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FULL PAPER

Association between MRI background parenchymal enhancement and lymphovascular invasion and estrogen receptor status in invasive breast cancer

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Objectives: In magnetic resonance imaging (MRI), background parenchymal enhancement (BPE) is associated with breast cancer risk, but the associations between BPE and clinical characteristics and histological features are unknown. This study aimed to investigate the association between BPE and clinical characteristics (including age, menopausal status, and tumor histological characteristics) in patients with invasive breast cancer.
Methods: This was a retrospective study of 163 patients with invasive breast cancer (164 lesions, 1 patient had bilateral cancer) confirmed by surgery and pathological examination, treated between January 2014 and December 2016 at our university (Kunming Medical University). The patients were divided into two groups: extremely minimal and mild enhancement (low BPE group, n = 78) *vs* moderate and marked enhancement (high BPE group, n = 86).
Results: Compared with the low BPE group, the high BPE group showed higher frequencies of patients < 50 years of age (88% *vs* 38%, $p < 0.0001$), premenopausal (87% *vs* 29%, $p < 0.0001$), T1 staging (35% *vs* 15%, $p = 0.027$), Grade II (57% *vs* 37%, $p = 0.03$), lymphovascular invasion (83% *vs* 13%, $p < 0.0001$), and positive estrogen receptor (ER) (79% *vs* 42%, $p < 0.0001$). The Spearman correlation coefficients (r) between BPE and age, menopausal status, lymphovascular invasion, and ER status were −0.521 ($p < 0.0001$), −0.588 ($p < 0.0001$), 0.697 ($p < 0.0001$), and 0.377 ($p < 0.0001$), respectively.
Conclusion: BPE is negatively associated with age and menopausal status, and is positively associated with lymphovascular invasion and positive ER status.
Advances in knowledge: BPE is not correlated with T staging and histological classification in patients with invasive breast cancer.

INTRODUCTION

Breast cancer is the second most common cancer worldwide and the first in females, with an estimated 1.67 million new cases diagnosed in 2012, representing 25% of all cancers.[1,2] The incidence rates vary across the world, ranging from 27 per 100,000 in Middle Africa and Eastern Asia to 92 in North America. In the United States, the birth-to-death probability of breast cancer in females is 12.4%.[3] Breast cancer is the fifth cause of cancer death worldwide, but the second cause of cancer death in less developed regions.[1,2]

In reality, the term "breast cancer" encompasses a wide variety of malignant diseases affecting the breast, with variable natural history, behavior, and prognosis.[4] Different histological subtypes may be encountered, and each cancer can be characterized based on estrogen receptors (ER), progesterone receptor (PR), and HER2 statuses,[5] as well as on molecular subtypes[6,7] and genomic signatures.[8,9] Nevertheless, a challenge in managing breast cancer is that many characteristics of the disease are observed on the surgical specimen, which may reveal surprises that will lead to additional surgeries, delayed treatments, anxiety, poor quality of life, and possibly poor prognosis. Therefore, predicting the features of the breast cancer as early as possible in the patients' management is of paramount importance. Imaging examinations during preoperative staging may yield important data about the cancer.[10]

MRI is an important component of preoperative staging. Indeed, the tumor extent is more accurately displayed by MRI compared with mammography or ultrasound.[11–14] In addition, MRI detects additional cancers in about 16% of patients with breast cancer.[15] On the other hand, the COMICE and MONET randomized trials suggested that

MRI could be superfluous in patients with breast cancer.[16,17] Nevertheless, MRI has been shown to be of value in females with dense breasts on mammography or with a high risk of multifocal/multicentric lesions.[18,19]

Breast density is determined by the amount of mammary gland,[20] and is an important risk factor of breast cancer.[21,22] The risk of breast cancer in a high-density mammary gland is 3–5 times of that in a low-density (adipose) mammary gland,[23–25] but the association between mammographic breast density and histological characteristics of the cancer is uncertain.[26–28]

In dynamic contrast-enhanced MRI, the enhancement of normal fibroglandular elements is called background parenchymal enhancement (BPE).[29] BPE is different from the breast density involved in mammography since mammographic breast density is mainly due to the amount and superposition of fibro-glandular tissues, while BPE is due to the vascularization of the breast.[29] Similar to mammographic breast density, BPE has been associated with the risk of breast cancer,[30–32] but this is controversial.[33]

It remains uncertain what are the factors influencing BPE and whether BPE is associated with the histological features of breast cancer. Therefore, the aim of this retrospective study was to investigate the association between BPE and clinical characteristics (including age, menopausal status, and tumor histological characteristics) in patients with invasive breast cancer. The results could provide additional data to improve the preoperative staging and overall management of females with breast cancer.

