The effects of former breastfeeding on contrast enhancement kinetics of normal breast parenchyma in dynamic MR mammography

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Dynamic magnetic resonance mammography (MRM) is the most sensitive method for detecting early invasive breast cancer, combining morphological information with functional characterization based on analysis of contrast enhancement (CE) kinetics of the breast (1). With the guidelines of the American Cancer Society, recommending annual screening MRM for women with an approximately 20-25% or greater lifetime risk of breast cancer, including women with a strong family history of breast or ovarian cancer and women who were treated for Hodgkin disease, this method will be increasingly used for the screening of asymptomatic women (2). Therefore, it is desirable to have comprehensive qualitative and quantitative data on morphological and kinetic features of the healthy breast from a large, unselected population of women; however, such studies are sparse (3). The appearance of normal breast parenchyma in MRM varies strongly between women. Several factors contribute to that variability. Endogenous hormonal variations, dependent on menopausal status and menstrual cycle phase, affect breast tissue composition (4-6), tissue relaxation times (7, 8), CE kinetics of normal breast parenchyma (9-12), and of breast lesions (11,13) in MRM. Exogenous hormones, such as postmenopausal hormone therapy or oral contraceptives have shown to increase parenchymal tissue / fat ratio (14), breast tissue perfusion (15), and CE kinetics in MRM (16,17). Few studies evaluated physiologic changes in the breast during lactation. They reported an increased breast size and density, high T2-weighted signal intensity (SI), and rapid CE followed by an early plateau of breast parenchyma due to increased vascular permeability (18, 19). Although, this enhancement type has shown to overlap with the qualitative enhancement characteristics of invasive malignancy in non-lactating women (18, 19) no study investigated whether these CE changes completely disappear after lactation.

Therefore, the purpose of the present study was to investigate differences in CE kinetics of normal breast parenchyma in MRM between women reporting former breastfeeding and women not reporting former breastfeeding.
Methods and Materials

Study Population

This prospective study was approved by the institutional review board and written informed consent was obtained from each participant prior to the study. Between June 2008 and September 2011 all women were enrolled from the Study of Health in Pomerania (SHIP), a prospective population-based cohort study in Northeast Germany, that includes a whole-body MRI examination (20). Additionally to the whole-body MRI women were offered participation in an optional MRM (21). Women with contraindications to an MRI examination, with known allergies to any kind of contrast agent or drugs, pregnant or breastfeeding women were not offered to undergo MRM. Of 1475 female study participants who were enrolled in the whole-body MRI examination a total of 652 (44.2%) agreed to undergo additional MRM.

All women underwent a structured interview to obtain information on history of breast diseases and breast surgery, history of childbirth, history of breastfeeding including breastfeeding duration, menopausal status, week of the menstrual cycle in premenopausal women, and medication history. Menopause was defined as cessation of menstrual bleeding for at least 12 months.

Dynamic Contrast-enhanced MR Mammography Examination

MR imaging was performed at 1.5 Tesla on a whole-body MR imager (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany). An intravenous access was established and the woman was placed in prone position with the uncompressed breasts suspended in a commercially available circularly polarized bilateral breast phased-array receiver coil (Siemens Medical Solutions). The pulse sequence protocol included axial dynamic, T1-weighted, time-resolved angiography with stochastic trajectories (TWIST), three-dimensional imaging (8.86 / 4.51 [repetition time msec / echo time msec]; 25° flip angle; 340-mm field of view; 0.9 x 0.7 x 1.5-mm voxels). Following acquisition of the first unenhanced sequence, an IV gadobutrol bolus (Gadovist, Bayer Healthcare, Leverkusen, Germany) was administered with a power injector at a dose of 0.1mmol/kg body weight at a rate of 1.0 mL/sec, followed by a saline flush (20 mL) injected at the same rate. The sequence was repeated five times without time gaps or motion correction. Each sequence lasted 58 seconds.

Inclusion and Exclusion Criteria

Inclusion criteria for analysis of normal breast parenchyma were females > 20 years.

Exclusion criteria were:
• perimenopausal women with cessation of menstrual bleeding for less than 12 months ($n=15$),
• women on postmenopausal hormone therapy ($n=24$),
• women on oral contraceptives ($n=69$),
• history of recent or previous breast disease or history of breast surgery including breast implants ($n=12$),
• breasts with complete involution precluding measurement of representative parenchyma ($n=68$), and
• breasts with so far unknown breast lesions identified on study scans ($n=97$).

