Radiology

Accuracy of Screening Mammography Varies by Week of Menstrual Cycle[1]

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Purpose: To investigate sensitivity, specificity, and cancer detection rate of screening mammography according to week of menstrual cycle among premenopausal women.

Materials and Methods: In this institutional review board–approved HIPAA-compliant study, sensitivity, specificity, and cancer detection rate of 387 218 screening mammograms linked to 1283 breast cancers in premenopausal women according to week of menstrual cycle were studied by using prospectively collected information from the Breast Cancer Surveillance Consortium. Logistic regression analysis was used to test for differences in mammography performance according to week of menstrual cycle, adjusting for age and registry.

Results: Overall, screening mammography performance did not differ according to week of menstrual cycle. However, when analyses were subdivided according to prior mammography, different patterns emerged. For the 66.6% of women who had undergone regular screening (mammography had been performed within the past 2 years), sensitivity was higher in week 1 (79.5%) than in subsequent weeks (week 2, 70.3%; week 3, 67.4%; week 4, 73.0%; P = .041). In the 17.8% of women who underwent mammography for the first time in this study, sensitivity tended to be lower during the follicular phase (week 1, 72.1%; week 2, 80.4%; week 3, 84.6%; week 4, 93.8%; P = .051). Sensitivity did not vary significantly by week in menstrual cycle in women who had undergone mammography more than 3 years earlier. There were no clinically meaningful differences in specificity or cancer detection rate.

Conclusion: Premenopausal women who undergo regular screening may benefit from higher sensitivity of mammography if they schedule screening mammography during the 1st week of their menstrual cycle.

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Screening with mammography has been clearly shown to reduce mortality from breast cancer among women aged 40–69 years (1,2). However, on balance, the benefits of screening are less advantageous for women younger than 50 years (1–7), leading to controversy regarding whether women aged 40–49 years should undergo routine mammographic screening (8,9). Screening mammography is less sensitive (4–6) and less specific (5) in women aged 40–49 years than in older women. Improving the interpretive performance of mammography in premenopausal women could increase the net benefit of screening.

One explanation as to why screening mammography is less accurate in younger women is that they have a higher mammographic breast density than do older women (5,10–16). Previously, we reported that increased mammographic density explained 68% of the excess risk of having a false-negative result with mammography for women in their 40s compared with older women (17). Thus, the accuracy of mammography among premenopausal women might improve with screening at a point in their menstrual cycle when breast density is lower; several studies suggest this may occur during the follicular phase, which is the first half of the cycle (18–21). However, recent studies performed with continuous measures of breast density have shown that breast density changes during the menstrual phase are small and may not translate to clinically important improvements in mammography by themselves (20,21). To our knowledge, the only study in which researchers directly examined screening mammography accuracy according to menstrual cycle phase yielded inconclusive results (22). The researchers found that screening mammography performed during the follicular phase was 10% more sensitive and no more specific than screening mammography performed during the luteal phase; however, this difference was not significant because of the small number of women with cancer (n = 84).

Our purpose was to investigate the sensitivity, specificity, and cancer detection rate of screening mammography according to week of menstrual cycle among premenopausal women.

Advances in Knowledge

- For subsequent screening mammography performed in patients who had undergone mammography in the past 2 years, sensitivity was highest in week 1 of the menstrual cycle (79.5%) and lower in later weeks (week 2, 70.3%; week 3, 67.4%; week 4, 73.0%).
- For first screening mammography, sensitivity tended to be lower during the follicular phase (first half of the menstrual cycle) than during the luteal phase (second half of the menstrual cycle) (week 1, 72.1%; week 2, 80.4%; week 3, 84.6%; week 4, 93.8%).
- No clinically meaningful differences in specificity or cancer detection rates according to week of menstrual cycle were detected.

Implication for Patient Care

- Premenopausal women who undergo regular screening mammography may benefit from higher sensitivity if they schedule their examination during the 1st week of their menstrual cycle.

