Short Communication

Mammographic Breast Density, Dense Area, and Breast Area Differences by Phase in the Menstrual Cycle

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Abstract

Background: **Mammographic breast density may be greater in the luteal phase (days 15-30) than the follicular phase (days 1-14) of the menstrual cycle; this may have implications for when mammography screening should occur.**
Objective: **Examine whether percent breast density, breast area, or dense area differ by menstrual phase.**
Methods: **We identified 204 premenopausal women with regular periods who were <55 years (mean = 45.0 years) and had two screening mammograms within 9 to 18 months, with one screening between days 9 and 14, and one screening between days 22 and 35 of the menstrual cycle. We measured percent breast density, breast area, and dense area using the Cumulus software. We used linear regression to test for differences in breast density, breast area, and dense area from follicular to luteal phase, adjusting for change in weight and time between exams.**
Results: **The mean (SD) percent breast density was 35.8% (21.3) in the follicular phase and 36.7% (21.3) in the luteal phase. Multivariable analyses showed small but not statistically significant increases in percent density [1.1%; 95% confidence interval (95% CI), −0.2% to 2.3%] and breast area (16.7 cm^2; 95% CI, −2.8 to 36.2) and a statistically significant increase in dense area (13.1 cm^2; 95% CI, 0.1-26.1) in the luteal compared with the follicular phase.**
Conclusions: **Breast density, breast area, and dense area have small, but probably not clinically meaningful, increases in the luteal phase of the menstrual cycle. However, there are other factors that may differ by menstrual cycle phase that we were unable to assess (e.g., breast compression), which may ultimately influence mammographic sensitivity by menstrual cycle phase.** (Cancer Epidemiol Biomarkers Prev 2006;15(11):2303–6)

Background

For women under 50 years old, the question of screening efficacy has been controversial (1-3), in part, because mammographic breast density is significantly greater in younger women (4). Women's endogenous progesterone and estradiol concentrations fluctuate over the course of the menstrual cycle; estradiol levels consistently increase in the follicular phase, peaking at ovulation, and decline with some variation in the luteal phase, and progesterone levels increase in the luteal phase. Estrogen along with progesterone is hypothesized to increase mammographic breast density. This hypothesis is consistent with the observed influence of postmenopausal hormone therapy on breast density; estrogen with progestin significantly increases breast density, whereas estrogen alone does not (5-8). It follows that mammographic density should be higher in the luteal phase, which may decrease mammographic sensitivity (4). Three small studies suggest there is higher mammographic breast density (9, 10) and lower mammographic sensitivity (11) in the luteal phase (days 16-30) of the menstrual cycle compared with the follicular phase (days 1-15; refs. 9-11).

The objective of this study was to examine whether mammographic breast density (measured as percent breast density and total dense area) is greater in the luteal phase of the menstrual cycle compared with the follicular phase in a population-based sample of women undergoing screening mammography.

Materials and Methods

This retrospective observational case series study took place within Group Health, an integrated group practice in western Washington State with ~550,000 members. Group Health has a population-based Breast Cancer Screening Program that women are invited to join when they turn 40 years old or when they join Group Health (12, 13). Self-reported demographic and breast cancer risk factor information are gathered by a self-administered questionnaire from women when they join the Breast Cancer Screening Program and at each screening mammogram (13). Women are also asked to provide information about their menstrual cycle on the day of their mammogram. Between 1996 and mid-2001, we asked women to report the first day of their last menstrual period. In mid-2001, we changed our questionnaire to gather categorical information on a woman's first day of their last menstrual period (1-7, 8-14, 15-21, 22-35, or >35 days ago). For this study, we wanted to ensure we were comparing breast densities from different phases in a woman's menstrual cycle; thus, we limited our comparison to women having mammograms in the second (days 8-14 for follicular) and fourth weeks (days 22-35 for luteal) of the menstrual cycle. This study was reviewed and approved by Group Health's Institutional Review Board.

