

Background Parenchymal Enhancement (BPE): A Clue to Increased Breast Cancer Risk

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Background Parenchymal Enhancement (BPE)

- ▶ Normal enhancement of the patient's fibroglandular tissue during CE-MRI
- ▶ Assessment of volume of enhancement and the intensity of enhancement
 - ▶ Determined on first post-contrast image at approx. 90 seconds
- ▶ BPE not necessarily related to amount of fibroglandular parenchyma present
 - ▶ i.e. patient with extremely dense tissue a little to no BPE

Normal BPE

- ▶ Previously all enhancement was thought to be abnormal
- ▶ Normal breast parenchyma enhances and fluctuates with hormonal cycles or exogenous hormones

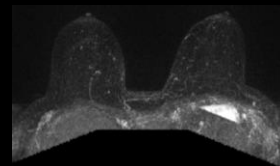
Factors Affecting BPE

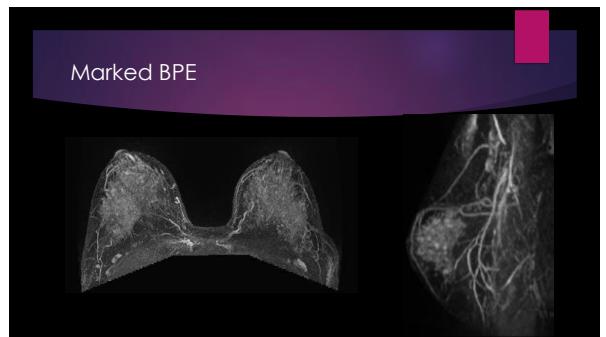
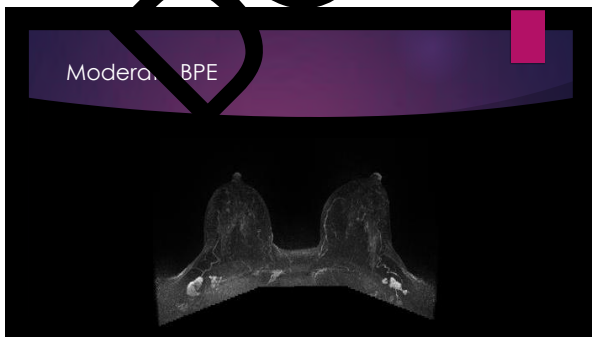
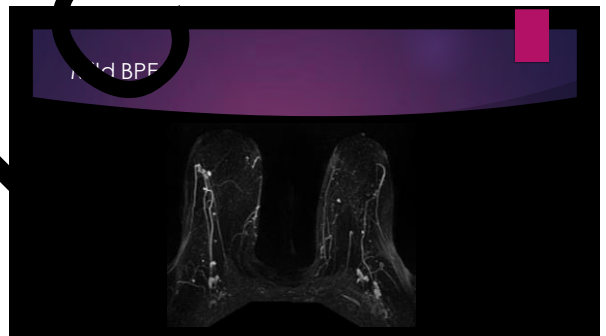
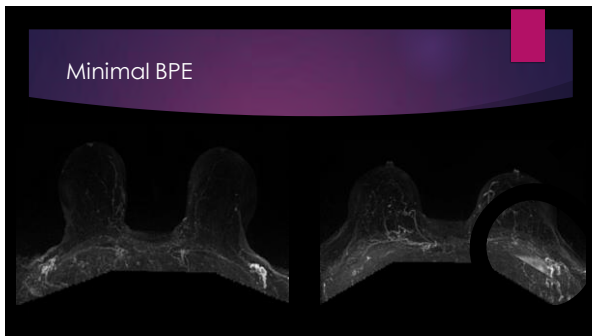
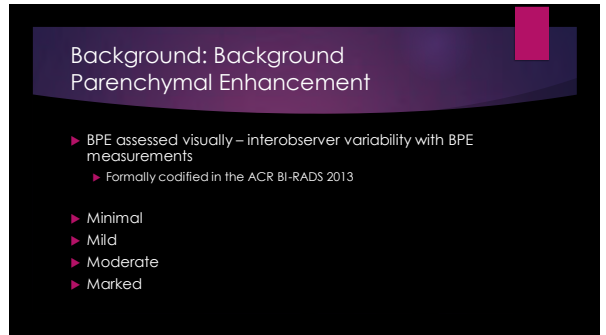
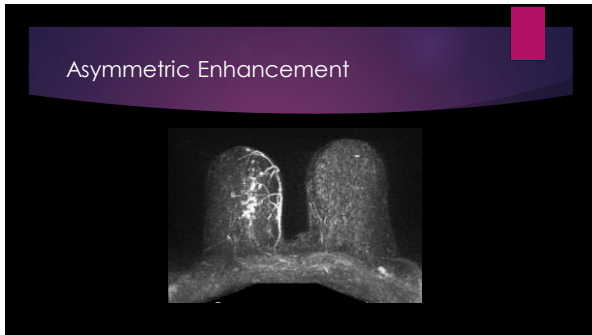
- ▶ Endogenous and exogenous estrogen as determined by menstrual cycle
- ▶ Menopausal status
- ▶ HRT use
- ▶ Tamoxifen use
- ▶ BPE varies between individuals, and varies over time in the same individual