METHODS AND MATERIALS

Study design and patients

This was a retrospective study of 163 patients (164 lesions) with invasive breast cancer confirmed by surgery and pathological examination, treated between January 2014 and December 2016 at our university. The study was approved by the ethics committee of our university. The need for individual consent was waived by the committee because of the retrospective nature of the study.

The inclusion criteria were: (1) underwent pre-operative MRI of both breasts; (2) underwent surgery; (3) available histopathological data; and (4) no missing clinical data. The exclusion criteria were: (1)<18 years of age; (2) pregnant or lactating; or (3) history of BI-RADS six lesion.

MRI

All cases underwent preoperative MRI. An ACHIEVA 3.0 T superconducting magnetic resonance scanner (PHILIPS, Best, The Netherlands), an EWS workstation, and breast coils were used. The patients underwent breast MRI scanning, dynamic enhancement, and diffusion-weighted imaging (DWI) of the two breasts.

The parameters for T_1 weighted imaging (WI) and T_2WI fat suppressed sequences were: T_1WI: repeat time (TR) 400 ms, echo time (TE) 10 ms; T2WI: TR 5000 ms, TE 60 ms; DWI: TR 3300 ms, TE 71 ms; layer thickness of 4 mm; spacing of layers of 1 mm. Dynamic enhancement: TR 4.1 ms, TE 1.2 ms, layer thickness of 4 mm, no spacing. Field of view (FOV) was 350 × 350 mm. The dynamical enhancement sequences included six sequences: mask scanning was conducted before intravenous injection of the contrast agent, followed by five sequences of continuous scanning immediately after the injection of the contrast agents. The scanning time of each sequence was 120 s. The BPE were observed on the images of the second sequence. The contrast agent was Gd-DTPA, at a dose of 0.1 mmol/kg; 15 ml of normal saline were injected after Gd-DTPA.

Image analysis

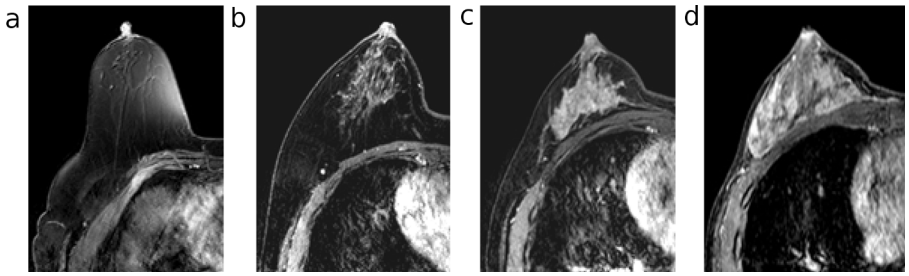
The contralateral images were used as reference for patients with unilateral breast cancer. For patients with bilateral breast cancer, the images at a layer without lesion were used as reference. Images were analyzed by two attending radiologists with >5 years of experience in breast imaging diagnosis. The consistency between the two radiologists was good ($\kappa > 0.85$). All disagreements were solved by discussion.

According to the Breast Imaging Reporting and Data System (BI-RADS) issued in 2013 by the American College of Radiology (ACR),[34] BPE was divided into four categories: minimal enhancement, mild enhancement, moderate enhancement, and marked enhancement (Figure 1). The patients were divided into two groups: cases with minimal enhancement and mild enhancement were in the low BPE group ($n = 78$) and those with moderate and marked enhancement were in the high BPE group ($n = 86$).

