

Background Parenchymal Enhancement (BPE) in Healthy Subjects and Breast Cancer Patients: A Quantitative Evaluation and Comparison with Diffusion-weighted Imaging

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Introduction: With nearly 200,000 women diagnosed with breast cancer each year [1], predictive noninvasive MRI biomarkers can prove to be extremely advantageous in staging, grading, and monitoring treatment for various tumor types. Recent studies have shown the usage of MRI to correlate with prognostic factors of breast cancer such as hormone receptor status (estrogen, progesterone, and her2/neu receptors) [2-5]. Furthermore, background parenchymal enhancement (BPE) has been correlated with breast cancer risk; an increased BPE correlates significantly with higher odds ratios for developing breast cancer [4-5]. This finding motivates comparative studies with other MR cancer biomarkers and molecular prognostic factors to both fully understand and optimally employ BPE as a screening tool. In this study, we measured BPE from dynamic contrast enhanced MRI in a cohort of healthy controls and breast cancer patients with various cancer subtypes. We compared these results with molecular prognostic factors and diffusion-weighted imaging biomarkers of vascularity and cellularity obtained with intravoxel incoherent motion (IVIM) analysis [6-8].

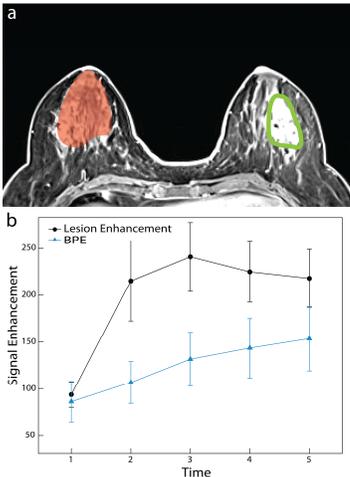


Figure 1 (a) T1-weighted contrast enhanced image of breast cancer patient with ROI highlighted in red, lesion is outlined in green (note: FGT tissue based on $ADC \geq 2 \mu m^2/ms$) (b) Contrast enhancement curves of BPE and lesion (IDC with DCIS).

Methods: 32 patients with confirmed lesions and 18 subjects obtaining MR screening evaluation were scanned in a full body Siemens 3T MRI scanner (Siemens Medical Solutions, Erlangen, Germany) using a 7-channel breast coil. Patients underwent a standard bilateral MRI breast examination using contrast enhancement along with diffusion-weighted imaging (DWI). The DWI protocol used a twice-refocused, bipolar gradient single-shot turbo-spin echo (TSE) sequence (TR/TE = 2000 / 103 ms, 108 x 128 matrix, 18 matrix axial slices, 2.7 x 2.7 x 4 mm voxel, single direction) with b-values of 0, 30, 70, 100, 150, 200, 300, 400, 500, 800 s/mm^2 . Contrast enhancement curves were derived from T1-weighted sagittal 3D VIBE images (resolution 1.4 x 0.9 x 1.5 mm) at one time point before Gd-DTPA injection and at 4 post-contrast intervals. BPE values were calculated as both maximum value (BPE_{max}) and percent increase from baseline ($BPE_{\%}$) at the final time point (~6 mins following injection). Signals were averaged over from ROIs in normal fibroglandular tissue (FGT) in the contra-lateral breast to the lesion location for patients and in the largest FGT region in screening patients. FGT ROI selection was qualitatively guided by apparent diffusion coefficient (ADC) maps from DWI protocol to avoid fatty tissue; $ADC \geq 2 \mu m^2/ms$ suggested FGT. If lesions were found in both breasts, ROIs were chosen in the largest FGT region of either breast. Lesion contrast enhancement (LCE) values were sampled from (a) the initial slope estimated from the difference of the first two time points and (b) maximum absolute (LCE_{max}) and percent lesion enhancement ($LCE_{\%}$). Other clinical data included pre-MRI fine-needle aspiration (FNA) biopsy for initial diagnosis and/or post-MRI tissue biopsy for pathological analysis. DWI signal intensity decays derived from lesion ROIs were used to calculate IVIM parameters (perfusion fraction - f_p , pseudodiffusivity - D_p , and tissue diffusivity - D_t) [6-7]. Statistical t-tests were performed to compare mean

BPE values of screening patients (control) versus different tumor histological subtypes or different hormone receptor groups. Pearson correlations were performed between BPE values and LCE values and IVIM parameters of the lesion and ADC of FGT.