This left 367 women in the final study sample (Table1).

Data Analysis

First, images were postprocessed using the Syngo 2008A MultiModality Workplace (Siemens Medical Solutions, Erlangen, Germany). Image subtraction was done to identify any mass and non-mass-like enhancement that was defined as early-phase contrast enhancement apparent in the first postcontrast image, because this has been associated with malignant tumor growth (22-25). To limit possible bias in the reproducibility of measurement resulting from variable repartitioning of fibroglandular tissue throughout the breast, measurements were performed in two slices above and two slices below the nipple, where breast tissue is usually constant and more homogeneous (10, 15). Second, a region of interest (ROI) was drawn manually to include all fibroglandular tissue of the breast in the four slices selected, while excluding visible fat, cysts, or non-mass-like enhancement (Figure 1). Third, for evaluation of baseline T1 SI and CE at 1-5 min after gadobutrol injection a time-SI curve was created automatically for each ROI on a pixel-by-pixel basis representing mean values of T1 SI and standard deviations for all dynamic frames. Percentage contrast enhancement was calculated as $\frac{\text{SI}_{(t1-5)} - \text{baseline SI}}{\text{baseline SI}} \times 100$, where $\text{SI}_{(t1-5)}$ is the signal intensity after administration of gadobutrol (10, 12, 15). To exclude interreader variability only one radiologist (KH, with more than 7 years of experience in breast MR imaging) performed all analyses.

Statistical Analysis

Because the time courses of contrast enhancement were similar in both breasts, we modeled the mean contrast enhancement across both breasts in all further analyses. Regarding descriptive statistics differences between pre- and postmenopausal women were tested for significance using t-tests for continuous variables and Chi$^2$ test for categorical variables.

Two-level random effects models were used to analyze mean contrast enhancement across both breasts, using the STATA xtmixed routine with six time points at level 1 and individuals at level 2. This approach takes the correlated longitudinal data structure into account (26). Regression model building was based on deviance tests using restricted
maximum likelihood estimates to evaluate variance components of the model. A random intercept model strongly outperformed a model without random effects (Chi²= 3816.0, df= 1: p< 0.001), as did a linear time random slope model vs. the random intercept model (Chi²= 1019.31, df= 2: p< 0.001). An unstructured covariance matrix was chosen because it outperformed an independent matrix in the random slope model (Chi²= 5.4, df= 1: p=.02). Full maximum likelihood estimation was used to evaluate fixed-effects terms in the models. All models included age and BMI. A p-value <0.05 was labeled statistically significant. Analysis was performed using STATA 12 (StataCorp LP, College Station, Texas, USA) and SPSS 15.0.1 (SPSS GmbH Software, Munich, Germany).
Table 1: Subject characteristics and descriptive statistics Note.-Data are given as means (± standard deviation) and total numbers (percentage). BMI= body mass index.

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Fig. 1: Method of quantitative analysis of contrast enhancement in normal breast parenchyma. Figures show how the region of interest (ROI) was drawn to measure
T1 signal intensity of normal breast parenchyma in a 34 years old woman. On the unenhanced image without subtraction (a) no cysts were seen, and on the first enhanced image with subtraction (b) no non-mass-like enhancement was identified. Therefore, the manually drawn ROI included all visible parenchyma (a).

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Results

Study Population

The mean age of our study population was 50.8 years (25-81 [age range], ±11.4 [standard deviation]). Out of 367 women, 165 (45.0%) were premenopausal and 202 (55.0%) were postmenopausal. As expected, both groups differed significantly on age (Table 1). A total of 315 women reported to gave birth to at least one child. Of those 277 women reported breastfeeding of at least one month. With regard to childbirth, the number of births, and breastfeeding, there were no significant differences between pre- and postmenopausal women (Table 1). However, the duration of breastfeeding was significantly longer in pre- than in postmenopausal women.

No woman reported adverse events from gadobutrol administration.