Pathological data

All cases were confirmed by pathological examination. All cases were assessed for ER, PR, and human epidermal growth factor receptor 2 (HER2) statuses by immunohistochemistry. The results were determined routinely by pathologists. Cases with

Figure 1. (a) Minimal enhancement. (b) Mild enhancement. (c) Moderate enhancement. (d) Marked enhancement.



≥10% of ER- and PR-positive cells were positive. HER2 ++ and +++ were positive.

Statistical analysis

The continuous data were tested using the Kolmogorov–Smirnov test and were found to have skewed distributions. Categorical data were presented as frequencies and analyzed using the χ^2 test. The non-parametric Spearman correlation analysis was performed for data with significant differences. Statistical analyses were performed using SPSS 17.0 (IBM, Armonk, NY, USA). Two-sided p-values < 0.05 were considered statistically significant.

RESULTS

Characteristics of the patients

Among the 163 patients, there were 89 cases of left breast, 73 cases of right breast, and 1 case of bilateral breast cancer, for a total of 164 lesions. Patients were 22–69 years of age (median, 47 years). Compared with the low BPE group, the high BPE group showed higher frequencies of patients < 50 years of age (88% *vs* 38%, $p < 0.0001$), pre-menopausal (87% *vs* 29%, $p < 0.0001$), T1 staging (35% *vs* 15%, $p = 0.027$), Grade II (57% *vs* 37%, $p = 0.03$), lymphovascular invasion (83% *vs* 13%, $p < 0.0001$), and positive ER (79% *vs* 42%, $p < 0.0001$) (Table 1). There were no significant differences for N stage, PR, and HER2 (Table 1).

Correlations

The Spearman correlation coefficients (r) between BPE and age, menopausal status, lymphovascular invasion, and ER status were −0.521 ($p < 0.0001$),−0.588 ($p < 0.0001$), 0.697 ($p < 0.0001$), and 0.377 ($p < 0.0001$), respectively. There were no statistically significant correlation between BPE and T staging and histological classification ($p > 0.05$) (Table 2).

DISCUSSION

In MRI, BPE is associated with breast cancer risk, but the association between BPE and clinical characteristics and histological features is unknown. Therefore, this study aimed to investigate the association between BPE and clinical characteristics (including age, menopausal status, and tumor histological characteristics) in patients with invasive breast cancer. The results showed that BPE is negatively associated with age and menopausal status, and is positively associated with lymphovascular invasion and positive ER status. BPE is not correlated with T staging and histological classification in patients with invasive breast cancer.

According to BI-RADS 2013, BPE can be divided into four categories[34]: extremely mild enhancement, mild enhancement, moderate enhancement, and severe enhancement. Although there are studies focusing on the quantitative classification of BPE (reviewed in Bignotti et al[35]) there is still a wide variability in the quantitative assessment of breast BPE and the measurement is still somewhat subjective. Kuhl et al[36] listed a series of factors influencing tissue enhancement: distribution of vessels and microvessels; dose, concentration, and permeability of the contrast agent; and duration of T1 of different tissues. Among them, distribution of vessels and permeability of the contrast agent were the most important factors.[36] There are three main blood supplies for the mammary gland[37]: (1) vessels in the median part that derive from perforating branches of the internal thoracic artery (also known as the internal mammary artery); (2) vessels in the lateral part that derive from the rami pectorales arteriae thoracoacromialis and branches of the lateral thoracic artery; and (3) lateral cutaneous branch of the intercostal artery. Since the arteries run from the peripheral part to the central part of the mammary gland, the BPE often starts from the margin of

Table 1. Comparison of age, menopausal status, and histological features between the low and high BPE groups