Symmetric v. Asymmetric Enhancement

- ▶ Symmetric- mirror-image enhancement, suggestive of benign BPE
 - ▶ Preferential enhancement- occurs depending on localization of blood supply
 - ▶ i.e. UOQ commonly seen, or along inferior aspect of the breast
- ▶ Asymmetric- more prominent in one breast; can be due to benign or malignant causes

Symmetric Enhancement





BPE Assessment

- ▶ Similar to breast density, the presence of BPE can affect image interpretation [DeMartini, Hamby] and risk [King]
- ▶ Important to get BPE categorization right
- ▶ Melsaether et al. – with training inter-reader agreement increased and was sustained; intra-reader agreement greater over time

King V, Brooks JD, Bernstein JL, Reiner AS, Pike MC, Morris EA. Background parenchymal enhancement of breast MR imaging and breast cancer risk. *Radiology* 2011; 220:59-67.
DeMartini WB, Liu F, Paacock S, et al. Background parenchymal enhancement on breast MRI: impact on diagnostic performance. *AJR* 2012; 178:1875-1880.
Hamby NM, Liberman L, Denhaw DD, Brennan S, Morris EA. Background parenchymal enhancement on baseline screening breast MRI: impact on biopsy rate and short-interval followup. *AJR* 2011; 176:219-224.

Breast Density and Risk – Relationship to BPE

- ▶ The link between increased *mammographic* breast density and breast cancer risk is well established
- ▶ Less understood about the relationship between BPE on MRI and breast cancer risk
 - ▶ Work thus far has had mixed results due to differences in study design, variability in patient populations, and approaches to assessing BPE

BPE and Breast Cancer Risk?

- ▶ Several studies have reported on the association of BPE with breast cancer and evidence for BPE having role as an additional marker for higher risk for breast cancer - DeLeo, Dontchos, King, Telegrafo
- ▶ Other investigations have found no association between BPE and BC - Bennani-Baiti, DeMartini, Melsaether, Albert

"On the basis of the premise that fibroglandular tissue under the influence of hormone fluctuation may be more susceptible to neoplastic transformation, increasing MRI BPE has recently emerged as a risk factor for breast cancer" – Sippo et al.

BPE and Breast Cancer Risk - King

- ▶ Compared with the OR for a normal control, the OR for breast cancer increased significantly with increasing BPE
- ▶ **The increased odds of breast cancer associated with moderate or marked BPE is evident in pre- and postmenopausal women**
- ▶ Breast cancer odds also increased with increasing FGT, but the BPE findings remained significant after adjustment for FGT
- ▶ **BPE has the potential to serve as an additional tool for risk stratification in high-risk women undergoing breast MR imaging screening**

King V et al. Background Parenchymal Enhancement of Breast MR Imaging and Breast Cancer Risk. *Radiology* 2011; 220:59.

