REPORTS

Variation in Mammographic Breast Density by Time in Menstrual Cycle Among Women Aged 40–49 Years

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Background: **Mammography is less effective for women aged 40–49 years than for older women, which has led to a call for research to improve the performance of screening mammography for younger women. One factor that may influence the performance of mammography is breast density. Younger women have greater mammographic breast density on average, and increased breast density increases the likelihood of false-negative and false-positive mammograms. We investigated whether breast density varies according to time in a woman's menstrual cycle.** ***Methods:*** **Premenopausal women aged 40–49 years who were not on exogenous hormones and who had a screening mammogram at a large health maintenance organization during 1996 were studied (n = 2591). Time in the menstrual cycle was based on the woman's self-reported last menstrual bleeding and usual cycle length.** ***Results:*** **A smaller proportion of women had ''extremely dense'' breasts during the follicular phase of their menstrual cycle (24% for week 1 and 23% for week 2) than during the luteal phase (28% for both weeks 3 and 4) (two-sided *P* = .04 for the difference in breast density between the phases, adjusted for body mass index). The relationship was stronger for women whose body mass index was less than or equal to the median (two-sided *P*<.01), the group who have the greatest breast density.** ***Conclusions/Implications:*** **These findings are consistent with previous evidence suggesting that scheduling a woman's mammogram during the follicular phase (first and second week) of her menstrual cycle instead of during the luteal phase (third and fourth week) may improve the accuracy of mammography for premenopausal women in their forties. Breast tissue is less radiographically dense in the follicular phase than in the luteal phase. [J Natl Cancer Inst 1998;90:906–10]**

Routine screening by mammography has been clearly shown to reduce mortality from breast cancer *(1).* However, the benefits are less for women under the age of 50 years *(2–7),* which has led to a controversy as to whether women aged 40–49 years should be regularly screened by mammography *(8).* Mammography has been shown to be less sensitive *(2,3),* less specific *(4–6),* and less effective in terms of reducing mortality *(7)* among women aged 40–49 years than in older women. Nonetheless, mammography is recommended for women in their forties by most organizations that make screening recommendations *(1,8),* and the use of mammography is high among younger women *(1,9).*

One hypothesis as to why mammography is not as effective among younger women is that a higher proportion of young women have dense breast tissue *(10–13),* and increasing breast density decreases the detection of cancer, i.e., reduces the sensitivity of mammography *(14,15).* Increased breast density may also reduce the specificity of mammography by leading to a greater need for additional work-up of uncertain mammographic findings [*(16);* Lehman et al.[1]]. Thus, it is likely that increased breast density explains, at least in part, the reduced sensitivity and reduced specificity of mammography among younger women.

Recently, a panel of experts who participated in the National Institutes of Health Consensus Conference on Breast Cancer Screening for Women Ages 40–49 emphasized the need for research on new approaches to improve the performance of mammography among younger women *(17,18).* One such approach may be to screen women at a time in their menstrual cycle that is optimal in terms of the accuracy of screening *(19).* A recent study by Baines et al. *(20)* reported a sensitivity of 60% for women in their forties who were screened during the follicular phase of their menstrual cycle compared with 49% for women who were screened during the luteal phase, although this difference was not statistically significant. We investigated whether breast density varies by time in the menstrual cycle. Evidence for such an association is supported by pathologic studies *(21–23)* of changes in the breast structure during the menstrual cycle and by studies *(24–27)* that show a hormonal influence on mammographic breast density.

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See ''Notes'' following ''References.''

Subjects and Methods

Sample Selection and Data Collection

Eligible subjects were premenopausal women aged 40–49 years who had a screening mammogram during the period from June 1, 1996, through December 31, 1996, in one of six regional mammography centers of the Group Health Cooperative, a large staff-model health maintenance organization. Women aged 40–49 years at Group Health Cooperative have a mammogram when referred by their physicians; in addition, women with at least one risk factor (family history of breast cancer, nulliparity, late age at first birth, or early age at menarche) are sent an invitation/reminder as part of the centralized Breast Cancer Screening Program *(28).* No woman was included more than once in this analysis.