	Low BPE ($n = 78$)		High BPE ($n = 86$)		p
Age, year					<0.0001
<50	30	38%	76	88%	
>50	48	62%	10	12%	
Menopausal status					<0.0001
Pre-menopausal	23	29%	75	87%	
Post-menopausal	55	71%	11	13%	
T staging					0.027
T1	12	15%	30	35%	
T2	32	41%	24	28%	
T3	19	24%	21	24%	
T4	15	19%	11	13%	
N staging					0.559
N0	35	45%	36	42%	
N1	19	24%	27	31%	
N2	16	21%	12	14%	
N3	8	10%	11	13%	
Histological grade					0.030
Grade I	38	49%	26	30%	
Grade II	29	37%	49	57%	
Grade III	11	14%	11	13%	
Lymphovascular invasion					<0.0001
No	68	87%	15	17%	
Yes	10	13%	71	83%	
ER					<0.0001
Negative	45	58%	18	21%	
Positive	33	42%	68	79%	
PR					0.09
Negative	34	44%	21	24%	
Positive	44	56%	65	76%	
HER2					0.203
Negative	30	38%	25	29%	
Positive	48	62%	61	71%	

BPE, background parenchymal enhancement; ER, estrogen receptor; PR, progesterone receptor.

Table 2. Correlations between BPE and age, menopausal status, and other factors

BPE	Age	Menopausal status	Lymphovascular invasion	ER	T staging	Histological type
Correlation coefficient (r)	−0.521	−0.588	0.697	0.377	−0.048	0.144
P	<0.0001	<0.0001	<0.0001	<0.0001	0.164	0.065

BPE, background parenchymal enhancement.

the gland, and gradually transits to the central region, with the final enhancement of the posterior areola. This kind of distribution of vessel inflow is called the "frame sign." Meanwhile, the permeability of the contrast agent is determined by the formulation of the contrast agent.

Besides the vascular distribution of the mammary glands and formulation of the contrast agent, the menstrual period is an important factor affecting BPE.[38,39] The estrogen and progesterone levels in the body vary with the menstrual cycle. Estrogen can accelerate the proliferation of epithelial cells, and progesterone can further enhance this effect of estrogen. In addition, estrogen can also increase the vascular permeability of the tissue and promote local microcirculation.[38–40] The levels of estrogen and progesterone in premenopausal females are higher than those in postmenopausal females, and the proliferation of mammary epithelial cells and local microcirculation are significantly higher than those in postmenopausal females, which results in a more obvious BPE in premenopausal females than that in postmenopausal females.[31,32,40–42] Blood estrogen and progesterone levels are associated with age, which gradually decrease with age. Especially, in postmenopausal females, the periodic proliferation of mammary epithelial cells terminates and the lobus glandularis tissue degenerates, leaving only large ducts and some fibrous adipose tissues,[43] leading to a gradual decrease of BPE. The present study revealed that BPE was negatively associated with age and menopausal status, as supported by the above literature.

ER and PR expressions increase correspondingly with increasing levels of estrogen and progesterone.[44] Estrogen and progesterone levels are associated with BPE[38,39]; therefore, it could be hypothesized that BPE is associated with ER and PR statuses in patients with breast cancer. The present study suggests that BPE was positively associated with ER, as supported by Dontchos et al,[30] Kim et al,[42] and Ozturk et al.[45] Progesterone is an important intermediate for the biosynthesis of estrogen, androgen, and adrenocorticosteroids. The structure and action mechanism of PR are also complex. There are many factors that influence the synthesis of hormones, of which one or more factors may affect the expression of PR.[46] This may be the reason for the lack of associated between PR and BPE in the present study. Vreeman et al[47] showed an association between BPE and PR negativity. This warrants further study.

In addition, the present study showed that lymphovascular invasion was higher in the high BPE group, and the degree of BPE was positively associated with lymphovascular invasion in invasive breast cancer. This could be associated with the development of the mammary vascular network among different people. People with a good development of the mammary vascular network have abundant supplying arteries, draining veins, capillary network, and lymphatic network, and thus have more significant BPE in dynamic contrast-enhanced MRI. In case of breast cancer in a high BPE breast, the tumor cells are more likely to erode and destruct the surrounding capillaries and lymph capillaries, leading to lymphovascular invasion.

The overexpression of the HER2 is one of the important factors that affect the growth and metastasis of breast cancer. HER2-positive invasive breast cancer usually has a high grade, high T staging, and a higher possibility of metastasis, and thus has a poor prognosis. Currently, the association between BPE and the expression of HER2, T staging, N staging, and histological classification are still unclear in the present study and the literature,[42,45] and additional study is necessary.