BPE Correlates with Risk of Breast Cancer

- ▶ To investigate whether background parenchymal enhancement (BPE) and breast cancer would correlate by searching for any significant difference of BPE pattern distribution in case of benign or malignant lesions
- ▶ 386 patients, including 180 pre-menopausal (group 1) and 206 post-menopausal (group 2)
- ▶ MR images classified normal BPE as minimal, mild, moderate or marked
- ▶ The 2 groups were subdivided into 3 categories based on MRI findings (negative, benign and malignant lesions)
 - ▶ The distribution of BPE patterns within the two groups and within the three MR categories was calculated

Telegrafo M, et al. Breast MRI background parenchymal enhancement (BPE) correlates with the risk of breast cancer. *Magnetic Resonance Imaging* 2016; 34(2): 173-178.

BPE and BC Risk - Telegrafo

- ▶ Statistically significant difference in the distribution of BPE types in negative patients and benign lesions as compared with malignant ones ($p < 0.05$)
- ▶ Significantly higher prevalence of moderate and marked BPE was found among malignant lesions
- ▶ A predominance of minimal and mild BPE among negative patients (group 1: 60% and 36%, respectively; group 2: 68% and 32%, respectively) and benign lesions (group 1: 54% and 38%, respectively; group 2: 75% and 17%, respectively) was found

Meta-Analysis – BPE as a Risk Factor for Breast Cancer [Thompson et al.]

Review of literature (18 studies)

Table 2. Pooled Association between Higher BPE Levels and Presence of Breast Cancer Separately for Populations with High Risk and Average Risk

Population	Quadrant BPE	No.	F (%)	Pooled Odds Ratio	95% CI	P Value
High risk	At least mild BPE	2	18.6	2.1	1.6-2.8	<.001
	At least moderate BPE	9	53.0	2.4	1.9-3.2	<.001
	Average risk	2	81.3	0.6	0.3-1.2	.19
Average risk	At least moderate BPE	5	49.2	0.8	0.5-1.3	.39
	At least mild BPE	1	19.4	1.8	1.2-2.7	.003
	High risk	1	9.8	22.5	1.6-3.1	<.001
High risk	At least mild BPE	5	33.0	1.8	1.2-2.9	.004
	At least moderate BPE	9	53.0	2.4	1.9-3.2	<.001
	High risk	1	1.9	1.0	1.0-1.0	.866
High risk	At least moderate BPE	4	27.7	1.7	1.1-2.7	.017
	At least mild BPE	1	19.4	2.2	1.6-3.0	.002
	High risk	1	2.0	1.0	1.0-1.0	.866

Meta-Analysis: BPE as a Risk Factor

- ▶ Results showed that greater than minimal BPE was associated with higher odds of breast cancer in women with high risk
- ▶ Association was not found in women with average risk
- ▶ suggests higher levels of BPE may have the potential to predict the development of breast cancer, particularly invasive cancer especially among women with high risk

Meta-Analysis: BPE as a Risk Factor

- ▶ Finding consistent regardless of study design, methods of BPE assessment, varied timing of BPE measurement, and BPE assessment by different radiologists
- ▶ Validation analysis of case-control studies after removing unmatched studies further produced similar effect sizes for the association between at least mild BPE or at least moderate BPE) and breast cancer

