Original Research

Influence of Menstrual Cycle Timing on Screening Breast MRI Background Parenchymal Enhancement and Diagnostic Performance in Premenopausal Women

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Abstract

Objective: To assess the influence of menstrual cycle timing on background parenchymal enhancement (BPE) and performance on screening breast magnetic resonance imaging (MRI) in premenopausal women at high risk for developing breast cancer.

Methods: After Institutional Review Board approval, all screening breast MRIs performed from January 2007 through November 2010 in premenopausal women in whom day from last menstrual period was recorded were identified. Prospectively recorded BPE levels and Breast Imaging Reporting and Data System MRI assessments were extracted from our database. Subject outcomes were determined by using biopsy, imaging follow-up, and linkage with the regional tumor registry (minimum 12-month follow-up). Associations of BPE levels (minimal/mild versus moderate/marked) with menstrual cycle phase (follicular [day 0–15] versus luteal [day 16–35]) and week (1, 2, 3, or 4) were compared. Differences in MRI performance metrics, including abnormal interpretation rate (AIR), positive biopsy rate (PBR), cancer yield, sensitivity, and specificity, were compared between menstrual cycle phase and menstrual cycle week.

Results: Three-hundred twenty examinations in 244 premenopausal women met inclusion criteria with nine cancers diagnosed. BPE levels were not associated with menstrual cycle phase or week ($P > 0.05$). MRI performance metrics (ie, AIR, PBR, cancer yield, sensitivity, or specificity) did not differ significantly based on menstrual cycle phase or menstrual cycle week ($P > 0.05$).

Conclusions: Obtaining screening breast MRI exams during specific phases or weeks of the menstrual cycle in premenopausal women does not reliably produce MRI examinations with lower BPE levels or improved performance.

Key words: breast; MRI; menstrual cycle; background parenchymal enhancement; BPE.

Key Messages

- Performing screening breast magnetic resonance imaging (MRI) exams in high-risk premenopausal women in the early phase of the menstrual cycle does not reliably reduce background parenchymal enhancement.
- Performing screening breast MRIs in high-risk premenopausal women in the early phase of the menstrual cycle does not improve screening MRI diagnostic performance.

Introduction

Breast magnetic resonance imaging (MRI) is a valuable tool for the detection of breast cancer, and it is supported for annual screening of women at high risk for breast cancer (1, 2). Breast cancer diagnosis on MRI depends on contrast enhancement. However, normal breast tissue also enhances to varying degrees, known as background parenchymal enhancement (BPE). Accordingly, the fifth edition of the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) includes the description of level of BPE as a key component of the breast MRI report (3).

The amount of BPE present on breast MRI is affected by circulating hormones. In small studies of premenopausal women, the overall number of enhancing areas in normal tissue has been demonstrated to fluctuate during the menstrual cycle (4) and decrease with tamoxifen use (5). Furthermore, several other studies demonstrated that BPE decreases after menopause and increases in postmenopausal women when given hormone replacement therapy (6, 7). Several studies have demonstrated that breast MRI contrast enhancement is greatest during the later or luteal phase of the menstrual cycle (4, 8–12). More recently, preliminary studies indicate higher levels of BPE are associated with greater breast cancer risk (13, 14).

It has been proposed that increasing BPE levels can decrease MRI accuracy and detection sensitivity. Thus, some have advocated that screening MRIs be restricted to the earlier phase of the menstrual cycle for premenopausal women (15), creating scheduling challenges for facilities and patients. This widespread practice has been implemented without robust data. In fact, two prior studies have shown no impact of BPE levels on cancer detection rates (16, 17). The effect of menstrual cycle timing on breast MRI diagnostic accuracy has not yet been fully assessed. Accordingly, we sought to investigate the influence of menstrual cycle timing in premenopausal women on BPE levels and diagnostic performance on screening breast MRIs.

Methods**Study population**

This retrospective study was approved by our Institutional Review Board, which waived requirements for informed consent. The study was compliant with the Health Insurance Portability and Accountability Act.