Dilorenzo et al[48] examined the BPE in relation to the molecular subtypes of breast cancer in 82 Italian females. They reported that luminal B tumors (mostly ER-positive and PR-lowly positive/negative) were associated with low BPE, while triple-negative breast cancer was associated with high BPE. This is in contradiction with the present study, which showed that ER-positive tumors were associated with high BPE. Those conflicting data could be due, at least in part, to the differences in breast tumor classification, and only very few triple-negative breast cancer patients were included in this study. In addition, differences in breast cancer pathogenesis and life habits between Chinese and Europeans could also be involved. Indeed, age at diagnosis of breast cancer in China is about 10 years younger than in the United States and Europe.[49] In addition, the epidemiology changed abruptly in the recent decades due to the economic boom.[50] Consumption of soy foods also modulate the risk of breast cancer in Chinese females compared with Europeans.[51] Finally, Chinese females are known to have small and mammographically dense breasts.[52] Taken together, those factors could explain part of the discrepancy between the two studies, but additional studies are necessary.

This study is not without limitations. Firstly, this was a retrospective study with a limited sample size from a single center. Secondly, the menstrual cycle was not considered when patients were examined with MRI. Thirdly, race,[53] child-bearing history, family history, obesity,[54] and history of hormone drugs could not be taken into account because of the limited data in the medical charts. Further study is needed to verify the results.

CONCLUSION

In conclusion, BPE is negatively correlated with age and menopausal status, and is positively correlated with lymphovascular

invasion and positive ER status. BPE is not correlated with T staging and histological classification in patients with invasive breast cancer.