Association between MRI BPE and Future Primary Breast Cancer Risk

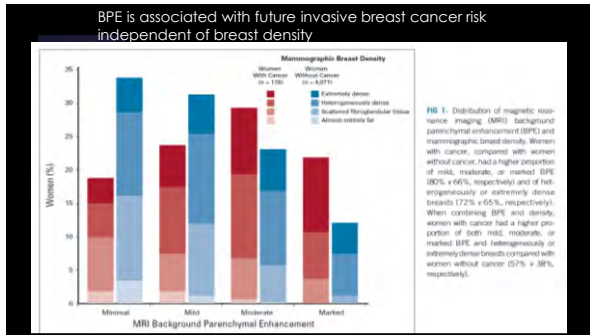
- ▶ More women with cancer had mild, moderate, or marked BPE than women without cancer (80% v 66%, respectively)
- ▶ Compared with minimal BPE, increasing BPE levels were associated with significantly increased cancer risk
- ▶ BPE should be considered for risk prediction models for women undergoing breast MRI

Arauz VA, et al. Population-Based Assessment of the Association Between Magnetic Resonance Imaging Background Parenchymal Enhancement and Future Primary Breast Cancer Risk. *J Clin Oncol* 2019; 37(12):1644-1653.

Table 2. Association Between Baseline MRI BPE and Breast Cancer Risk

Population	Baseline BPE		Multiple BPE Measures per Woman	
	Women With Cancer, No. (%) ^a	Women Without Cancer, No. (%) ^b	Women With Cancer, No. (%) ^a	Women Without Cancer, No. (%) ^b
Total	47 (27)	47 (27)	142 (83)	142 (83)
Minimal	38 (22)	38 (22)	104 (61)	104 (61)
Mild	47 (27)	47 (27)	142 (83)	142 (83)
Moderate	47 (27)	47 (27)	142 (83)	142 (83)
Marked	47 (27)	47 (27)	142 (83)	142 (83)

Association between MRI BPE and Future Primary Breast Cancer Risk



BPE as an Independent Risk Factor [Sippo et al. AJR 2018]

TABLE 1: Results of the Logistic Regression Generalized Estimating Equation Analysis Assessing the Association Between Background Parenchymal Enhancement and Odds of Cancer Diagnosis, Adjusted for Age, Mammographic Breast Density, and Screening Indication

Variable	Adjusted Odds Ratio (95% CI)	P
Age	1.01 (0.99-1.03)	0.02
Background parenchymal enhancement		
Minimal or mild	Reference	0.00
Moderate or marked	2.44 (1.14-4.94)	0.02
Mammographic breast density		
Heterogeneously dense	Reference	0.00
Extremely dense	1.52 (0.78-2.94)	<0.01
Screening indication		
Family history	Reference	0.00
Personal history of breast cancer	1.62 (0.81-3.27)	0.00
High-risk lesion	1.69 (0.85-3.35)	0.00
BRCA mutation or thoracic radiation	0.61 (0.24-1.93)	0.00

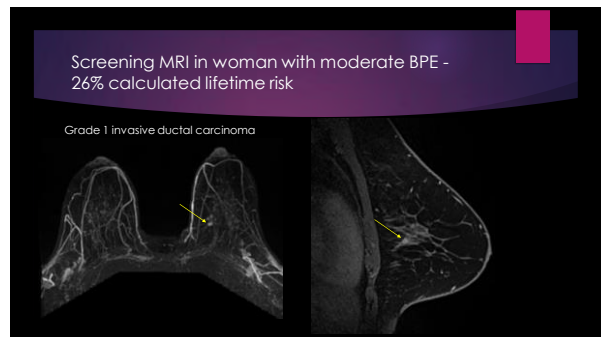
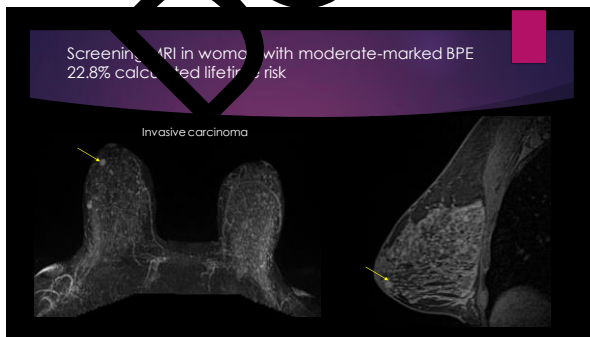
- Study cohort – 4686 screening MRIs in 2446 patients high risk patients (BRCA, thoracic radiation, personal history, family history)
- 85% minimal or mild BPE
- 15% moderate or marked BPE