Materials and Methods

Study Population

Information was collected at the following six National Cancer Institute–funded Breast Cancer Surveillance Consortium mammography registries *(http://breastscreening.cancer.gov)* (23): Carolina Mammography Registry, Colorado Mammography Project, New Hampshire Mammography Network, New Mexico Mammography Project, Vermont Breast Cancer Surveillance System, and Group Health Cooperative in western Washington. At the registries, workers collected demographic and clinical information, including radiologists' assessments and recommendations based on the mammographic interpretation, as well as patient risk factors, at each mammographic examination. Data were pooled at a central Statistical Coordinating Center (Seattle, Wash) for analysis. Each registry and the Statistical Coordinating Center received institutional review board approval for active or passive consenting processes or a waiver of consent to enroll participants, link data, and perform analytic studies. All procedures were compliant with the Health Insurance Portability and Accountability Act, and all registries and the Statistical Coordinating Center received a Federal Certificate of Confidentiality and other protection for the identities of women, physicians, and facilities.

We included both screen-film and digital screening mammograms obtained between 1996 and 2007 in premenopausal women aged 35–54 years with no history of breast cancer, mastectomy, or breast augmentation; these images had been interpreted by more than 770 radiologists. Women were considered premenopausal if they reported that their last menstrual period began no more than 35 days before the date of mammography and that they were not currently using hormone therapy. We excluded mammograms in women who reported oral contraceptive use at the time of the examination (n = 42 214, 9.8%). We excluded women whose last menstrual period occurred more than 35 days before mammography.

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Abbreviation:
BI-RADS = Breast Imaging Reporting and Data System

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Potential conflicts of interest are listed at the end of this article.

Data Collection and Definitions

Demographic and risk factor information, including birth date, race, ethnicity, menopausal status, hormone therapy use, oral contraceptive use, height, weight, and time since last mammography were collected with a questionnaire at each mammographic examination. For date of last menstrual period, one registry asked women to provide the date of their last menstrual period; two registries asked women to provide the date of the 1st day or the beginning of their last menstrual period; two registries asked in either of these ways in different study years; and one registry asked for the 1st day of the last menstrual period either as a date or as 1–7, 8–14, 15–21, 22–35, or more than 35 days ago depending on the study year (24). We used the self-reported time since last menstrual period to calculate each woman's week in her menstrual cycle on the day of mammography, as follows: week 1, 0–7 days since last menstrual period; week 2, 8–14 days since last menstrual period; week 3, 15–21 days since last menstrual period; and week 4, 22–35 days since last menstrual period. The follicular phase was defined as week 1 or 2. The luteal phase was defined as week 3 or 4.

Mammography was considered a screening examination if the radiologist or technician indicated the examination was performed for routine screening and if he or she obtained bilateral routine images (25). To avoid misclassifying diagnostic mammography as a screening examination, we excluded mammograms obtained in women who had undergone a breast imaging examination within the prior 9 months.

Mammograms were classified as first mammograms when the Breast Cancer Surveillance Consortium database contained no prior mammograms, no indication of comparison images, and no self-report of prior mammography. Mammograms were classified as subsequent mammograms if they were obtained in a patient who *(a)* had undergone mammography within the prior 2 years or *(b)* had undergone mammography more than 3 years previously. Classification was based on a combination of mammograms in the database and on the self-reported date of last mammography, as recorded on the questionnaire.

The American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) four-category terminology was used to classify mammographic breast density as almost entirely fat, scattered fibroglandular tissue, heterogeneously dense, or extremely dense (26). Mammographic assessments were collected by using the BI-RADS lexicon (26). We considered a mammogram positive if it was given a BI-RADS score of 0 (additional imaging evaluation needed), 4 (suspicious abnormality), or 5 (highly suggestive of malignancy) or if it was given a score of 3 (probably benign finding), with a recommendation for immediate follow-up (25). We considered a mammogram negative if it was given a BI-RADS score of 1 (negative) or 2 (benign finding) or if it was given a score of 3 (probably benign finding), with either no recommendation for follow-up or a recommendation for short-interval or routine follow-up (25).