Modeling Contrast Enhancement after Injection of Gadobutrol

Contrast enhancement was higher in women reporting breastfeeding compared to women reporting non-breastfeeding (Table 2, Figure 2). Adding an additional three interaction effect between breastfeeding, menopausal status and time did lead to a different evaluation across menopausal status (Chi² (df=6)=5.4; p=.50) (Table 2). Contrast enhancement was lower in postmenopausal women and higher in women reporting former breastfeeding (Figure 3). Adding the number of children and the time interaction to the model led to minor changes (Chi² (df=6)=2.9; p=.82) (Table 2).
<table>
<thead>
<tr>
<th>Variables</th>
<th>Signal intensity</th>
<th>p-Value</th>
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<tr>
<td>Fixed part</td>
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<tr>
<td>Time&lt;sup&gt;2)&lt;/sup&gt;</td>
<td>40.8 (32.3; 49.2)</td>
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<tr>
<td>Age</td>
<td>13.1 (7.4; 18.8)</td>
<td>&lt;.001</td>
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<tr>
<td>I: Age * T&lt;sup&gt;3)&lt;/sup&gt;</td>
<td>-2.7 (-7.1; 1.8)</td>
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<td>Menopause</td>
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<tr>
<td>I: Menopause* T&lt;sup&gt;3)&lt;/sup&gt;</td>
<td>-12.8 (-22.8; -2.9)</td>
<td>0.03</td>
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<td>Breastfeeding</td>
<td>-2.3 (-11.9; 7.3)</td>
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<td>I: Breastfeeding*T&lt;sup&gt;3)&lt;/sup&gt;</td>
<td>9.9 (2.4; 17.4)</td>
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<tr>
<td>RI</td>
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<tr>
<td>RS (time)</td>
<td>5.4 (5.0; 5.9)</td>
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<tr>
<td>Corr. RI, RS</td>
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<tr>
<td>Log likelihood</td>
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</table>

**Table 2:** Breastfeeding-related changes in absolute signal intensity stratified by menopausal status - Legend: Results are based on a random effects model for the outcome mean signal intensity in both breasts. CI = Confidence Interval; I = interaction; T = time; RI = random intercept; RS = random slope; Corr = correlation. #1) Unstandardized beta weights are reported. 2) Displayed is the change from baseline to the last measurement point only. 3) Only the interaction terms at the last measurement point are displayed. BMI was additionally included as control variables. P-values refer to the overall effect for any variable.

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Fig. 2: Variation in contrast enhancement as a function of self reported breastfeeding or non-breastfeeding. Results correspond to the calculations in Table 2. In women reporting non-breastfeeding mean contrast enhancement was 8.02, 12.44, 16.70, 20.09, and 22.06% at 1, 2, 3, 4, and 5 min respectively. Contrast enhancement increased significantly (P < 0.001) in women reporting breastfeeding to 9.74, 16.61, 21.72, 25.83, and 29.02%.

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**Fig. 3:** Variation in contrast enhancement as a function of self reported breastfeeding or non-breastfeeding stratified by menopausal status. Results correspond to the calculations in Table 2. In premenopausal women reporting non-breastfeeding mean contrast enhancement was 9.05, 14.92, 19.90, 24.17, and 26.19% at 1, 2, 3, 4, and 5 min respectively. Contrast enhancement increased significantly ($P < 0.001$) in premenopausal women reporting breastfeeding to 12.38, 20.89, 26.44, 31.24, and 34.93%. In postmenopausal women reporting non-breastfeeding mean contrast enhancement was 5.14, 8.52, 12.72, 15.10, and 16.64 increased significantly ($P < 0.001$) in postmenopausal women reporting breastfeeding: 6.67, 12.09, 16.97, 19.90, and 22.60%.

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Conclusion

This prospective population-based study assessed contrast enhancement (CE) kinetics of normal breast parenchyma based on the analysis of 367 MRM datasets of healthy women from a general population cohort. Our results indicate that:

1. CE of normal breast parenchyma is approximately 30% higher in premenopausal than in postmenopausal women.
2. CE of normal breast parenchyma is higher in women reporting former breastfeeding than in women without former breastfeeding.
3. The significant difference in CE of normal breast parenchyma between women with and without former breastfeeding remains constant after menopause.

Therefore we conclude that:

1. When analyzing dynamic contrast kinetics curves of breast mass and non-mass lesions the impact of patient-related factors, especially menopausal status and former breastfeeding should be considered precisely.
2. Strong enhancing breast parenchyma may impair lesion detection in women after breastfeeding compared to women without breastfeeding.
3. However, further research is required to investigate the influence of breastfeeding duration on normal breast parenchymal contrast enhancement.
References

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