At the time of their mammogram, the women in this study completed a self-administered questionnaire on demographic factors and breast cancer risk factors, including age at first birth, personal and family history of breast cancer, height, and weight. Questions were also asked about their menstrual status, their use of oral contraceptives and hormone replacement therapy, the date when their last menstrual period began, and the usual length of their menstrual cycle. These procedures were approved by the Group Health Cooperative Institutional Review Board, in accord with an assurance filed with and approved by the U.S. Department of Health and Human Services.

The mammograms were read by 26 radiologists. The radiologists recorded breast density according to the classification system of the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) *(29).*

Of 5755 age-eligible women, 5581 (97%) completed the questionnaire. Of these, 1882 were ineligible because they were not having regular menstrual periods (defined as a woman's self-report of no longer having periods, of not having periods regularly, or of a last menstrual period more than k days prior to the mammogram, where k = the reported average cycle length plus 7 days) or because they reported having regular periods but were currently on hormone replacement therapy. Other exclusionary criteria were a history of breast cancer (n = 47), breast augmentation (n = 58), currently using oral contraceptives (n = 291), and an indication for examination (as recorded by the radiologist) specified as the evaluation of a breast problem, follow-up of a prior indeterminate mammogram, or not specified (n = 342). A further 370 (12%) of the 2961 eligible women were omitted from our analysis because one of the key data items (date of last menstrual period, cycle length, or breast density) was missing. Thus, 2591 eligible women with complete data were available for analysis.

Variable Definition and Data Analysis

Time in the woman's menstrual cycle was based on the date of the mammogram, her self-reported date of last menstrual period, and her self-reported usual cycle length. The question addressing the last item allowed three categories of response: 25 days or fewer, 26–30 days, and 31 days or more. For purposes of our analysis, these categories were assumed to be 24, 28, and 32 days, respectively. The date of the next menstrual period was estimated by adding the cycle length to the date of the last period. Because the luteal phase of the menstrual cycle is fairly consistently the 12–15 days before menstrual bleeding, independent of cycle length [page 4 of *(30)*], we defined week of menstrual cycle by counting backward from the estimated date of the next cycle. We defined week 4 as the 7 days before the estimated date of the next cycle, week 3 as the 8th to 14th day before the next cycle, week 2 as the 15th to 21st day before the next cycle, and week 1 as more than 21 days before the next cycle. Women whose mammogram was up to 7 days after the estimated date of the next cycle (i.e., those whose menstrual period was up to 7 days overdue) were also placed in week 4. Women whose menstrual period was more than 7 days overdue were omitted (*see above*).

Breast density was recorded as ''almost entirely fat,'' ''scattered fibroglandular tissue,'' ''heterogeneously dense,'' or ''extremely dense,'' based on the BI-RADS classification system *(29).* For the less than 1% of women for whom breast density differed between breasts, we chose the more dense category. Because only 103 (4.0%) of the study subjects had density classified as ''almost entirely fat,'' this category was combined with ''scattered fibroglandular tissue'' to form the category ''predominantly fat.''

The associations of time in menstrual cycle and other factors with breast density were tested by maximum likelihood ordered logistic regression models, with the use of two-sided statistical tests. Density was the dependent variable and was coded as a three-level ordinal variable. Time in menstrual cycle was tested two ways: as a four-value categorical variable representing week in the cycle and as follicular (weeks 1 and 2) versus luteal (weeks 3 and 4) phase. Adjustment factors were included in the model if they changed the β-coefficient for the association of menstrual phase with breast density by 10% or more. Body mass index was calculated as weight in pounds divided by height in inches squared and was included as an adjustment factor in all models as a categorical variable representing octiles of the distribution. Other adjustment factors tested were education, age at first birth, and length of menstrual cycle (as linear variables) as well as race and family history of breast cancer (as categorical variables). None of these factors met our criteria for inclusion in the model. Women with information missing on the adjustment factors (0%–1.7%) were excluded from analyses that included the factor.