We performed a review of our established, prospectively collected breast MRI database to identify all screening breast MRI examinations performed at our institution between January 1, 2007, and November 30, 2010, in women age 18 years or older. We included MRIs performed on premenopausal women with self-reported day of menstrual cycle, recorded as 0–35 days from onset of last menstrual period. Because the inclusion criteria were applied at the MRI examination level, women with multiple examinations in the study

interval could contribute more than one examination to the analysis set if all inclusion criteria were met for each MRI performed.

For the study cohort, breast MRI and patient outcomes data were obtained from the Consortium Oncology Data Integration (CODI) project, which is a solid tumor clinical research database developed and maintained by the Fred Hutchinson Cancer Research Center in collaboration with the University of Washington. Data sources for CODI include our institutional pathology database, our prospectively recorded breast MRI data forms, and the Cancer Surveillance System (CSS) regional tumor registry (part of the National Cancer Institute's Surveillance, Epidemiology, and End Results program). The CSS registry has ascertained 95% or higher completeness according to the North American Association of Central Cancer Registries.

MRI technique

Two MRI scanning protocols were used during the study period as clinical practice and technology evolved, and both were consistent with the guidelines established by the ACR breast MRI accreditation program (18). For both protocols, images were acquired in the axial plane, and sequences included a precontrast fat-suppressed T2-weighted fast spin echo sequence followed by a T1-weighted dynamic contrast-enhanced (DCE) sequence with one precontrast and at least three postcontrast fat-suppressed 3D fast gradient echo acquisitions.

From January 2007 through January 2010, MRI was performed on a GE LX 1.5 tesla (T) scanner (GE Healthcare, Waukesha, WI) using a dedicated eight-channel breast coil (GE coil, GE Healthcare or Sentinelle coil, Invivo, Gainesville, FL). DCE was performed with the following parameters: TR/TE = 5.5/2.7; flip angle = 10°; FOV = 32–38 cm, slice thickness = 1.6 mm; matrix size = 420 × 420, and initial contrast-enhanced acquisition centered at 90 seconds after contrast administration. After January 2010, MRI was performed on a Philips Achieva 3T scanner (Philips Healthcare, Best, The Netherlands) using a dedicated 16-channel breast coil (MammoTrak SENSE coil, Philips Healthcare). DCE was performed with the following parameters: TR/TE = 5.9/3; flip angle = 10°; FOV = 22–33 cm; slice thickness = 1.3 mm; matrix size = 440 × 660; and initial contrast-enhanced acquisition centered at 110 seconds after contrast administration. For both protocols, DCE initial postcontrast acquisitions were centered between 90 and 120 seconds after contrast administration, and delayed acquisitions were centered between 7.5 and 8.0 minutes after contrast administration. For both protocols, gadolinium contrast material (Omniscan, GE Healthcare) was power injected (0.1 mmol/kg at 2 mL/s) followed by a 20 mL saline flush. All MRIs were processed using a commercially available computer-aided evaluation system (CADstream, Merge Healthcare, Chicago, IL), which incorporates a motion-correction algorithm and provides automated kinetic-enhancement synopses.

Breast MRI interpretation and patient outcomes

All breast MRIs were interpreted prospectively at the time of clinical presentation by one of seven fellowship-trained breast radiologists with 1–10 years of breast MRI experience. During interpretation, all exams were presented in the axial plane with coronal and sagittal reformats available for review. As part of the clinical interpretation, BPE was assigned one of four levels based on the amount and intensity of fibroglandular tissue enhancement and in accordance with the then-anticipated and now formalized fifth edition of the ACR BI-RADS atlas (3): minimal, mild, moderate, or marked. Background

parenchymal enhancement was determined primarily using axial subtracted and maximum intensity projection images (Figure 1), both of which were created by subtracting the precontrast T1-weighted axial images from the first postcontrast T1-weighted axial images using a motion-correction algorithm from the computer-aided evaluation system (CADstream). In cases of substantial interscan patient motion that were not adequately corrected by this algorithm, BPE was determined by visual comparison of the initial postcontrast and precontrast images to avoid overestimation of BPE attributable to artifact. All MRI variables (including BPE, BI-RADS assessment, and management) and clinical variables (including patient age, clinical indication for high-risk screening, and self-reported day in menstrual period) were recorded in the CODI database and later extracted.