To determine cancer status after mammography, each mammography registry linked to a state cancer registry or regional Surveillance, Epidemiology, and End Results program. Five of the six sites also linked to pathology databases. A woman was considered to have breast cancer if she received a diagnosis of invasive carcinoma or ductal carcinoma in situ within 12 months after screening mammography and before her next mammographic screening (25).

We calculated the sensitivity of mammography as the proportion of positive mammograms among women in whom breast cancer was diagnosed within 1 year after their examination (25,26). Specificity was defined as the proportion of negative mammograms among women without cancer during 1-year follow-up (25,26). The cancer detection rate was calculated as the proportion of mammograms with a positive assessment and that resulted in the diagnosis of cancer within 12 months after the examination. Data are presented as a rate per 10000 mammograms (25,26).

Statistical Analysis

We calculated the distributions of population characteristics and mammogram outcomes by week of menstrual cycle. We used a χ^2 test to compare the age distribution at first mammography versus that at subsequent mammography.

Since mammography performance and characteristics of screen-detected cancers depend on prior mammography exposure (27), analyses were performed overall and subdivided according to prior mammography. Unadjusted sensitivity, specificity, and cancer detection rate, as well as exact binomial 95% confidence intervals, were calculated according to week of menstrual cycle. We used logistic regression to test for associations between these performance measures and week of menstrual cycle, adjusting for age (as a continuous linear term) and mammography registry. To compare sensitivity (or equivalently, false-negative rates), we modeled the odds of a negative mammogram among women in whom breast cancer was diagnosed. To compare specificity (or equivalently, false-positive rates), we modeled the odds of a positive mammogram among women without a breast cancer diagnosis. Odds ratios are reported with 95% likelihood ratio confidence intervals, with week 4 selected as the reference group because the biologic activity in the breast is greatest in that week. Reported *P* values were calculated with likelihood ratio tests, testing for an overall association between week of menstrual cycle and each performance measure.

We examined histology and tumor size of cancers detected at first mammography versus these detected at subsequent mammography.

We conducted several sensitivity analyses to assess the potential influence of differences in data collection and our inclusion criteria on study results. We repeated all analyses by excluding data from individual registries one at a time. We restricted analyses to sites that specifically ask for the 1st day or beginning of the last menstrual period. We excluded obese (body mass index ≥30) and underweight (body mass index <18.5) women, because weight can influence the hormonal balance and menstrual cycle. We removed women whose time since last menstrual cycle exceeded 28 days to omit long menstrual cycles that are

more likely to be anovulatory. We estimated models separately for women aged 35–44 years and women aged 45–54 years to account for the relation between age and whether the screening was first mammography or subsequent mammography.

We used a two-sided α value of .05 to determine statistical significance. Analyses were performed with statistical software (SAS, version 9.2; SAS Institute, Cary, NC).

Results

We included 387 218 screening mammograms obtained in premenopausal women (Table 1). Women included in the study were primarily aged 40–49 years. Only 17.8% of mammograms were first mammograms, and 66.6% of women had undergone previous mammography within the prior 2 years. Age, prior mammography, breast symptoms, and BI-RADS breast density did not vary by week of menstrual cycle. Women who had not undergone prior mammography were younger than women who had ($P < .001$): Of the 64 258 women who were undergoing mammography for the first time, 36.1% were aged 35–39 years, 50.8% were aged 40–44 years, 10.7% were aged 45–59 years, and only 2.4% were aged 50–54 years. In contrast, of the 296 706 women who were undergoing subsequent mammography, only 5.9% were aged 35–39 years, 41.0% were aged

Table 1

Distribution of Population Characteristics and Mammography Outcomes by Week in Menstrual Cycle among 387 218 Screening Mammograms in Premenopausal Women between 1996 and 2007