Results

Table 1 presents the study population stratified by age, race, quartiles of body mass index, age at first birth, family history of breast cancer (first- or second-degree relative), and length of menstrual cycle. More than 85% of the population was white, and 60% had some education beyond high school (data not shown), a reflection of both the Group Health Cooperative population and the self-selection for mammography in this younger population. As expected, a large proportion of the women had breast cancer risk factors, including a family history of breast cancer (45%), nulliparity (32%), or late age at first birth (29%), because these factors initiated an invitation/reminder from the Breast Cancer Screening Program.

Table 1 also gives the association of demographic and other characteristics with mammographic breast density. Body mass index had the strongest association with breast density. Fifty-three percent of women in the lowest quartile of body mass index were characterized as having extremely dense breasts compared with 5% of the women in the highest quartile of body mass index. Race, age at first birth, and length of menstrual cycle were also associated with breast density, even after adjustment for body mass index.

For all women combined, phase in the menstrual cycle was associated with breast density after adjustment for body mass index (P = .04) (Table 2). Further adjustment for age, race, education, age at first birth, nulliparity, family history of breast cancer, and length of menstrual cycle did not change the magnitude of the effect (data not shown). A larger proportion of women were categorized as having extremely dense breasts during the luteal phase (28% for both weeks 3 and 4) than during the follicular phase (24% for week 1 and 23% for week 2). The effect of time in the cycle was not statistically significant (P = .19) when expressed as a four-category week-in-cycle variable.

The association of time in cycle with density was generally similar in subgroups of women characterized by the factors in Table 1 (data not shown). However, when we stratified women by body mass index (less than or equal to versus above the median), the association of menstrual phase with density was stronger for women whose body mass index was less than or equal to the median (P<.01) and not apparent for those whose body mass index was above the median (P = .86) (Table 2). Among the leaner women, those who had mammograms during the luteal phase of their cycles were more likely to be classified as having extremely dense breasts (46% for week 3 and 45% for week 4) than those who had their mammograms during the follicular phase (40% for week 1 and 35% for week 2) (P = .04 for variation by week in cycle and P<.01 for follicular

Table 1. Distribution of women aged 40–49 years, by mammographic breast density and demographic and other characteristics

Characteristic	No. of women*	Mammographic breast density			Body mass-adjusted *P* value‡
		Predominantly fat,† %	Heterogeneously dense, %	Extremely dense, %	
Age, y					
40–44	1430	32	41	27	
45–49	1161	30	46	24	.56
Race					
White (non-Hispanic)	2248	33	43	24	
Black/African-American	90	26	46	29	<.001
Asian/Pacific-Islander	156	15	37	48	<.01
Hispanic	63	35	49	16	.29
Other	34	29	50	21	.24
Quartiles of body mass index§					
Lowest	631	8	40	53	
2nd	640	22	48	31	<.001
3rd	616	33	52	16	
Highest	660	60	35	5	
Age at first birth, y					
<25	558	39	44	17	
25–29	446	34	45	22	<.001
⩾30	732	28	44	28	
Nulliparous	825	27	41	32	
Family history of breast cancer					
No	1431	31	43	26	
Yes (first- or second-degree relative)	1160	32	44	25	.86
Length of menstrual cycle, days					
⩽25	596	28	46	26	
26–30	1839	31	43	26	.04
⩾31	156	47	33	21	

*Some groups of women may not add up to total because of missing data.
†Includes American College of Radiology Breast Imaging codes for ''almost entirely fat'' and ''scattered fibroglandular tissue'' *(29)*.
‡Two-sided.
§Body mass index (BMI) = weight divided by height square.