We identified all premenopausal women who had two screening mammograms within 9 to 18 months of each other between 1996 and 2004, where one mammogram was in the

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Table 1. Population characteristics of the same premenopausal women at two mammograms during different phases in their menstrual cycle

	Follicular (N = 204), mean (SD)	Luteal (N = 204), mean (SD)	Difference (luteal-follicular, N = 204), mean (SD)
Age (y)	45.6 (4.2)	45.7 (4.1)	0.04 (1.2)
Body mass index (kg/m^2)	25.5 (5.9)	25.6 (6.2)	0.12 (1.8)
Weight (kg)	70.6 (17.6)	70.9 (18.2)	0.25 (4.6)
Day in menstrual cycle*	11.2 (2.4)	25.5 (3.5)	
Time between exams (d)			415.3 (62.9)†
Percent breast density	35.8 (21.3)	36.7 (21.3)	0.9% (9.2)
Breast area	940.3 (326.9)	957.7 (323.6)	17.4 (140.9)
Dense area	312.1 (211.7)	323.6 (200.4)	11.5 (97.4)
	%	%	
1st mammogram	51.0	49.0	
BI-RADS breast density			
1 (entirely fatty)	1.0	0.5	
2 (scattered fibroglandular)	20.9	23.0	
3 (heterogeneously dense)	53.7	53.0	
4 (extremely dense)	24.4	23.5	

NOTE: Menstrual cycle: follicular = days 7 to 15 or week 2 of cycle; luteal = days 21 to 35 or week 4 of cycle.
*Available for 130 women with continuous data; 74 women reported week in menstrual cycle.
†Mean absolute value of the difference.

follicular and one mammogram was in the luteal phase of the menstrual cycle. To be eligible, women had to be <55 years, had to report having regular menstrual cycles, and have <35 days since their last menstrual cycle at both mammograms. We identified 232 women who met our eligibility criteria and who had no previous breast cancer, bilateral breast biopsies, or breast augmentation/reduction and who were not using hormone therapy, raloxifene, tamoxifen, or oral contraceptives. We further excluded women whose craniocaudal films could not be located (n = 14), whose films had poor mammographic quality (n = 3), whose parity changed between exams (n = 4), or who had missing weight values at either exam (n = 7), leaving a total sample size of 204 women.

Mammographic Breast Density Measurement

We digitized the craniocaudal projection of the left breast from the follicular and luteal phase mammograms using a Kodak Lumysis 85 scanner. We used the Cumulus software developed at the University of Toronto to measure percent breast density, breast area, and dense area measured per pixel. We converted dense area and breast area measures to area in centimeters using the conversion 6.76×10^4 cm^2/pixel (14). We randomly ordered all images to be read by a single reader in nine batches, with images from the same woman randomly intermixed throughout the same batch. We included five duplicate images in each batch for a total of 45 quality control images. The average difference in quality control samples was 1.1% (SD, 4.8%) for percent density, 8.5 cm^2 (SD, 43.5 cm^2) for dense area, and 0.8 cm^2 (SD, 12.1 cm^2) for breast area, which translates into concordance correlation values of 0.96, 0.97, and 0.999, respectively.

The clinical radiologist assigned Breast Imaging Reporting Data System (BI-RADS; ref. 15) breast density measures as part of the clinical interpretation (1, entirely fat; 2, scattered fibroglandular; 3, heterogeneously dense; 4, extremely dense).

Analysis

We evaluated the crude within women breast density and breast area differences from the follicular to the luteal phase using paired t test. We used linear regression to test whether there were any differences in percent density, dense area, and total breast area between the follicular to luteal phase. We adjusted for difference in weight and time between exams (where time was negative for women whose first mammogram was in the luteal phase) because of their effect on breast density; no other variables were included because women were their own controls. We also complete a sensitivity analyses, excluding women >50 years, women with screening mammograms <12 months apart, obese women (body mass index > 35 kg/m^2), and extremely lean women (body mass index < 18.5 kg/m^2; n = 115 after all exclusions).

Results

Women were on average 45.0 years of age (SD, 4.1 years) and were borderline overweight (body mass index = 25.6; SD, 6.3) at their first exam (data not shown). On average, the two mammograms were 415 days apart (SD, 62.9 days). Just over half (51.0%) of the first mammograms were in the follicular phase of the cycle (Table 1). There was an average change in weight from the follicular to luteal phase of the cycle of 0.25 kg (SD, 4.6 kg). Just over 20% of women lost ≥2 kg, and 24% gained ≥2 kg between exams, 9% lost between 0.5 and 1.9 kg between exams, and 18% gained between 0.5 and 1.9 kg between exams. Percent density strongly decreased with increasing body mass index: 45.4% for <25 kg/m^2, 25.4% for 25% to 29.9% kg/m^2, and 17.2% for ≥30 kg/m^2. Percent breast density and dense breast area had no association with age in this relatively young, premenopausal cohort (data not shown). Percent density and dense area were slightly higher in parous women compared with nonparous women (data not shown). Breast area decreased with age and increased with body mass index (data not shown).