Characteristic	1st Week in Menstrual Cycle (n = 109 437)	2nd Week in Menstrual Cycle (n = 102 919)	3rd Week in Menstrual Cycle (n = 91 092)	4th Week in Menstrual Cycle (n = 83 770)
Age (y)				
35–39	13 164 (12.0)	12 265 (11.9)	11 094 (12.2)	10 315 (12.3)
40–44	47 290 (43.2)	45 232 (43.9)	39 712 (43.6)	34 423 (41.1)
45–49	36 891 (33.7)	34 390 (33.4)	30 494 (33.5)	28 072 (33.5)
50–54	12 092 (11.0)	11 032 (10.7)	9792 (10.7)	10 960 (13.1)
Prior mammography				
None	18 254 (17.9)	16 941 (17.6)	15 319 (18.0)	13 744 (17.6)
≤2 years prior	67 446 (66.2)	64 197 (66.8)	56 501 (66.5)	52 115 (66.8)
3–4 years prior	9667 (9.5)	8878 (9.2)	7742 (9.1)	7171 (9.2)
>5 years prior	6489 (6.4)	6130 (6.4)	5419 (6.4)	4951 (6.3)
Missing*	7581 (6.9)	6773 (6.6)	6111 (6.7)	5789 (6.9)
Most severe breast symptom reported				
Lump	2517 (2.4)	2366 (2.4)	2152 (2.4)	1878 (2.3)
Nipple discharge	618 (0.6)	560 (0.6)	510 (0.6)	445 (0.5)
Pain	2007 (1.9)	1902 (1.9)	1776 (2.0)	1434 (1.7)
Other/not otherwise specified	1875 (1.8)	1851 (1.8)	1629 (1.8)	1428 (1.7)
None	100 068 (93.4)	93 982 (93.4)	83 112 (93.2)	76 931 (93.7)
Missing*	2352 (2.1)	2258 (2.3)	1913 (2.2)	1654 (2.1)
BI-RADS breast density				
Almost entirely fat	3385 (3.5)	3132 (3.4)	2813 (3.5)	2849 (3.9)
Scattered fibroglandular tissue	31 631 (32.7)	29 262 (32.2)	26 175 (32.6)	25 222 (34.3)
Heterogeneously dense	47 405 (49.0)	44 867 (49.4)	39 174 (48.8)	35 216 (47.8)
Extremely dense	14 290 (14.8)	13 645 (15.0)	12 094 (15.1)	10 313 (14.0)
Missing*	12 726 (11.6)	12 013 (11.7)	10 836 (11.9)	10 170 (12.1)
Mammogram assessment				
Negative	95 876 (87.6)	90 209 (87.7)	79 807 (87.6)	73 750 (88.0)
Positive	13 561 (12.4)	12 710 (12.3)	11 285 (12.4)	10 020 (12.0)
Cancer within 12 Months				
No	109 059 (99.7)	102 587 (99.7)	90 781 (99.7)	83 508 (99.7)
Yes	378 (0.3)	332 (0.3)	311 (0.3)	262 (0.3)
Finding				
True-positive (sensitivity)	299 (79.1)	256 (77.1)	225 (72.3)	207 (79.0)
False-negative	79 (20.9)	76 (22.9)	86 (27.7)	55 (21.0)
True-negative (specificity)	95 797 (87.8)	90 133 (87.9)	79 721 (87.8)	73 695 (88.2)
False-positive	13 262 (12.2)	12 454 (12.1)	11 060 (12.2)	9813 (11.8)

Note.—Data are numbers of women. Data in parentheses are percentages. Unless otherwise indicated, percentages were calculated for women with known values.

* Percentages were calculated for the total number of women.

40–44 years, 39.4% were aged 45–49 years, and 13.8% were aged 50–54 years.

We found that 12.3% of mammograms were positive, and 0.3% of mammograms led to a diagnosis of breast cancer. Overall, the percentage of true-positive (sensitivity) and true-negative (specificity) mammograms did not differ significantly (P = .21 and P = .14, respectively) by week in menstrual cycle; however, sensitivity was lower in week 3 (72.3%) than in other weeks (77.1%–79.1%) (Table 1).

When we subdivided the sample according to prior mammography, different patterns emerged within the strata (Tables 2, 3). In women undergoing mammography for the first time, a borderline significant association between week in menstrual cycle and sensitivity was observed after adjusting for age and registry (P = .051), with weeks 1 and 2 having lower sensitivity (72.1% and 80.4%, respectively), and thus higher false-negative rates, than weeks 3 and 4 (84.6% and 93.8%, respectively). The greatest estimated difference in odds of a false-negative finding was between weeks 1 and 4 (odds ratio, 6.04; 95% confidence interval: 1.50, 40.90; P = .009).