Table 2. Association of time in menstrual cycle with mammographic breast density among women aged 40–49 years, for all women and women stratified by body mass index (BMI)*

	Week in menstrual cycle†	No. of women	Mammographic breast density			BMI-adjusted *P* value (two-sided) for week§	BMI-adjusted *P* value (two-sided) for phase‖
			Predominantly fat,‡ %	Heterogeneously dense, %	Extremely dense, %		
All women	1	545	34	42	24		
	2	650	29	48	23	.19	.04
	3	643	32	41	28		
	4	753	31	41	28		
BMI ⩽ median	1	266	15	45	40		
	2	326	17	48	35	.04	<.01
	3	310	14	41	46		
	4	370	14	41	45		
BMI > median	1	269	52	41	8		
	2	315	41	48	11	.26	.86
	3	322	48	41	11		
	4	370	47	41	12		

*BMI = weight divided by height squared.
†*See* ''Subjects and Methods'' section for classification scheme.
‡Includes American College of Radiology Breast Imaging Reporting and Data System codes for ''almost entirely fat'' and ''scattered fibroglandular tissue'' *(29)*.
§*P* value for association of week (as a four-value categorical variable) with breast density (three-level ordinal variable).
‖*P* value for association of follicular phase (weeks 1 and 2) versus luteal phase (weeks 3 and 4) with breast density (three-level ordinal variable).

versus luteal phase, adjusted for body mass index).

When we further divided each week in the menstrual cycle into two time periods, we found a large variation in breast density over the menstrual cycle (data not shown). Women whose mammograms were on the last 3 days of week 2 had the lowest percentage with extremely dense breasts (19%), and those with mammograms on the first 4 days of week 4 had the highest percentage (30%).

Discussion

We found that, for premenopausal women aged 40–49 years, there was a small but statistically significant variation in breast density by time in the menstrual cycle. Having a mammogram during the follicular phase reduced the likelihood of breast density being classified as ''extremely dense'' in comparison with having a mammogram during the luteal phase. This association (decreased breast density in the follicular phase of the menstrual cycle) was stronger for women whose body mass index was equal to or lower than the median, a group that is much more likely to be characterized as having extremely dense breasts, than for women whose body mass index was above the median.

It is biologically plausible that mammographic breast density, which is a measure of the proportion of the breast occupied by connective and epithelial tissue, would vary by time in the menstrual cycle as a result of the effects of variation in the levels of circulating hormones. Evidence suggests that increased hormone levels are associated with increased breast density. Premenopausal women have more dense breasts than postmenopausal women of the same age *(11–13)*. Meyer et al. *(27)* found that premenopausal women classified as P2 or DY by the Wolfe classification of mammographic parenchymal patterns had somewhat higher levels of luteal phase progesterone but not estrogen. In addition, hormone replacement therapy has been reported to reduce the age-related decline in breast density and, in some women, to increase breast density *(24–26)*. There is also evidence from pathologic studies *(21–23)* of human breast tissue that epithelial cell proliferation, lobule size, and stromal edema are all greater in the luteal phase.

Magnetic resonance imaging (MRI) studies of the breast *(31,32)* further support our findings. A study by Fowler et al. *(31)*, in which eight premenopausal women had repeated MRI scans across several menstrual cycles, found that parenchymal volume increased during the luteal phase. The lowest volume was found immediately before ovulation, and the volume increased by 39% during the luteal phase. The increase during the second half of the cycle was not due solely to an increased water content of tissue, but it was also due to increased tissue growth. Graham et al. *(32)* found similar results.

Therefore, our general finding of lower breast density during the follicular phase than during the luteal phase is consistent with several lines of research *(21–27)*. In addition, our finding of the time of the lowest density in the days before ovulation and the highest density several days before the start of the next cycle is consistent with the two MRI studies *(31,32)*.