More than half of the women had BI-RADS breast density evaluated as heterogeneously dense, and approximately one quarter of the women had BI-RADS density evaluated as extremely dense and one quarter as scattered fibroglandular (Table 1). We evaluated the distribution of percent breast density by BI-RADS category. The mean (range) percent density was as follows: 2.6% (0.3-3.8) for entirely fatty, 14.6% (0.0-54.3) for scattered fibroglandular, 35.8% (6.5-81.4) for heterogeneously dense, and 59.0% (17.8-87.2) for extremely dense (data not shown).

Figure 1 shows the distribution of percent mammographic breast density differences between the luteal and follicular phases of the menstrual cycle, stratified by the phase of menstrual cycle for the first mammogram under study. The mean [95% confidence interval (95% CI)] percent breast

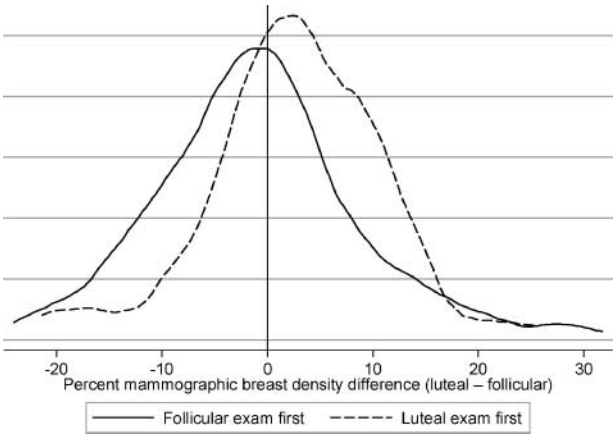

Figure 1. Distribution of percent mammographic breast density difference between the luteal and follicular phases of the menstrual cycle, stratified by the phase of menstrual cycle that came first. Key: Mammographic breast density decreases over time and with age. Thus, we would expect to see a greater increase in percent mammographic breast density between menstrual cycle phases in women who had their first mammogram in the luteal phase (earlier in time and at a younger age).

density was 36% (95% CI, 33-39) in the follicular phase and 37% (95% CI, 34-40) in the luteal phase (Table 2). The range of percent density differences from the follicular to luteal exams was −20.5% to 31.7% (mean = 0.9%; 95% CI, −0.4 to 2.1); 111 women's density increased (mean = 7.2%; SD, 6.3%), and 93 women's density decreased (mean = −6.5%; SD, 5.8%; data not shown).

We observed slightly higher percent density (1.1%) and breast area (16.7 cm^2) and significantly higher dense breast area (13.1 cm^2) in the luteal phase compared with the follicular phase. Differences in breast area were greater between cycles when we limited our analyses to normal weight women, but differences in percent density and breast area were smaller. Limiting the analyses to women ≤50 and to women with ≥12 months between screening exams slightly strengthened our findings for all density outcomes. In analyses limited to normal weight women, women ≤50, and women with ≥12 months between screening mammograms, increases in the luteal phase were smaller and less significant for percent density (0.5%; 95% CI, −0.8 to 1.8) and dense area (8.5 cm^2; 95% CI, −4.6 to 21.7) and larger and more significant for total area (21.6 cm^2; 95% CI, 0.8-42.3).

Discussion

We observed slightly higher percent density, dense area, and breast area in the luteal phase of the menstrual cycle; however, these increases were only statistically significant for dense breast area. Theoretically, any decrease in breast density should help improve mammographic interpretation, with greater differences for women with more dense breasts. However, the question remains as to what magnitude of increase in density measures translates into clinically important differences that could influence mammography performance.

Our observed magnitude of increase in breast density (1.1%) is comparable with results from the only other study that has examined continuous breast density measures in the same women at different phases in the menstrual cycle (10). In Ursin et al.'s study (10), they examined two breast density measures from days 7 to 10 and days 24 to 27 in 11 women ages 30 to 45 years (median = 35 years) using similar measurement strategies to our study. They observed a 1.2% statistically significant increase in breast density in the luteal phase; 55% of the women had an increase.

