics with %DBV and ADBV differed between DISC treatment groups. Additionally, tests for interaction did not suggest that associations of the age women started using hormonal contraceptives and duration of hormone use with %DBV and ADBV differed for women who had and had not completed a full-term pregnancy. Because only

women who began using hormonal contraceptives at a young age were long-term users, tests of interaction between the age women started using hormones and duration of use in association with %DBV and ADBV were not performed.

Discussion

In this study of reproductive characteristics and breast density in young women, parity and the age women started using hormonal contraceptives were inversely associated with %DBV and ADBV, while duration of hormonal contraceptive use was positively associated with these measures of breast density. Age at menarche, menstrual cycle length and history of breast feeding were not associated with %DBV or ADBV. None of the menstrual and reproductive variables evaluated were associated with ANDBV in adjusted analysis.

Our study had several strengths. Data collection was performed using standardized procedures by trained personnel, and numerous quality controls were in place to ensure data integrity. %DBV and ADBV were measured by MRI, which is a tomographic rather than projection technique and therefore not impaired by high parenchymal breast density, making it especially effective for younger women with dense breast tissue. MRI can easily distinguish dense fibroglandular breast tissue from fatty breast tissue with a high degree of contrast and gives three-dimensional information not provided by mammography. Even though %DBA and %DBV are highly correlated [5, 14, 16], volumetric measures of percent breast density by three-dimensional imaging have been reported to be more strongly associated with breast cancer risk compared to area measures [2]. We adjusted for adiposity, which is strongly related to %DBV, using percent fat mass measured by DXA, which yields accurate and precise estimates of adiposity [17, 18]. We also were able to adjust for childhood BMI *z*-score, which was an independent predictor of breast density in our analysis, using data available from the original DISC trial.

Our study also had some limitations. In particular, all participants had elevated LDL-C as children when they were randomized in DISC and met several additional eligibility criteria, which could reduce generalizability of findings. Data on the association of LDL-C with breast density are inconsistent with significant inverse associations with %DBA [19] and null associations [20] reported after adjusting for adiposity. We observed a non-significant inverse correlation of LDL-C with %DBV in the current analysis ($r = -0.12$, $p = 0.11$) after adjustment for age and BMI. LDL-C also was not correlated with ADBV in analysis adjusted for age and BMI. Moreover, only 14 (8.0 %) participants included in analyses had high LDL-C levels at follow-up visits based on National Cholesterol Education Program guidelines [21], and none were using cholesterol-lowering medications.

We measured breast density by MRI, whereas most studies on the association of breast density with breast cancer risk factors measured breast density by mammography. Because MRI measures the three-dimensional volume of breast tissue, whereas mammography estimates breast density from a two-dimensional projected image of the breast, absolute values of density differ by modality with breast density measured by MRI being about 1.5 times lower than that measured using mammography [22]. Nevertheless, because breast density measured by MRI and mammography are highly correlated [5, 14, 16], the association of breast cancer risk factors with breast density would not be expected to differ depending on the modality used to measure density.

Few studies have evaluated breast composition in young women. However, in a study of women aged 15–30 years by Boyd et al. [5], the median percent breast water was 45 %, which is substantially larger than the median %DBV of 24.9 % (interquartile range 11.0–42.5 %) that we observed. Age was strongly inversely associated with percent water in the

Boyd study, and the younger age of participants in that study compared to ours could have contributed to this discrepancy. Furthermore, thicker MRI sections used in the Boyd study were more likely to contain mixtures of water and fat, which may have contributed to higher overall percent water values.

Parity is inversely related to breast cancer risk. In our analysis, parous women had borderline significantly lower %DBV and significantly lower ADBV compared to nulliparous women. These results are consistent with the majority of studies that have investigated associations of parity with %DBV [23], %DBA [24–28], and ADBA [26–28]. Similar results also were observed in a prospective follow-up study of nulliparous women; in that study, %DBA decreased by 12.0 % following a first full-term pregnancy, which was significantly greater than the 3.1 % decrease observed in women who remained nulliparous over the same time period [29]. Thus, decreased breast density could partly mediate the inverse association of parity with breast cancer risk. This is supported by a recent study in which adjusting for %DBA or ADBA attenuated the association of parity with breast cancer risk [26]. Even so, the degree of attenuation was modest (≤16.4 %), leading the authors to surmise that breast density explains only a small proportion of parity-related breast cancer risk reduction.