Outcomes of benign or malignant (invasive breast cancer or ductal carcinoma in situ [DCIS]) breast pathologies were determined by using biopsy, imaging surveillance, and linkage with the regional tumor registry with a minimum of 12 months of follow-up for each examination. For high-risk lesions (defined as atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ, radial scar/complex sclerosing lesion, or phyllodes tumor) diagnosed on core needle biopsy, outcomes were based on excisional biopsy results.

Statistical analysis

All statistical outcome definitions were derived from the fifth edition of the ACR BI-RADS Atlas Follow-Up and Outcome Monitoring section (3). Abnormal interpretation rate (AIR) was defined as the percentage of all study examinations receiving BI-RADS assessments

of 0, 3, 4, or 5. BI-RADS 0 and 3 assessments were included as “abnormal” because they resulted in recommendations for immediate (BI-RADS 0) or short-term follow-up (BI-RADS 3) imaging before the next routine screening examination. A negative MRI was defined as an exam with a final BI-RADS assessment of 1 or 2. A positive MRI was defined as an exam with a final BI-RADS assessment of 4 or 5. True positives were defined as positive MRI examinations with tissue diagnoses of malignancy within the follow-up interval, defined as 365 days of the MRI date. False positives were defined as positive MRIs without tissue diagnoses of malignancy in the follow-up interval. True negatives were defined as negative MRI examinations without tissue diagnoses of malignancy in the follow-up interval. False negatives (FNs) were defined as negative MRI examinations with tissue diagnoses of malignancy in the follow-up interval. Positive biopsy rate (PBR) was defined as the percentage of biopsies performed based on abnormal interpretation that resulted in a tissue diagnosis of cancer. Cancer yield was defined as the percentage of biopsy-proven malignancies resulting from positive MRIs. For examinations with multiple lesions with separate BI-RADS category assessments, each MRI was assigned the single highest-order actionable BI-RADS assessment category according to the following hierarchy: BI-RADS category $5 > 4 > 0 > 3 > 2 > 1$. Because the study cohort was a screening population, there were no BI-RADS 6 assessments.

Background parenchymal enhancement levels were dichotomized into categories of low BPE (minimal or mild) versus high BPE (moderate or marked) for analysis. Women in the study cohort reported days after last menstrual cycle ranging from 0 to 35. Thus,

Figure 1. Example of minimal (A), mild (B), moderate (C), and marked (D) background parenchymal enhancement on contrast-enhanced axial bilateral breast MRI maximal-intensity projection image.

Figure 2. Flow chart of the study profile according to the Standards of Reporting of Diagnostic Accuracy recommendations.

menstrual cycle phase was categorized as early/follicular (days 0–15) versus late/luteal (days 16–35) and according to week in cycle (week 1 = day 0–7; week 2 = day 8–15; week 3 = day 16–23; and week 4 = day 24–35). Background parenchymal enhancement categories were compared between menstrual cycle and week using chi-square analysis. For women who had multiple examinations during the study interval, the relationship of a change in BPE assessment between examinations (using the first two MRIs performed for women with more than two examinations) with menstrual cycle phase was examined using chi-square test. For phase and week in cycle, the AIR was compared using chi-square test; PBR and cancer yield were compared using Fisher's exact test; and MRI specificity was compared using a Z-score statistic.

Results

In total, 1196 screening MRIs in 1156 women who were at least 18 years old were performed from January 1, 2007, to November 30, 2010, (1128 postmenopausal, 351 unknown menopausal status, and 477 premenopausal). From 477 examinations in premenopausal women, 320 examinations in 244 women had reported cycle day of 0–35 from last menstrual period and comprised the analysis set. A flow chart summarizing patient selection for the study is provided in [Figure 2](#).