Sippo: BPE as an Independent Risk Factor

- Moderate or marked BPE at screening was found to be associated with greater risk of developing breast cancer within 1 year, compared to minimal or mild BPE
- Confirms relationship between higher BPE and BC risk
- Multivariable model adjusted for multiple possible confounding risk factors (age, breast density, screening indication) – BPE remained an independent predictor in higher-risk patients having screening MRI

Sippo: BPE as an Independent Risk Factor

- Identifying patients with hormonally responsive breast tissue is important – this combined with other clinical factors could allow for more tailored screening, treatment and prevention strategies for those at high risk [Sippo]
- BPE could be utilized as an imaging biomarker to improve risk assessment, and also for consideration for chemoprevention



Relationship between BPE on High-risk Screening MRI and Future BC Risk

- ▶ Screening MRIs divided into 2 cohorts: cancer cases, control patients (matched by age and high-risk indication at a 2:1 ratio)
- ▶ Nonsignificant differences in age, race, ethnicity, breast density and chemoprevention therapy between the groups

Grimm L, et al. Relationship between Background Parenchymal Enhancement on High-risk Screening MRI and Future Breast Cancer Risk. *Acad Radiol* 2019; 24(1):49-75.

TABLE 2. Odds Ratios of Breast Cancer by Median BPE Level

Characteristic	Cancer Cohort (n = 41)	Control Cohort (n = 122)	Odds Ratio*	P Value
BPE				.01
Minimal	21 (34)	69 (57)	1.0	
Mild	31 (51)	36 (30)	2.8 (1.4–5.7)	
Moderate	7 (11)	16 (13)	1.4 (0.5–3.9)	
Marked	2 (3)	1 (1)	4.6 (0.6–144.8)	
BPE (Bichotomous)				.004
Minimal	21 (34)	69 (57)	1.0	
Mild, moderate, or marked	40 (66)	53 (43)	2.5 (1.3–4.8)	

BPE, background parenchymal enhancement.
Unless otherwise indicated, data are numbers of subjects, with percentages in parentheses.
* Numbers in parentheses are 95% confidence intervals. The first row in each group is the reference variable for the odds ratio calculations.

Median BPE in cancer cohort significantly greater than the control cohort

BPE threshold of minimal vs combined mild, moderate, or marked was chosen to dichotomize the BPE measurements

patients with greater than minimal BPE were 2.5 times more likely to develop future cancer

BPE: Indicator for Prognostic Outcome?

- ▶ Association between BPE and breast cancer molecular subtype/prognostic factors was evaluated
- ▶ No significant association was present between high BPE and the following: HER2+ tumors, basal tumors, tumors with axillary nodal disease, high nuclear grade tumors, high Ki-67 index tumors or larger tumors
- ▶ Patients with high BPE may be at increased risk for breast cancer but not necessarily for cancer subtypes with a poor prognosis

Ha, R et al. Evaluation of association between background parenchymal enhancement on MRI and breast cancer subtype. *International Journal of Gynecology and Obstetrics* 2018; 121:327-331

BPE Assessment

- ▶ Given the important clinical implications of the level of BPE on breast MRI, it is becoming increasingly important to accurately determine BPE level
- ▶ Currently, BPE is typically evaluated subjectively
 - ▶ Interobserver variability for BPE fair ($\kappa = 0.28$) – Grimm, AJR 2015
 - ▶ Method to automate under investigation