Compared to nulliparous women in our study, women who had completed one full-term pregnancy had considerably lower %DBV and ADBV, but these measures of breast density did not decline further with increasing number of pregnancies. This is in contrast to findings from a pooled analysis of 4 case–control studies by Woolcott and colleagues in which a pattern of decreasing %DBA and ADBA with increasing number of pregnancies was observed [26]. Few of the women in our study had completed more than one pregnancy, and differences in findings could be due to our small numbers, leading to imprecise estimates. Our participants were young and all were premenopausal, whereas participants in Woolcott's study were older and most were postmenopausal, which also could have contributed to differences. Longer follow-up of our cohort should clarify the reason for the discrepancy.

Parity also was significantly positively associated with ANDBV in our unadjusted analysis, but this association was explained by its correlation with percent body fat, which was strongly and significantly related to ANDBV. After adjustment for percent fat, parity was no longer associated with ANDBV. Thus, in our data, the inverse association of parity with %DBV appears to be driven by its inverse association with ADBV. These results are in contrast to studies in older women in which inverse associations of parity with %DBA appear to be due to a combination of its inverse association with ADBA and direct association with ANDBA [27, 28].

In this study of young women, status of hormonal contraceptive use categorized as never, former or current was not associated with %DBV or ADBV. However, few women never used hormonal contraceptives resulting in imprecise estimates for this category. Similar to our finding, current oral contraceptive use was not associated with %DBV or ADBV in a study of young women 15–30 years old, [5] and ever use of oral contraceptives was not associated with %DBVorADBVin women 49–59 years old [23]. Hormonal contraceptive use categorized as ever or past use also generally is not associated with %DBA [28, 30, 31] or ADBA [28] in adjusted analyses, although positive associations with %DBA [32] and both positive [32] and inverse [31] associations with ADBA have been reported.

Few studies have investigated associations of duration of hormonal contraceptive use or age when women started using hormonal contraceptives with breast density measures. In contrast to our finding that women who used hormonal contraceptives for a longer duration

had higher %DBV and ADBV, duration of use was not associated with %DBA or ADBA in one study [31] or with Wolfe category of breast density in another [33]. Similarly, in contrast to our finding that women who started using hormonal contraceptives at a younger age had higher %DBV and ADBV, the age women started using hormonal contraceptives was not associated with %DBA in the one prior study that evaluated the association [24]. Reasons for these discrepancies are unclear but could be related to differences in ages of participants at assessment of breast density, different methods employed to measure breast density, differences in covariates included in models, and changes in hormonal contraceptive formulations over time. In our analysis, the age women started using hormonal contraceptives and duration of use were not associated with ANDBV, suggesting that the associations of these variables with %DBV were due to their associations with ADBV.

The age women started using hormonal contraceptives and duration of use were strongly inversely correlated. In mutually adjusted analysis, the age women started using hormonal contraceptives but not duration of use remained significantly associated with %DBV and ADBV, suggesting that the age women started using hormonal contraceptives was the characteristic of hormonal contraceptive use associated most strongly with breast density. However, we caution that our sample size and duration of follow-up were limited to disentangle these effects, and results could differ in a larger study with longer follow-up.

Younger age at menarche is an established breast cancer risk factor, and an inverse association of age at menarche and ADBA was reported in one study after adjustment for BMI and other confounders [31]. Positive associations with ADBA [27] and Breast Imaging Reporting and Data System (BI-RADS) classification of breast density [34, 35] also have been reported. However, similar to us, most studies do not report an association of age at menarche with %DBV, [5, 23] %DBA, [24, 25, 27, 28, 30, 32, 36–38] ADBV [5, 23] or ADBA [28, 32, 39] in adjusted analysis. We adjusted for BMI *z*-score at 8–10 years of age because in previous analyses, we observed strong inverse associations with %DBV and ADBV that were independent of current BMI. BMI *z*-score is inversely correlated ($r = -0.30$, $p = 0.0001$) with age at menarche. However, results were unchanged in analysis that did not adjust for childhood BMI *z*-score.

Shorter menstrual cycle length is associated with increased risk of breast cancer in some studies. However, we did not detect an association of cycle length with %DBV or ADBV in women not using hormonal contraceptives. Few studies have evaluated the association of menstrual cycle length with breast density measures. Menstrual cycle length was not associated with %DBA or ADBA in pre- and perimenopausal women in the Study of Women's Health Across the Nation [36]. However, it was significantly inversely associated with BI-RADS classification of breast density in younger premenopausal women less than 45 years old in an analysis from the Group Health Cooperative of Puget Sound, Seattle [35]. Differences in findings across studies could be related to measurement error in self-reported menstrual cycle length that has been reported to vary by individual characteristics. [40, 41].