For subsequent mammography performed within 2 years after the previous examination (Table 2), sensitivity varied significantly with week in menstrual cycle after adjusting for age and registry (P = .041): Week 1 had the highest sensitivity (79.5%) compared with weeks 2, 3, and 4 (sensitivity, 67.4%–73.0%). For women in whom previous mammography had been performed 3 or more years prior, unadjusted sensitivity was highest during the follicular phase (82.8%–93.1% vs 78.3%–85.1% in the luteal phase). For this subgroup, the logistic regression model adjusting for both age and registry did not converge because of sample size limitations across registry sites. When registry was dropped from the model, these observed differences were not significant (P = .13).

For specificity, even though some of the associations were significant because of the large sample sizes, differences according to week in cycle were modest for first and subsequent examinations; in fact, most results differed by less than 1.0% (Table 2). We observed no

Table 2

Sensitivity, Specificity, and Cancer Detection Rate of Screening Mammography and Adjusted Odds Ratios and 95% Confidence Intervals by Week in Cycle, Subdivided by Time Since Prior Mammography

Time Since Prior Mammography and Week in Cycle	Women with Cancer		Women without Cancer		Cancer Detection Rate	
	Sensitivity (%)	False-Negative Odds Ratio	Specificity (%)	False-Positive Odds Ratio	Cancer Detection Rate per 10 000 Examinations	Odds Ratio
No prior mammography*						
Week 1	72.1 (59.2, 82.9)	6.04 (1.50, 40.90)	83.5 (83.0, 84.1)	1.02 (0.96, 1.08)	21.9 (15.7, 29.8)	1.05 (0.65, 1.71)
Week 2	80.4 (67.6, 89.8)	3.97 (0.93, 27.66)	83.9 (83.3, 84.4)	0.99 (0.93, 1.05)	26.0 (18.9, 34.9)	1.25 (0.79, 2.02)
Week 3	84.6 (71.9, 93.1)	2.58 (0.57, 18.32)	83.7 (83.1, 84.3)	1.01 (0.95, 1.07)	25.5 (18.1, 34.8)	1.23 (0.76, 2.01)
Week 4	93.8 (79.2, 99.2)	Reference	83.9 (83.3, 84.5)	Reference	21.1 (14.1, 30.3)	Reference
Mammography performed within prior 2 years†						
Week 1	79.5 (73.6, 84.6)	0.68 (0.42, 1.10)	89.3 (89.1, 89.6)	1.04 (1.00, 1.08)	23.9 (20.3, 27.9)	1.28 (1.00, 1.65)
Week 2	70.3 (63.5, 76.5)	1.14 (0.71, 1.82)	89.2 (89.0, 89.5)	1.05 (1.01, 1.09)	19.5 (16.2, 23.2)	1.04 (0.80, 1.36)
Week 3	67.4 (60.2, 74.0)	1.24 (0.78, 2.00)	89.1 (88.9, 89.4)	1.06 (1.02, 1.11)	20.4 (16.8, 24.4)	1.09 (0.84, 1.43)
Week 4	73.0 (65.3, 79.7)	Reference	89.8 (89.5, 90.0)	Reference	18.8 (15.3, 22.9)	Reference
Mammography performed 3 or more years prior‡						
Week 1	82.8 (71.3, 91.1)	1.17 (0.42, 3.49)§	86.4 (85.9, 86.9)	1.01 (0.94, 1.08)	29.7 (21.9, 39.4)	1.02 (0.66, 1.58)
Week 2	93.1 (83.3, 98.1)	0.39 (0.10, 1.41)§	86.1 (85.5, 86.6)	1.03 (0.96, 1.11)	32.6 (24.2, 43.1)	1.13 (0.74, 1.75)
Week 3	78.3 (63.6, 89.1)	1.54 (0.52, 4.74)§	87.3 (86.7, 87.9)	0.94 (0.87, 1.01)	25.1 (17.3, 35.2)	0.87 (0.54, 1.40)
Week 4	85.1 (71.7, 93.8)	Reference	86.6 (86.0, 87.2)	Reference	29.7 (20.8, 41.1)	Reference

Note.—Data in parentheses are 95% confidence intervals. Week 1 comprised days 0–7; week 2, days 8–14; week 3, days 15–21; and week 4, days 22–35. Unless otherwise specified, odds ratios were adjusted for age (linear) and registry.