One limitation of this study is the measurement error inherent in rating breast density and in the woman's self-report of time in the menstrual cycle. Breast density was classified by use of the standardized BI-RADS rating scheme *(29)*, but it was measured by multiple radiologists, which would have increased the variability of the measure. However, our measure of density was sufficiently precise to be associated with multiple risk factors (Table 1) consistent with the findings of others *(11–13)*. Our measure of time in the menstrual cycle was based on the woman's self-report of her last menstrual bleeding and of her usual cycle length. Because we asked about cycle length, we were able to separate the follicular phase from the luteal phase more accurately; nonetheless, there could be substantial misclassification. However, the measurement error in the measures of breast density and week in the cycle should be independent; i.e., it is unlikely that there could be systematic errors between the woman's self-reporting of her menstrual cycle and the radiologist's reporting of mammographic breast density. If the measurement errors were independent, our results would be an underestimate of the true association *(33)*. On the other hand, the measure of self-reported time in the menstrual cycle reflects the type of measure that would be used in actual clinical practice, so the relationship presented here reflects the amount of difference in breast density one might expect if mammograms were timed on the basis of a woman's self-report of her menstrual cycle.

Another study limitation is that, since this was an observational study, the results are subject to confounding factors associated with both time in the menstrual cycle and breast density, which could have led to a spurious association between them. While body mass index and several breast cancer risk factors were associated with breast density, none of these factors would be expected to be associated with the time a women comes in for a mammogram. Furthermore, statistical adjustment for multiple predictors of density had little effect on the findings.

The importance of the findings of this study relates to the fact that radiographic breast density is associated with a decrease in the sensitivity of mammography *(14,15)* and a decrease in the specificity [*(16);* Lehman et al.[1]]. Thus, timing mammograms to coincide with a woman's follicular phase of her cycle might improve the accuracy of mammography for women in their forties. Our results support the findings from a recent study by Baines et al. *(20)* of younger women in the Canadian National Breast Screening Study. Baines et al. found a lower sensitivity (49%) for mammograms obtained during the luteal phase than during the follicular phase (60%) among women aged 40–44 years at the onset of screening. However, this difference was not statistically significant, which was partly a result of the great difficulty of collecting information on sufficient numbers of women with false-negative mammograms so that factors associated with sensitivity could be studied. (In the study by Baines et al., of the approximately 32 000 mammograms among young women, 39 were classified as false-negatives.) The Canadian study *(20)* did find a statistically significantly greater risk of a false-negative versus a true-negative mammographic examination during the luteal phase than during the follicular phase for young women who ever used exogenous hormones (i.e., a significantly lower predictive value of a negative examination). Baines et al. found no difference in specificity by phase of menstrual cycle.

Several considerations may limit the implications of our findings as suggestive that the timing of mammograms would improve diagnostic accuracy. First, although fewer women had extremely dense breasts during the follicular phase than during the luteal phase, much of the shift was into the heterogeneously dense category. The association between density and sensitivity *(14,15)* and between density and specificity (Lehman et al.[1]) appears to be linear, with the greatest accuracy in the fatty categories. Thus, the shift in density observed in this study may have limited impact on the accuracy of mammography.

Also, there are other possible reasons for the decreased effectiveness of mammography among younger women other than any effect of breast density. In particular, sensitivity might be reduced among younger women as a result of a faster tumor growth rate *(34)*, which could increase the likelihood that the tumor would become clinically detectable between screenings.

There are also practical limitations to scheduling a mammogram during the follicular phase of the menstrual cycle. Women cannot always predict when their cycle will begin, and it would add a level of complexity to the task of scheduling mammograms. On the other hand, many women experience breast tenderness during the end of the luteal phase *(30)*, so avoiding this time could reduce the discomfort of mammography.

In conclusion, to our knowledge, this is the first study to report an association between phase of the menstrual cycle and mammographic breast density. The results from this study are consistent with the suggestive findings of Baines et al. *(20)* that sensitivity of mammography appears to be greater during the follicular phase. If these results are confirmed by future studies, timing of a woman's mammographic examination during the follicular phase of her menstrual cycle may improve the accuracy of mammography for women in their forties.

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Notes

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