Conclusions

In this study of menstrual and reproductive correlates of breast density in young women, parous women had lower %DBV compared to nulliparous women, and this association appears to have been driven by lower ADBV in parous women. Although there were no trends of decreasing %DBV and ADBV with increasing number of pregnancies, few women had more than one pregnancy, and longer follow-up is needed to clarify this association. The age women started using hormonal contraceptives also was inversely associated while duration of use was positively associated with %DBV, and similar to parity, at least in young women, these associations appear to be due to their associations with ADBV. These

results are consistent with the hypothesized involvement of sex hormones in determination of breast density. Replication of these novel findings in other cohorts is needed.

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Table 1

Participant characteristics

Descriptive characteristics	*N*	Mean (5–95 % CI)
Age (y)	176	27.2 (27.0–27.3)
Total body fat (%)	176	35.4 (34.1–36.7)
BMI (kg/m^2)	176	25.0 (24.3–25.8)
Height (cm)	176	165.2 (164.2–166.1)
BMI *z*-score at 8–10 years old	176	0.2 (0.1–0.3)
Age at which started using hormones (y)	165	19.3 (18.8–19.8)
Duration of hormone use by users (y)	165	5.6 (5.1–6.2)
Age at menarche (y)	176	12.9 (12.7–13.1)
Menstrual cycle length (days)[a]	71	28.0 (27.4–28.6)
	N	%
Race		
White	158	89.8
Non-white	18	10.2
Education		
High school, vocational or technical school	18	10.2
Some college	41	23.3
Bachelor degree	92	52.3
Graduate degree	25	14.2
Number of full-term pregnancies		
0	129	73.3
1	28	15.9
2–4	19	10.8
Ever breast fed		
Yes	37	21.0
No	139	79.0
Hormonal contraceptive use		
Never	11	6.2
Former	62	35.2
Current	103	58.5
Smoking status		
Never	97	55.1
Former	37	21.0
Current	42	23.9
Breast density measures	*N*	Geometric mean (5–95 % CI)
Percent dense breast volume	176	19.2 (16.5–22.4)
Absolute dense breast volume (cm^3)	176	78.5 (69.1–89.2)

[a] Includes only participants not currently using hormonal contraceptives

Table 2

Geometric mean and 95 % confidence interval (CI) for percent dense breast volume at the DISC06 follow-up visit

	Unadjusted[a]			Adjusted for non-reproductive variables[b]		Also adjusted for reproductive variables[c]	
	N	Mean (5–95 % CI)	*p*[d]	Mean (5–95 % CI)	*p*[d]	Mean (5–95 % CI)	*p*[d]
No. of full-term pregnancies							
0	129	22.1 (18.7–26.0)	**<0.001**	20.5 (17.8–23.6)	**0.03**	20.8 (17.5–24.6)	**0.04**
1	28	15.2 (11.4–20.2)		16.1 (12.4–20.9)		16.7 (12.3–22.7)	
2–4	19	10.9 (7.8–15.1)		15.9 (11.6–21.8)		16.0 (11.4–22.5)	
Nulliparous							
Yes	129	22.1 (18.8–26.0)	**<0.001**	20.5 (17.8–23.6)	0.09	20.8 (17.5–24.6)	0.15
No	47	13.2 (10.4–16.7)		16.0 (13.0–19.7)		16.4 (13.1–20.6)	
Ever breast fed							
Yes	37	14.0 (10.8–18.1)	**0.02**	17.2 (13.1–22.6)	0.45	20.6 (13.9–30.5)	0.78
No	139	20.9 (17.6–24.9)		19.7 (17.1–22.8)		19.2 (16.0–22.9)	
Hormone use							
Never	11	15.6 (7.6–32.1)	0.71	22.4 (13.8–36.3)	0.69	21.4 (13.1–34.9)	0.80
Former	62	18.6 (14.0–24.6)		19.4 (16.6–22.7)		19.5 (16.6–22.9)	
Current	103	20.0 (17.3–23.2)		18.7 (16.3–21.6)		18.8 (16.0–22.0)	
Age at which started using hormones (y)							
12–17	47	22.4 (17.5–28.6)	**0.02**	21.7 (17.5–26.8)	**<0.001**	21.6 (17.7–26.2)	**<0.001**
18–19	50	21.1 (18.4–24.3)		22.0 (19.9–24.3)		22.1 (19.5–25.1)	
20–21	32	18.3 (13.2–25.2)		18.9 (13.8–25.9)		19.1 (13.7–26.8)	
22–28	36	15.3 (11.4–20.5)		14.7 (12.3–17.5)		14.4 (12.0–17.4)	
Duration of hormone use (y)							
0–2.0	45	13.8 (9.3–20.7)	**0.04**	15.8 (14.4–17.3)	**<0.001**	15.8 (14.5–17.1)	**<0.001**
2.1–5.0	45	21.9 (17.7–27.1)		20.3 (18.3–22.5)		20.8 (19.0–22.6)	
5.2–8.0	45	19.4 (12.8–29.5)		19.4 (14.1–26.8)		19.2 (13.8–26.7)	
8.4–13.5	41	23.5 (18.5–29.9)		22.0 (19.0–25.6)		21.8 (19.0–25.2)	
Age at menarche (y)							
<12	35	16.4 (11.6–23.1)	**0.01**	18.9 (13.7–25.9)	0.70	21.2 (15.4–29.1)	0.95
12–13	110	18.2 (15.0–22.0)		18.9 (15.8–22.6)		18.6 (15.0–22.9)	