Patient and MRI examination features

The mean patient age for patients included in the study was 42 years (range 26–56 years). Indications for screening breast MRI included

Table 1. Summary of Patient ($n = 244$) and Examination Characteristics According to Menstrual Cycle Phase

	Menstrual Cycle Phase	
	Follicular (Day 0–15)	Luteal (Day 16–35)
No. of exams	215 (67.2%)	105 (32.8%)
No. of patients	177 ^a	94 ^a
Age	41.5 (26–56)	42.0 (26–55)
Indication		
Genetic/family history	116 (53.9%)	47 (44.8%)
Personal history	87 (40.5%)	54 (51.4%)
Other	12 (5.6%)	4 (3.8%)

^aOf patients, 27 of 244 had examinations included in both follicular and luteal phase categories.

genetic/family history (163/320, 50.9%), personal history of breast cancer (141/320, 44.1%), and other (16/320, 5.0%) ([Table 1](#)).

Of the 320 total examinations in the analysis set, 215 were performed in the follicular phase, and the remaining 105 were performed in the luteal phase. Of the 244 women included, 63 had multiple examinations (50 women with two and 13 women with three examinations). In total, 177/244 (72.5%) women had at least one MRI performed during follicular phase and 94/244 (38.5%) had at least one MRI performed during luteal phase, with 27/244 subjects (11%) included in both categories because they had at least one MRI performed in each of the luteal and follicular phases. Mean age for women who underwent MRI during the follicular phase was 41.5 years (range 26–56 years), which was similar to the mean age of 42.0 years (range

26–55 years) for women scanned during the luteal phase, Indications for MRI were similar based on follicular versus luteal phases (Table 1).

Association of BPE assessments with menstrual cycle phase

Twenty-three exams were missing BPE data and were excluded from analysis for BPE-related comparisons. Of the resulting 297 examinations, 169 MRIs were classified as having low BPE (56.9%), and 128 MRIs were deemed to have high BPE (43.1%). There was no significant difference in the frequency of high BPE when comparing MRIs performed during the follicular versus luteal phase (43.7 versus 42.0%, $P = 0.79$). Furthermore, the rate of high BPE classification on MRI was not significantly different when stratified by menstrual cycle week (45.3% for week 1; 42.2% for week 2; 40.3% for week 3; and 45.5% for week 4, $P = 0.92$) (Tables 2 and 3).

Of the 63 women who had multiple examinations (50 women with two and 13 women with three examinations), 54 also had complete BPE data for each exam. Of these 54 women, 32 (59.3%) had both exams performed during the same phase of the menstrual cycle (24 follicular and 8 luteal), with the remaining 22 women undergoing MRIs during different menstrual cycle phases. Women who had their examinations performed during different phases of the menstrual cycle were not statistically more likely to have a change in BPE level (12/22 changed between low and high BPE, 54.6%) than were women scanned during the same phase of their menstrual cycle (12/32 changed, 37.5%, $P = 0.22$, Table 4). An example of a patient in whom BPE did not change between menstrual cycle phases is provided in Figure 3.

Impact of menstrual cycle phase on MRI performance

Overall, 67.2% (215/320) of MRIs were performed in the follicular phase, and 32.8% (105/320) in the luteal phase. The AIR for all study examinations was 20.0% (64/320), with no significant differences in AIRs for follicular versus luteal phase (21.0 versus 18.1%, respectively, $P = 0.55$). In addition, there were no significant differences in positive biopsy rate (PBR) (13.3 versus 10.5%, respectively, $P = 0.76$), cancer yield (2.8 versus 1.9%, respectively, $P = 0.80$), or specificity (81.3 versus 83.5%, respectively, $P = 0.63$) based on menstrual cycle phase (Table 2). Similarly, there were no significant differences in MRI performance metrics when compared by menstrual cycle week (Table 3).