Results: Fig. 1 shows a T1-weighted contrast enhanced image of a breast cancer patient with FGT and lesion ROIs highlighted along with contrast enhancement curves of the normal tissue (BPE) and lesion. $BPE_{\%}$ values showed stronger correlation than BPE_{max} with tumor type and LCE values. Significantly higher mean BPE values were found in patients with breast cancer ($N=32$, $BPE_{\%} = 40.62 \pm 25.79$) versus normal screening patients ($N=18$, $BPE_{\%} = 21.46 \pm 8.86$, $p=0.013$). Fig 2a shows larger BPE value differences between normal cases and those with ductal carcinoma in situ (DCIS) ($N=3$, $BPE_{\%} = 64.93 \pm 20.59\%$, $p=0.065$) and a significant difference between normal versus more malignant lesions ($BPE_{\%} = 38.11 \pm 25.22\%$, $N=29$, $p=0.038$ - adenocarcinoma: $N=1$, $BPE_{\%} = 61.7\%$; invasive lobular carcinoma (ILC): $N=3$, $BPE_{\%} = 31.39 \pm 24.26\%$; invasive ductal carcinoma (IDC): $N=18$, $BPE_{\%} = 43.24 \pm 28.0\%$; and IDC with DCIS: $N=8$, $BPE_{\%} = 64.93 \pm 20.59\%$). Fig. 2b shows the different ADC values of FGT in comparison to aggressiveness. No statistical difference was observed between ADC values in these groups, nor did ADC of FGT correlate significantly with BPE in the same patients. Regarding BPE in patients with lesions, group comparisons and Pearson correlations of BPE with lesion molecular prognostic factors and lesion IVIM biomarkers (D_t , f_p , D_p) showed no significant findings. In Fig. 2c, $BPE_{\%}$ values showed significant correlation with the $LCE_{\%}$ in the same patients ($r=0.492$, $p=0.008$).

Discussion/Conclusion: Recent observations relating BPE to breast cancer risk are an intriguing result whose microscopic underpinning requires exploration, i.e. vascular (blood volume, flow, permeability) vs. parenchymal (extracellular and extravascular space) changes. No correlation of ADC with BPE was seen. Since normal FGT ADC is relatively insensitive to vascular flow [9], we may surmise that BPE is dominated by vascular volume/flow factors, but this remains to be proven. The distinction of BPE values between patients with different lesion types, and the correlation of lesion and parenchymal enhancement levels, may point to common factors that influence the microstructure and microvasculature in both healthy and cancerous tissue. These results may clarify the sensitivity of BPE to breast physiology and thereby improve its prognostic capability, e.g. for DCIS. A larger study may further elucidate the significance of these promising trends.

References: 1. Amer. Cancer Society. 2011. 2. Iima, M. Radiology, 2011. 260(2) 3. Jeh, S.K. J Magn Reson Imaging, 2011. 33(1). 4. Jansen, S.A. Eur Radiol, 2011. 21(7). 5. King, V. Radiology, 2011. 260(1). 6. Sigmund, E.E. Magn Reson Med, 2011. 65(5). 7. Lemke, A. Invest Radiol, 2009. 44(12). 8. Thoeny, H.C. Radiology, 2006. 241(3). 9. Baron, P. NMR Biomed, 2010. 23(4).

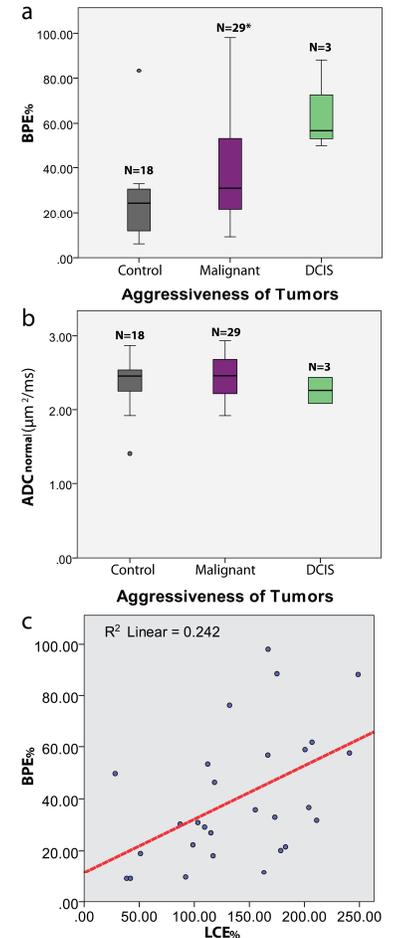


Figure 2 (a) Box plot of aggressiveness of tumor vs. $BPE_{\%}$ (b) ADC values of FGT in comparison to aggressiveness of tumors (c) Comparison of $BPE_{\%}$ vs $LCE_{\%}$ ($p=0.008$) *indicates significant ($p < 0.05$) difference from control.