	Unadjusted[a]			Adjusted for non-reproductive variables[b]		Also adjusted for reproductive variables[c]	
	N	**Mean (5–95 % CI)**	***p*[d]**	**Mean (5–95 % CI)**	***p*[d]**	**Mean (5–95 % CI)**	***p*[d]**
14+	31	27.9 (20.6–37.8)		20.8 (16.5–26.1)		21.0 (16.4–26.7)	
Menstrual cycle length (days)[e]							
≤27	18	19.4 (10.0–37.7)	0.39	21.1 (14.1–31.5)	0.15	20.0 (14.9–26.8)	0.17
28	26	19.8 (15.5–25.2)		18.9 (14.2–25.2)		20.2 (16.2–25.2)	
29+	27	17.2 (11.5–25.8)		17.1 (13.7–21.2)		17.9 (14.4–22.3)	

[a] Geometric means estimated from linear mixed effects models including clinic as a random effect and reproductive variables as fixed effects

[b] Geometric means estimated from linear mixed effects models including clinic as a random effect and adjusted for percent body fat from DXA, race (white vs. non-white), education (attended college), current smoker (yes/no), and BMI z-score at 8–10 years old as fixed effects

[c] Geometric means estimated from linear mixed effects models as described above under b also including parity (models for ever breast fed, hormone use, age at which started using hormones, duration of hormone use, age at menarche, menstrual cycle length), and age at which started using hormones (models for number of full-term pregnancies, nulliparous, ever breast fed, age at menarche, menstrual cycle length) as fixed effects

[d] *p* values from Wald test of coefficients in linear mixed effects models with number of full-term pregnancies, age at which started using hormones, duration of hormone use, age at menarche, and menstrual cycle length modeled as continuous variables. *P* values < 0.05 are bolded

[e] Includes only participants not currently using hormonal contraceptives

Table 3

Geometric mean (cm^3) and 95 % confidence interval (CI) for absolute dense breast volume at the DISC06 follow-up visit