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REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359–E386. doi: https://doi.org/10.1002/ijc.29210
2. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers Cet al. *GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet*. International Agency for Research on Cancer: Lyon; 2013. [Available from: Available from: http://globocan.iarc.fr, accessed on 20/03/2018..
3. Siegel RL, Miller KD, Jemal A, statistics C. Cancer statistics, 2018. *CA Cancer J Clin* 2018; **68**: 7–302018;. doi: https://doi.org/10.3322/caac.21442
4. Sharma GN, Dave R, Sanadya J, Sharma P, Sharma KK. Various types and management of breast cancer: an overview. *J Adv Pharm Technol Res* 2010; **1**: 109–26.
5. Bertos NR, Park M. Breast cancer - one term. *many entities? J Clin Invest* 2011; **121**: 3789–96.
6. Hon JDC, Singh B, Sahin A, Du G, Wang J, Wang VY, et al. Breast cancer molecular subtypes: from TNBC to QNBC. *Am J Cancer Res* 2016; **6**: 1864–72.
7. Dai X, Li T, Bai Z, Yang Y, Liu X, Zhan J, et al. Breast cancer intrinsic subtype classification, clinical use and future trends. *Am J Cancer Res* 2015; **5**: 2929–43.
8. Esteva FJ. Genomic signatures in breast cancer: limitations of available predictive data and the importance of prognosis. *Clin Adv Hematol Oncol* 2015; **13**(6 Suppl 6): 25–31.
9. Falato C, Tobin NP, Lorent J, Lindström LS, Bergh J, Foukakis T. Intrinsic subtypes and genomic signatures of primary breast cancer and prognosis after systemic relapse. *Mol Oncol* 2016; **10**: 517–25. doi: https://doi.org/10.1016/j.molonc.2015.11.004
10. Lee SC, Jain PA, Jethwa SC, Tripathy D, Yamashita MW. Radiologist's role in breast cancer staging: providing key information for clinicians. *Radiographics* 2014; **34**: 330–42. doi: https://doi.org/10.1148/rg.342135071
11. Hede K. Preoperative MRI in breast cancer grows contentious. *J Natl Cancer Inst* 2009; **101**: 1667–9. doi: https://doi.org/10.1093/jnci/djp461
12. Lehman CD, Gatsonis C, Kuhl CK, Hendrick RE, Pisano ED, Hanna L, et al. Mri evaluation of the contralateral breast in women with recently diagnosed breast cancer. *N Engl J Med* 2007; **356**: 1295–303. doi: https://doi.org/10.1056/NEJMoa065447
13. Berg WA, Gutierrez L, NessAiver MS, Carter WB, Bhargavan M, Lewis RS, et al. Diagnostic accuracy of mammography, clinical examination, us, and MR imaging in preoperative assessment of breast cancer. *Radiology* 2004; **233**: 830–49. doi: https://doi.org/10.1148/radiol.2333031484
14. Liberman L, Morris EA, Dershaw DD, Abramson AF, Tan LK. Mr imaging of the ipsilateral breast in women with percutaneously proven breast cancer. *AJR Am J Roentgenol* 2003; **180**: 901–10. doi: https://doi.org/10.2214/ajr.180.4.1800901
15. Peters NHGM, Borel Rinkes IHM, Zuithoff NPA, Mali WPTM, Moons KGM, Peeters PHM. Meta-Analysis of Mr imaging in the diagnosis of breast lesions. *Radiology* 2008; **246**: 116–24. doi: https://doi.org/10.1148/radiol.2461061298
16. Peters NHGM, van Esser S, van den Bosch MAAJ, Storm RK, Plaisier PW, van Dalen T, et al. Preoperative MRI and surgical management in patients with nonpalpable breast cancer: the MONET - randomised controlled trial. *Eur J Cancer* 2011; **47**: 879–86. doi: https://doi.org/10.1016/j.ejca.2010.11.035
17. Turnbull L, Brown S, Harvey I, Olivier C, Drew P, Napp V, et al. Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. *The Lancet* 2010; **375**: 563–71. doi: https://doi.org/10.1016/S0140-6736(09)62070-5
18. Biglia N, Bounous VE, Martincich L, Panuccio E, Liberale V, Ottino L, et al. Role of MRI (magnetic resonance imaging) versus conventional imaging for breast cancer presurgical staging in young women or with dense breast. *Eur J Surg Oncol* 2011; **37**: 199–204. doi: https://doi.org/10.1016/j.ejso.2010.12.011
19. Houssami N, Ciatto S, Macaskill P, Lord SJ, Warren RM, Dixon JM, et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. *JCO* 2008; **26**: 3248–58. doi: https://doi.org/10.1200/JCO.2007.15.2108
20. EN L, Zhou CW, Li J. Factors affecting the breast density and its diagnostic value in breast disease. *J Pract Radiol* 2013; **29**: 1570–2.
21. Titus-Ernstoff L, Tosteson ANA, Kasales C, Weiss J, Goodrich M, Hatch EE, et al. Breast cancer risk factors in relation to breast density (United States. *Cancer Causes Control* 2006; **17**: 1281–90. doi: https://doi.org/10.1007/s10552-006-0071-1
22. McCormack VA, Silva dosS I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiology Biomarkers & Prevention* 2006; **15**: 1159–69. doi: https://doi.org/10.1158/1055-9965.EPI-06-0034
23. Manning MA, Duric N, Littrup P, Bey-Knight L, Penner L, Albrecht TL. Knowledge of breast density and awareness of related breast cancer risk. *J Canc Educ* 2013; **28**: 270–4. doi: https://doi.org/10.1007/s13187-013-0457-1
24. Price ER, Hargreaves J, Lipson JA, Sickles EA, Brenner RJ, Lindfors KK, et al. The California breast density information group: a collaborative response to the issues of breast density, breast cancer risk, and breast density notification legislation. *Radiology* 2013; **269**: 887–92. doi: https://doi.org/10.1148/radiol.13131217
25. Yaghjyan L, Colditz GA, Rosner B, Tamimi RM. Mammographic breast density and breast cancer risk: interactions of percent density, absolute dense, and non-dense areas with breast cancer risk factors. *Breast Cancer Res Treat* 2015; **150**: 181–9. doi: https://doi.org/10.1007/s10549-015-3286-6
26. Ahmadinejad N, Movahedinia S, Movahedinia S, Shahriari M. Association of mammographic density with pathologic findings. *Iran Red Crescent Med J* 2013; **15**: e16698. doi: https://doi.org/10.5812/ircmj.16698