AI: Automation of BPE Assessment

- ▶ CNN developed to quantify BPE (and FG) - For quantifying the amount of BPE, the CNN method yielded accuracy of 0.829 and Pearson correlation of 0.955 – Ha, R et al. *J Digital Imaging* 2019
- ▶ BPE estimated qualitatively with the standard BI-RADS scale and quantitatively with a semi-automatic and an automatic software interface showed BI-RADS scores correlated with the automatic ($r = 0.55, p < 0.001$) and semi-automatic scores ($r = 0.60, p < 0.001$) = BPE quantitative evaluation is feasible with both semi-automatic and automatic software and correlates with radiologists' estimation – Tagliafico A, et al. *BJR* 2015

Summary

- ▶ BPE has been found to be a biomarker for breast cancer risk
- ▶ Variations in methods of BPE assessment need to become standardized

"The exact interplay of BPE with other established risk factors must be further elucidated to identify those women for whom BPE may be used to personalize screening strategies"

References

- Ring V, Bzdok JB, Bernstein J, Bhanu AS, Pike MC, Morris EA. Background parenchymal enhancement of breast MR imaging and breast cancer risk. *Radiology* 2011; 260:30-40.
- DeMartini WB, Liu F, Ricciola S, et al. Background parenchymal enhancement on breast MRI: impact on diagnostic performance. *AJR* 2012; 178:1667-1670.
- Hornby LM, Eberman L, Dierker DD, Brennan S, Moran EA. Background parenchymal enhancement on baseline contrast breast MRI: impact on recall rate and short-term follow-up. *AJR* 2011; 176:18-24.
- DeLeo MJ 3rd, et al. Breast MRI fibroglandular volume and parenchymal enhancement in BRCA1 and BRCA2 mutation carriers before and immediately after risk-reducing salpingo-oophorectomy. *AJR Am J Roentgenol* 2015; 204(3):484-493.
- Dorkoch BN, et al. Are qualitative assessments of background parenchymal enhancement amount of fibroglandular tissue on MR images, and mammographic density associated with breast cancer risk? *Radiology* 2015; 237(2):371-380.
- Ring V, et al. Background parenchymal enhancement of breast MR imaging and breast cancer risk. *Radiology* 2011; 260(1):50-60.
- Helander M, et al. Breast MR background parenchymal enhancement (BPE) correlates with the risk of breast cancer. *Magn Reson Imaging* 2015; 33(1):116-120.
- Benzonatti B, et al. MRI background parenchymal enhancement is not associated with breast cancer. *PLoS One* 2015; 10(10):e0142879 [PubMed citation appears in *PLoS One* 2015; 10(10):e0142879].
- DeMartini WB, et al. Background parenchymal enhancement on breast MRI: impact on diagnostic performance. *AJR Am J Roentgenol* 2012; 178(6):1673-1676.
- Melisiother A, et al. Background parenchymal enhancement over exam time in patients with and without breast cancer. *J Magn Reson Imaging* 2017; 45(1):74-83.

References

- Albaril M, et al. The relationship of breast density in mammography and magnetic resonance imaging in high-risk women and women with breast cancer. *Clin Imaging* 2015; 39(6):987-992.
- Thompson CM, et al. The Association of Background Parenchymal Enhancement of Breast MRI with Breast Cancer: A Systematic Review and Meta-Analysis. *Radiology* 2019; 292: 552-561.
- Arasu VA, et al. Population-Based Assessment of the Association Between Magnetic Resonance Imaging Background Parenchymal Enhancement and Family History of a Primary Breast Cancer Risk. *J Clin Oncol* 2019; 37(12): 954-963.
- Grimm J, et al. Relationship between Background Parenchymal Enhancement on High-Risk Screening MRI and Future Breast Cancer Risk. *Acad Radiol* 2019; 26: 69-75.
- Ho, R, et al. Evaluation of association between degree of background parenchymal enhancement on MRI and breast cancer subtype. *Clin Imaging* 2018; 50: 27-310.



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