	Unadjusted[a]			Adjusted for non-reproductive variables[b]		Also adjusted for reproductive variables[c]	
	N	Mean (5–95 % CI)	*p*[d]	Mean (5–95 % CI)	*p*[d]	Mean (5–95 % CI)	*p*[d]
No. of full-term pregnancies							
0	129	88.7 (71.0–110.9)	**<0.001**	85.3 (72.4–100.6)	**<0.001**	84.6 (69.3–103.3)	**<0.001**
1	28	69.7 (52.4–92.7)		62.8 (52.6–75.0)		65.1 (52.6–80.6)	
2–4	19	57.5 (45.0–73.6)		62.1 (54.8–70.3)		60.6 (52.6–69.9)	
Nulliparous							
Yes	129	88.8 (71.2–110.8)	**<0.001**	85.3 (72.4–100.5)	**<0.001**	84.6 (69.4–103.1)	**0.002**
No	47	64.3 (51.9–79.7)		62.5 (55.4–70.6)		63.3 (55.4–72.3)	
Ever breast fed							
Yes	37	67.3 (52.6–86.1)	0.06	67.9 (60.2–76.5)	0.11	81.2 (60.0–109.8)	0.81
No	139	86.2 (67.6–109.8)		81.6 (67.7–98.4)		77.2 (61.7–96.5)	
Hormone use							
Never	11	87.6 (51.6–148.8)	0.89	96.6 (60.9–153.2)	0.73	91.0 (57.2–144.9)	0.85
Former	62	78.0 (62.4–97.5)		75.1 (62.6–90.1)		75.6 (62.6–91.3)	
Current	103	80.6 (65.3–99.5)		78.9 (64.1–97.0)		79.0 (63.4–98.6)	
Age at which started using hormones (y)							
12–17	47	86.3 (69.6–106.9)	**<0.001**	86.2 (67.5–110.1)	**<0.001**	85.8 (68.6–107.2)	**<0.001**
18–19	50	101.1 (82.7–123.6)		96.2 (82.7–111.9)		97.0 (82.1–114.6)	
20–21	32	79.4 (52.1–121.0)		74.0 (54.5–100.4)		75.3 (54.2–104.8)	
22–28	36	58.6 (40.9–84.1)		53.7 (41.0–70.3)		52.6 (39.3–70.4)	
Duration of hormone use (y)							
0–2.0	45	60.3 (46.5–78.3)	**<0.001**	61.9 (56.3–68.0)	**0.003**	61.8 (56.2–68.0)	**0.004**
2.1–5.0	45	86.9 (80.3–94.1)		83.5 (74.6–93.4)		85.7 (76.1–96.5)	
5.2–8.0	45	80.9 (51.6–126.8)		82.3 (54.8–123.6)		81.2 (53.8–122.5)	
8.4–13.5	41	90.7 (78.8–104.4)		90.4 (76.8–106.3)		89.4 (77.4–103.2)	
Age at menarche (y)							
<12	35	78.1 (61.4–99.4)	0.34	80.0 (61.6–103.9)	0.47	88.0 (69.8–110.9)	0.49
12–13	110	77.6 (61.2–98.2)		79.8 (62.8–101.3)		76.3 (58.7–99.4)	

	Unadjusted[a]			Adjusted for non-reproductive variables[b]		Also adjusted for reproductive variables[c]	
	N	Mean (5–95 % CI)	*p*[d]	Mean (5–95 % CI)	*p*[d]	Mean (5–95 % CI)	*p*[d]
14+	31	88.1 (69.2–112.1)		72.6 (55.8–94.6)		73.5 (52.9–102.0)	
Menstrual cycle length (days)[e]							
20–27	18	85.7 (50.5–145.2)	0.31	83.4 (61.2–113.8)	0.37	74.7 (61.3–90.9)	0.79
28	26	84.7 (66.4–108.1)		82.3 (61.0–111.1)		82.7 (66.1–103.5)	
29+	27	71.1 (47.7–106.0)		72.1 (52.8–98.3)		73.0 (62.1–85.9)	

[a] Geometric means estimated from linear mixed effects models including clinic as a random effect and reproductive variables as fixed effects

[b] Geometric means estimated from linear mixed effects models including clinic as a random effect and adjusted for percent body fat from DXA, race (white vs. non-white), education (attended college), current smoker (yes/no), and BMI *z*-score at 8–10 years old as fixed effects

[c] Geometric means estimated from linear mixed effects models as described above under b also including parity (models for ever breast fed, hormone use, age at which started using hormones, duration of hormone use, age at menarche, menstrual cycle length), and age at which started using hormones (models for number of full-term pregnancies, nulliparous, ever breast fed, age at menarche, menstrual cycle length) as fixed effects

[d] *p* values from Wald test of coefficients in linear mixed effects models with number of full-term pregnancies, age at which started using hormones, duration of hormone use, age at menarche, and menstrual cycle length modeled as continuous variables. *P* values < 0.05 are bolded

[e] Includes only participants not currently using hormonal contraceptives

Table 4

Geometric Mean (cm^3) and 95 % Confidence Interval (CI) for absolute non-dense breast volume at the DISC06 follow-up visit