27. Ghosh K, Vierkant RA, Frank RD, Winham S, Visscher DW, Pankratz VS, et al. Association between mammographic breast density and histologic features of benign breast disease. *Breast Cancer Res* 2017; **19**: 134. doi: https://doi.org/10.1186/s13058-017-0922-6
28. Ghosh K, Brandt KR, Sellers TA, Reynolds C, Scott CG, Maloney SD, et al. Association of mammographic density with the pathology of subsequent breast cancer among postmenopausal women. *Cancer Epidemiology Biomarkers & Prevention* 2008; **17**: 872–9. doi: https://doi.org/10.1158/1055-9965.EPI-07-0559
29. Giess CS, Yeh ED, Raza S, Birdwell RL. Background parenchymal enhancement at breast MR imaging: normal patterns, diagnostic challenges, and potential for false-positive and false-negative interpretation. *Radiographics* 2014; **34**: 234–47. doi: https://doi.org/10.1148/rg.341135034
30. Dontchos BN, Rahbar H, Partridge SC, Korde LA, Lam DL, Scheel JR, 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; **276**: 371–80. doi: https://doi.org/10.1148/radiol.2015142304
31. King V, Brooks JD, Bernstein JL, Reiner AS, Pike MC, Morris EA. Background parenchymal enhancement at breast MR imaging and breast cancer risk. *Radiology* 2011; **260**: 50–60. doi: https://doi.org/10.1148/radiol.11102156
32. Hu X, Jiang L, Li Q, Gu Y. Quantitative assessment of background parenchymal enhancement in breast magnetic resonance images predicts the risk of breast cancer. *Oncotarget* 2017; **8**: 10620–7. doi: https://doi.org/10.18632/oncotarget.13538
33. Bennani-Baiti B, Dietzel M, Baltzer PA. Mri background parenchymal enhancement is not associated with breast cancer. *PLoS One* 2016; **11**: e0158573. doi: https://doi.org/10.1371/journal.pone.0158573
34. D'Orsi CJ, Sickles EA, Mendelson EB. ACR BI-RADS atlas, breast imaging reporting and data system. Reston. *American College of Radiology* 2013;.
35. Bignotti B, Signori A, Valdora F, Rossi F, Calabrese M, Durando M, et al. Evaluation of background parenchymal enhancement on breast MRI: a systematic review. *Br J Radiol* 2017; **90**: 20160542. doi: https://doi.org/10.1259/bjr.20160542
36. Kuhl CK, Jost P, Morakkabati N, Zivanovic O, Schild HH, Gieseke J. Contrast-Enhanced MR imaging of the breast at 3.0 and 1.5 T in the same patients: initial experience. *Radiology* 2006; **239**: 666–76. doi: https://doi.org/10.1148/radiol.2392050509
37. LP L, Li J, Deng QY. Anatomical observation of the main supplying arteries of the breast by color Doppler ultrasound. *J Ultrasound Clin Med* 2015; **17**: 586–9.
38. King V, Gu Y, Kaplan JB, Brooks JD, Pike MC, Morris EA. Impact of menopausal status on background parenchymal enhancement and fibroglandular tissue on breast MRI. *Eur Radiol* 2012; **22**: 2641–7. doi: https://doi.org/10.1007/s00330-012-2553-8
39. Hegenscheid K, Schmidt CO, Seipel R, Laqua R, Ohlinger R, Hosten N, et al. Contrast enhancement kinetics of normal breast parenchyma in dynamic Mr mammography: effects of menopausal status, oral contraceptives, and postmenopausal hormone therapy. *Eur Radiol* 2012; **22**: 2633–40. doi: https://doi.org/10.1007/s00330-012-2544-9
40. Arslan G, Çelik L, Çubuk R, Çelik L, Atasoy MM. Background parenchymal enhancement: is it just an innocent effect of estrogen on the breast? *Diagn Interv Radiol* 2017; **23**: 414–9. doi: https://doi.org/10.5152/dir.2017.17048