* P = .051 in women with cancer, P = .78 in women without cancer, and P = .71 for cancer detection rate.

† P = .041 in women with cancer, P = .013 in women without cancer, and P = .19 for cancer detection rate.

‡ P = .13 in women with cancer, P = .040 in women without cancer, and P = .72 for cancer detection rate.

§ Data were adjusted for age (linear) only, as model adjusted for site did not converge.

Table 3

Cancers, Noncancers, and Cancer Detection Rate Subdivided by Time Since Prior Mammography

	Women with Cancer		Women without Cancer		Cancer Detection Rate	
Time Since Prior Mammography	No. of Cancers	No. of False-Negative Findings	No. of Noncancers	No. of False-Positive Findings	No. of Examinations	No. of Detected Cancers
No prior mammography	201	38	64057	10419	64258	152
Mammography performed within prior 2 years	772	210	239487	25493	240259	499
Mammography performed 3 or more years prior	215	32	56232	7553	56447	166

significant differences in cancer detection rates by week in menstrual cycle.

Results of the sensitivity analyses resembled those presented in Tables E1–E11 (online).

Among women undergoing mammography for the first time, the 163 screen-detected cancers were more likely than ductal carcinoma in situ to be invasive in weeks 3 (n = 35, 79.6%) and 4 (n = 24, 80.0%) than in weeks 1 (n = 27, 61.4%) and 2 (n = 30, 66.7%); this did not hold true in women undergoing subsequent mammography. When we restricted the sample to all 149 invasive cancers (screen-detected cancers or otherwise) among women undergoing mammography for the first time, the association between sensitivity and week in cycle strengthened (week 1, 62.8%; 95% confidence interval: 46.7, 77.0; week 2, 75.0; 95% confidence interval: 58.8, 87.3; week 3, 85.4%; 95% confidence interval: 70.8, 94.4; week 4, 96.0%; 95% confidence interval: 79.6, 99.9; P = .0045). Large invasive tumors (15 mm in diameter or larger) were found more frequently among the 109 screen-detected invasive cancers (with known tumor size) in women undergoing mammography for the first time (n = 63, 57.8%) than in the 483 women undergoing subsequent mammography (n = 208, 43.1%); however, we detected no trends in invasive cancer tumor size according to week in menstrual cycle.

Discussion

Among premenopausal women who had undergone previous mammography in the prior 2 years, mammography was more sensitive in the detection of breast cancer in women who had udergone mammography during the 1st week of their menstrual cycle compared with those who underwent mammography during the 2nd, 3rd, or 4th week of the cycle. Our results are consistent with the findings of the Canadian National Breast Screening Study (22), which revealed a sensitivity of 59% during the first half of the menstrual cycle and 49% during the second half in 84 women who entered the study aged 40–44 years and developed breast cancer; however, this difference was not significant. Also like the Canadian study, our study showed no difference in specificity according to menstrual cycle phase.

If screening during the follicular phase increases the sensitivity of mammography in women who undergo regular screening, the mechanism may be lower mammographic breast density during that phase. In a cross-sectional study (18), we found that a significantly larger proportion of women were categorized as having extremely dense breasts during the luteal phase (28% for both week 3 and week 4) than during the follicular phase (24% and 23% for weeks 1 and 2, respectively). In another study in which we used paired quantitative measures of breast density obtained 9–18 months apart in 204 premenopausal women aged 40–55 years, we found a small nonsignificant increase in the percentage of breast density during days 22–35 compared with days 9–14 (1.1%, P = .09) (21). Several other studies have reported similarly small borderline significant increases in quantitative measures of breast density during the luteal phase (20); however, Hovhannisyan and colleagues (28) found no evidence of differences in density. In our study of 264030 women with a BI-RADS density measurement, we saw no difference in density according to phase of the menstrual cycle; this may have been due to measurement error introduced by the fact that breast density was rated by more than 770 community-based radiologists (29–32).