The previous study examining density by time in the menstrual cycle conducted at Group Health examined the distribution of BI-RADS density categories in different phases among 2,591 different women, rather than comparing density distributions in the same women at different menstrual cycle phases (9). Results from that study showed 23% to 24% of women had extremely dense breasts during the follicular phase compared with 28% during the luteal phase (P = 0.04 adjusted for body mass index). The largest study to date examining the influence of the menstrual cycle on mammographic quality included 8,887 women ages 40 to 44 years enrolled in the Canadian Breast Screening Study where they examined the odds of having a false-negative mammogram in the luteal compared with the follicular phase (11). They found an interaction with estrogen use, where women who had ever used hormones (oral contraceptives or estrogen therapy with or without progesterone) had a 1.5 higher likelihood of having a false-negative exam versus having a true negative exam in the luteal phase. The same relation was not observed in women who never used hormones.

We provided the distribution of percent mammographic breast density by BI-RADS density category to show there is important overlap in percent density measured continuously with categorical BI-RADS density. This is likely due to variation in clinical density interpretation by radiologists and multiple radiologists interpreting density for different women. Consistent with findings from other studies, our continuous

Table 2. Crude and multivariable adjusted percent mammographic breast density, dense breast area, and total breast area and 95% CI in luteal compared with follicular phase of the menstrual cycle for 204 premenopausal women

	Mean percent density (95% CI)	Mean dense breast area (95% CI), cm^2	Mean total breast area (95% CI), cm^2
Follicular phase*	36 (33-39)	312 (283-341)	940 (895-985)
Luteal phase†	37 (34-40)	324 (296-351)	958 (913-1002)
	Mean difference: luteal-follicular (95% CI)	Mean difference: luteal-follicular (95% CI)	Mean difference: luteal-follicular (95% CI)
Crude difference	0.9 (−0.4 to 2.1)	11.5 (−1.9 to 24.9)	17.4 (−2.0 to 36.9)
P	0.179	0.093	0.079
Adjusted difference‡	1.1 (−0.2 to 2.3)	13.1 (0.1-26.1)	16.7 (−2.8 to 36.2)
P	0.089	0.048	0.092

*Days 7 to 15 or week 2 of cycle.
†Days 21 to 35 or week 4 of cycle.
‡Adjusted for weight change and time between exams.

measure of percent density should have greater precision and thus greater ability to detect important changes in mammographic density between menstrual cycles than BI-RADS measures (16, 17).

We found slightly higher differences between phases for all density measures when we excluded women >50 years and when we excluded women with screening mammograms <12 months apart. Women >50 years are more likely to be perimenopausal and/or to have anovulatory menstrual cycles, supporting a slightly stronger relation between density and luteal phase. However, when we excluded obese women and very lean women, another group of women who are more likely to have anovulatory cycles, we saw greater differences in total breast area and smaller differences in percent density and dense area. Studies examining the effects of menstrual cycle phase are limited when menstrual cycle timing is based on recall (18) and when there are no serum measures of estradiol and progesterone to account for anovulatory cycles (19).

There are additional exposure measurement issues that deserve mention. We did not have information on the average menstrual cycle length for women, which could influence comparison time periods between women. However, we were careful to exclude women who self-reported irregular menstrual cycles or infrequent periods and women who were in day ≥35 of their menstrual cycle. In addition, our data collection instrument changed in mid-2001 from collecting specific day in the menstrual cycle to week in the cycle. We chose *a priori* to compare density readings from weeks 2 and 4 of the cycle, based on our previous findings of the greatest proportion of women having extremely dense BI-RADS rating during these two time points (9) and to ensure we were examining weeks far enough apart in a woman's cycle that they may have truly represented different phases in the menstrual cycle. However, progesterone levels are highest in week 3 of the menstrual cycle. We could have missed seeing clinically meaningful differences in breast density and breast area due to measurement error from any one of the above reasons.

The distribution of mammographic breast density we observed in this study is as would be expected in a group of premenopausal women: shifted towards higher breast density (4), suggesting our results should be generalizable to other populations of premenopausal women.

In summary, there are small but probably not clinically meaningful increases in percent breast density, dense area, and breast area in the luteal phase of the menstrual cycle. However, there are other potentially important factors that may differ by menstrual cycle phase that we were not able to assess (e.g., breast compression), which may ultimately influence mammographic sensitivity by menstrual cycle phase.

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