Nine cancers were diagnosed in patients included in the analysis set. Seven cancers were associated with MRIs performed during the follicular phase, with six detected on MRI and one a FN MRI examination, resulting in a sensitivity of 85.7% (6/7) (Figure 4). Note that two cancers diagnosed during the follicular phase had no BPE reported. Two cancers were associated with MRIs performed during the luteal phase, and both were detected on MRI, resulting in a sensitivity of 100% (2/2).

The single FN MRI examination occurred in a 41-year-old BRCA1 mutation carrier who underwent bilateral prophylactic mastectomy 11 months after the exam, yielding right breast DCIS on pathology (Figure 5). There were 56 false positive MRI examinations during the study interval: 39/215 (18%) in the follicular phase, and 17/105 (16%) in the luteal phase.

Table 2. Diagnostic and Background Parenchymal Enhancement (BPE) Outcomes According to Menstrual Cycle Phase

	Follicular (Day 0–15)	Luteal (Day 16–35)	P-value
Moderate/marked BPE	43.7% (86/197) ^a	42.0% (42/100) ^a	0.79
Abnormal interpretation rate	21.0% (45/215)	18.1% (19/105)	0.55
Positive biopsy rate	13.3% (6/45)	10.5% (2/19)	0.76
Cancer yield	2.8% (6/215)	1.9% (2/105)	0.80
Specificity	81.3% (169/208)	83.5% (86/103)	0.63

^aTwenty-three exams were missing BPE data and were excluded from analysis for BPE-related comparisons ($N = 297$ exams).

Table 3. Diagnostic and Background Parenchymal Enhancement (BPE) Outcomes According to Menstrual Cycle Week

	Menstrual Cycle Week				P-value ^a
	Days 0–7	Days 8–15	Days 16–23	Days 24–35	
Moderate/marked BPE	45.3%	42.2%	40.3%	45.5%	0.92
Abnormal interpretation rate	22.2%	19.6%	15.7%	22.9%	0.72
Positive biopsy rate	8.8%	18.2%	9.1%	12.5%	0.83
Cancer yield	1.9%	3.6%	1.4%	2.9%	0.84
Specificity	79.2%	83.2%	85.5%	79.4%	0.71

^aAll P -values >0.05 .

Table 4. Intra-patient Background Parenchymal Enhancement (BPE) across Two Examinations in Women Imaged in the Same Versus Different Phases of the Menstrual Cycle

BPE Measures across Exams	Exams Performed during the Same Phase	Exams Performed during Different Phases	Total
Same	62.5% (20/32)	45.5% (10/22)	55.6% (30/54)
Different	37.5% (12/32)	54.6% (12/22)	44.4% (24/54)
Total	32	22	54

Figure 3. Patient with multiple exams. Two postcontrast maximal-intensity projection images from MRI exams in a 47-year-old woman, with the first performed in the follicular phase (A) and the second performed in the luteal phase (B). There was no fluctuation of background parenchymal enhancement (BPE) between phases of the menstrual cycle, with marked BPE for each exam.

Figure 4. True positive examination. A bilateral breast MRI maximal-intensity projection image in a 42-year-old premenopausal woman with a personal history of treated breast cancer status post right mastectomy with myocutaneous flap reconstruction. The examination was obtained during the follicular phase of the menstrual cycle, assessed to have moderate background parenchymal enhancement, and interpreted as positive for a mass with adjacent satellite masses in the left breast (arrow). Biopsy yielded invasive lobular carcinoma.

Discussion

In this study of screening breast MRI in premenopausal women, we found no significant difference in the proportion of women demonstrating higher levels of BPE based on menstrual cycle phase.

Figure 5. False negative examination. A bilateral breast MRI postcontrast maximal-intensity projection image in a 41-year-old premenopausal woman with a BRCA1 gene mutation. The examination was obtained during the follicular phase of the menstrual cycle, assessed to have moderate background parenchymal enhancement, and interpreted as negative. The patient underwent bilateral prophylactic mastectomy, which revealed two foci of ductal carcinoma in situ in the right breast.