	Unadjusted[a]			Adjusted for non-reproductive variables[b]		Also adjusted for reproductive variables[c]	
	N	Mean (5–95 % CI)	*p*[d]	Mean (5–95 % CI)	*p*[d]	Mean (5–95 % CI)	*p*[d]
No. of full-term pregnancies							
0	129	254.5 (237.2–273.1)	**<0.001**	278.9 (266.0–292.4)	0.97	275.0 (259.6–291.4)	0.94
1	28	312.4 (261.9–372.5)		270.5 (202.9–360.5)		267.6 (203.3–352.1)	
2–4	19	427.5 (315.1–580.0)		283.8 (217.7–369.9)		274.6 (210.1–358.8)	
Nulliparous							
Yes	129	254.5 (237.3–273.0)	**0.001**	279.0 (266.5–292.1)	0.92	275.1 (260.1–291.0)	0.88
No	47	354.6 (288.6–435.7)		275.6 (218.2–348.1)		270.3 (216.8–337.0)	
Ever breast fed							
Yes	37	340.6 (287.4–403.7)	**0.001**	270.2 (213.6–341.8)	0.74	256.2 (207.0–317.0)	0.44
No	139	263.5 (247.2–280.8)		280.2 (265.4–295.8)		278.9 (262.8–296.0)	
Hormone use							
Never	11	351.8 (190.0–651.7)	0.65	239.4 (186.0–308.1)	0.32	239.0 (179.1–319.0)	0.39
Former	62	286.2 (221.7–369.5)		266.2 (240.7–294.4)		266.2 (241.5–293.5)	
Current	103	266.5 (231.8–306.5)		290.1 (258.8–325.1)		290.1 (258.8–325.3)	
Age at which started using hormones (y)							
12–17	47	240.9 (178.9–324.5)	0.32	264.9 (217.9–321.9)	0.76	264.8 (217.7–322.2)	0.77
18–19	50	304.9 (257.5–361.1)		293.2 (260.6–329.9)		293.3 (261.8–328.5)	
20–21	32	282.4 (228.9–348.4)		258.7 (233.3–286.9)		258.9 (230.6–290.6)	
22–28	36	270.8 (205.5–356.9)		273.2 (241.0–309.6)		273.0 (238.6–312.3)	
Duration of hormone use (y)							
0–2.0	45	316.3 (227.2–440.3)	0.44	271.5 (248.1–297.0)	0.68	271.5 (248.0–297.2)	0.67
2.1–5.0	45	267.5 (205.9–347.6)		283.5 (253.4–317.2)		283.5 (255.6–314.3)	
5.2–8.0	45	277.3 (231.0–332.9)		282.2 (255.6–311.5)		282.2 (255.6–311.6)	
8.4–13.5	41	252.7 (196.6–324.7)		275.1 (228.0–332.0)		275.1 (227.3–332.9)	
Age at menarche (y)							
<12	35	326.4 (236.8–449.9)	**0.004**	282.3 (218.7–364.2)	0.13	272.3 (203.5–364.4)	0.35
12–13	110	294.2 (261.0–331.7)		291.9 (275.6–309.2)		287.7 (279.2–296.3)	

	Unadjusted[a]			Adjusted for non-reproductive variables[b]		Also adjusted for reproductive variables[c]	
	N	Mean (5–95 % CI)	*p*[d]	Mean (5–95 % CI)	*p*[d]	Mean (5–95 % CI)	*p*[d]
14+	31	190.0 (152.5–236.8)		230.1 (216.0–245.2)		231.0 (212.1–251.4)	
Menstrual cycle length (days)[e]							
20–27	18	282.2 (185.3–429.8)	0.99	253.2 (213.0–301.1)	0.50	238.6 (192.4–295.8)	0.22
28	26	301.3 (253.8–357.7)		315.3 (281.2–353.5)		297.1 (247.6–356.7)	
29+	27	277.7 (192.2–401.3)		285.7 (244.2–334.4)		283.8 (220.3–365.6)	

[a] Geometric means estimated from linear mixed effects models including clinic as a random effect and reproductive variables as fixed effects

[b] Geometric means estimated from linear mixed effects models including clinic as a random effect and adjusted for percent body fat from DXA, race (white vs. non-white), education (attended college), current smoker (yes/no), and BMI *z*-score at 8–10 years old as fixed effects

[c] Geometric means estimated from linear mixed effects models as described above under b also including parity (models for ever breast fed, hormone use, age at which started using hormones, duration of hormone use, age at menarche, menstrual cycle length), and the age at which started using hormones (models for number of full-term pregnancies, nulliparous, ever breast fed, age at menarche, menstrual cycle length) as fixed effects

[d] *p* values from Wald test of coefficients in linear mixed effects models with number of full-term pregnancies, age started hormones, duration of hormone use, age at menarche, and menstrual cycle length modeled as continuous variables. *P* values < 0.05 are bolded

[e] Includes only participants not currently using hormonal contraceptives