41. Lim Y, Ko ES, Han B-K, Ko EY, Choi JS, Lee JE, et al. Background parenchymal enhancement on breast MRI: association with recurrence-free survival in patients with newly diagnosed invasive breast cancer. *Breast Cancer Res Treat* 2017; **163**: 573–86. doi: https://doi.org/10.1007/s10549-017-4217-5
42. Kim MY, Choi N, Yang J-H, Yoo YB, Park KS. Background parenchymal enhancement on breast MRI and mammographic breast density: correlation with tumour characteristics. *Clin Radiol* 2015; **70**: 706–10. doi: https://doi.org/10.1016/j.crad.2015.02.017
43. Qin NS, Wang DD, Wang XY. Correlation between breast density and age, menstrual state and breast cancer. *Chin J Med Imaging Tech* 2011; **27**: 1607–9.
44. Dunbier AK, Anderson H, Ghazoui Z, Folkerd EJ, A'Hern R, Crowder RJ, et al. Relationship between plasma estradiol levels and estrogen-responsive gene expression in estrogen Receptor–Positive breast cancer in postmenopausal women. *JCO* 2010; **28**: 1161–7. doi: https://doi.org/10.1200/JCO.2009.23.9616
45. Ozturk M, Polat AV, Sullu Y, Tomak L, Polat AK. Background parenchymal enhancement and Fibroglandular tissue proportion on breast MRI: correlation with hormone receptor expression and molecular subtypes of breast cancer. *J Breast Health* 2017; **13**: 27–33. doi: https://doi.org/10.5152/tjbh.2016.3247
46. Ruiz-Cortes ZT. Gonadal Sex Steroids: Production, Action and Interactions in Mammals. In: editor.*Ostojic SM*. London: Steroids - From Physiology to Clinical Medicine; 2012.
47. Vreemann S, Gubern-Mérida A, Borelli C, Bult P, Karssemeijer N, Mann RM. The correlation of background parenchymal enhancement in the contralateral breast with patient and tumor characteristics of MRI-screen detected breast cancers. *PLoS One* 2018; **13**: e0191399. doi: https://doi.org/10.1371/journal.pone.0191399
48. Dilorenzo G, Telegrafo M, La Forgia D, Stabile Ianora AA, Moschetta M. Breast MRI background parenchymal enhancement as an imaging bridge to molecular cancer sub-type. *Eur J Radiol* 2019; **113**: 148–52. doi: https://doi.org/10.1016/j.ejrad.2019.02.018
49. Song Q-K, Li J, Huang R, Fan J-H, Zheng R-S, Zhang B-N, et al. Age of diagnosis of breast cancer in China: almost 10 years earlier than in the United States and the European Union. *Asian Pac J Cancer Prev* 2014; **15**: 10021–5. doi: https://doi.org/10.7314/APJCP.2014.15.22.10021
50. Bray F, McCarron P, Parkin DM. The changing global patterns of female breast cancer incidence and mortality. *Breast Cancer Res* 2004; **6**: 229–39. doi: https://doi.org/10.1186/bcr932
51. FJ H, Chen JQ, soybean Cof, foods soy. Soy isoflavones and breast cancer incidence: differences between Chinese women and women in Western countries and possible mechanisms. *Food Sci Hum Wellness* 2013; **2**(3-4): 146–61.
52. Lai CWK, Law HKW. Mammographic breast density in Chinese women: spatial distribution and autocorrelation patterns. *PLoS One* 2015; **10**: e0136881. doi: https://doi.org/10.1371/journal.pone.0136881
53. Razzaghi H, Troester MA, Gierach GL, Olshan AF, Yankaskas BC, Millikan RC. Mammographic density and breast cancer risk in white and African American women. *Breast Cancer Res Treat* 2012; **135**: 571–80. doi: https://doi.org/10.1007/s10549-012-2185-3
54. Zhu W, Huang P, Macura KJ, Artemov D. Association between breast cancer, breast density, and body adiposity evaluated by MRI. *Eur Radiol* 2016; **26**: 2308–16. doi: https://doi.org/10.1007/s00330-015-4058-8