Furthermore, among women with multiple MRIs in the study period, the proportions of women exhibiting a categorical change in their BPE assessment did not differ if they were imaged in the same versus different menstrual cycle phases. Most importantly, we found that menstrual cycle timing had no effect on measures of MRI diagnostic performance including AIR, PBR, cancer yield, and specificity. These results suggest that there is no benefit to restricting screening breast MRI to specific phases or weeks of menstrual cycle in premenopausal women.

Because increasing mammographic breast density negatively affects screening mammography performance (19–21), some have questioned whether BPE could have a negative effect on breast MRI performance. Several early and relatively small (≤ 50 patients) studies found there is generally greater quantitative BPE in MRI examinations performed later in the menstrual cycle than in earlier phases (4, 8, 9). Four larger studies confirmed that quantitative BPE is greatest later in the menstrual cycle (10, 11, 12, 22), suggesting that performing breast MRI early in the menstrual cycle in premenopausal women could optimize performance. However, most of these studies used quantitative voxel-level methods of measuring enhancement, which could be more sensitive to subtle signal differences that are not as readily perceived by radiologists performing qualitative BPE assessments. Most notably, none of these studies evaluated the impact of enhancement on diagnostic performance.

Two studies examining qualitative BPE assessments in academic practices questioned the assumption that high BPE levels reduce MRI performance. DeMartini et al. demonstrated no significant difference in diagnostic accuracy for minimal/mild versus moderate/marked BPE among 736 women of all ages, although examinations performed in women exhibiting higher BPE did have an increased AIR when compared to those with lower BPE (30.5% versus 23.3%)(16). In a similar study evaluating 250 baseline high-risk screening MRI exams in 250 women, Hambly et al. also demonstrated significantly higher AIR (BI-RADS category 0, 3, 4, or 5 assessments) in patients with nonminimal BPE versus women with minimal BPE (17), yet they found no significant difference in biopsy rates among the BPE categories. In contrast, Ray et al. showed that women with moderate/ marked versus minimal/mild BPE on screening MRI in a community based study comprising 1726 patients had significantly increased AIR (26% versus 12%) and biopsy rates (32% versus 23%), with reduced specificity (75% versus 89%)(23). In our study of 297 exams

specifically in premenopausal women, we demonstrated no significant differences in moderate/marked BPE (43.7% versus 42.0%), AIR (21.0 versus 18.1%), PBR (13.3% versus 10.5%), cancer yield (2.8% versus 1.9%), and specificity (81.3% versus 83.5%) for follicular versus luteal phase of the menstrual cycle.

Our study focuses on premenopausal women showing that menstrual cycle timing provides no measurable effect on diagnostic performance and that menstrual cycle timing is not effective since BPE levels did not reliably correlate with phase or week of menstrual cycle. This suggests that limiting women to exams early in their menstrual cycle is unnecessary.

Our study has several important limitations. It took place at a single academic institution with dedicated breast radiologists, and the results may not be generalizable to practices that are less established. While no study to our knowledge has formally investigated the effects of oral contraception on BPE, we did not exclude nor control for patients taking oral contraception, and it is unknown how this would affect our data. Additionally, we did not identify or control for patients taking tamoxifen. Note that MRI exams were performed under different field strengths (1.5T before January 2010, and 3T after January 2010), yet it is unclear how this would affect the outcome of our study. Finally, we did not assess the effect of BPE on interpretation times.

In conclusion, our study suggests that the practice of scheduling breast MRIs performed in high-risk premenopausal women in the early/follicular phase of the menstrual cycle does not provide meaningful performance benefit and does not reliably lead to examinations with lower BPE. Our results suggest that screening breast MRI in premenopausal women may be scheduled throughout the menstrual cycle without adverse effect on MRI performance, thereby facilitating improved access.

Acknowledgments

This study was supported by grants from the following organizations: National Institutes of Health (NIH): R01CA151326 (S.C.P.), and Radiological Society of North America: Research Scholar Grant (H.R.). H.R. and S.C.P. received salary support from a grant sponsored by GE Healthcare as coinvestigators. This study was not related to that grant.

Conflict of interest statement

C.D.L. sits on the GE Healthcare advisory board. No other conflicts declared.

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