Mammographic breast density is a measure of the nonfat epithelial and stromal components of the breast, both of which are influenced by the menstrual cycle. Studies based on breast magnetic resonance (MR) imaging show that parenchyma volume is lowest immediately before ovulation and increases during the luteal phase (33,34). Recommendations for screening with MR imaging suggest that the examination be performed during the 2nd week of the menstrual cycle (35,36). Pathologic studies of human breast tissue revealed greater epithelial cell proliferation, lobule size, and stromal edema in the luteal phase (37–41). A meta-analysis reported breast epithelial cell mitosis, epithelial volume, and water tend to peak in the middle of week 4 (42).

A second mechanism for increased false-negative results during the luteal phase may be poorer breast compression for mammograms obtained in this phase, when many women experience breast tenderness and engorgement (42). Hovhannisyan et al (28) found a significantly higher compression force was needed to obtained film mammograms during week 4.

Why would there be a benefit of screening before ovulation for subsequent mammography but not first mammography? Mammography is less sensitive in women who undergo regular screening (27) because tumors tend to

be smaller in these women. The small changes in breast density that occur during the menstrual cycle may be enough to improve sensitivity for finding small tumors. In contrast, cancers detected at first mammography and those detected on mammograms obtained in women with no prior recent screening are larger on average and more easily detectable; therefore, small fluctuations in breast density or poorer breast compression may have less influence on the sensitivity of mammography in the detection of these established tumors.

Our finding of higher sensitivity after ovulation (weeks 3 and 4) in women who underwent first mammography is more difficult to interpret. Benign breast cysts enlarge in some women during the luteal phase (43); however, the menstrual cycle does not appear to affect breast tumor cell proliferation (44). Among first mammograms, screen-detected cancers were more likely to be invasive during the luteal phase, and the relationship between sensitivity and week in cycle strengthened when restricted to invasive tumors. Perhaps progesterone-dependent stromal edema during the luteal phase affects the stroma surrounding more established (larger) tumors differently than tumor stroma, making tumors easier to detect. Changes in stromal edema may alter normal stroma density more than tumor-induced fibrosis. This potentially heightened contrast between invasive tumors and normal stroma might enhance detection during the luteal phase.

One limitation of our study was the potential for measurement error inherent in estimating time in the menstrual cycle from self reporting and lack of information on actual day of ovulation. However, women tend to estimate their day of last menstrual cycle accurately (45). We assumed ovulation occurred on day 14, independent of a woman's cycle length, which we did not ascertain. Errors in the estimated week in cycle and the radiologists' assessments of the mammograms are unlikely to be correlated; thus, under reasonable measurement error scenarios, our results are likely attenuated toward the null (46). Still, our measure of self-reported time in the menstrual cycle reflects measures used in clinical practice, so the relationship presented here reflects the expected increase in sensitivity if mammography was timed on the basis of a woman's self-reported menstrual cycle.

Scheduling mammography on the basis of time in the menstrual cycle would have practical limitations and would add complexity to mammography scheduling because women cannot always predict when their cycle will begin. On the other hand, because many women experience breast tenderness during the end of the luteal phase, avoiding this time could also reduce the discomfort of mammography.

In conclusion, our findings suggest that in women who undergo screening at regular intervals, the sensitivity of screening mammography may be higher during the 1st week of the menstrual cycle. This finding is consistent with the findings of Baines et al (22) and is supported by a plausible biologic mechanism through breast density, stromal edema, or both, and its effect on imaging. However, our finding of the opposite effect among first screening mammograms, for which sensitivity was lowest in week 1 and highest in week 4, is unexpected. Future research is needed to understand this finding. In the meantime, for premenopausal women who choose to undergo regular screening, the sensitivity of mammography may be improved by timing subsequent mammography to occur during the 1st week of their menstrual cycle.

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