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"Exploring the intricacies of Background Parenchymal Enhancement and its correlation with Age, Breast Density and Lesion type using Contrast Enhanced Mammogram"

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ABSTRACT:
Background: Normal breast parenchymal enhancement may be seen in contrast-enhanced Enhanced Mammogram and Contrast-EnhancedMRI due to the usage of an intravenous contrast agent. It is imperative to describe Background Parenchymal Enhancement (BPE) in these modalities since it may influence the interpretation of imaging findings. BPE, in turn, can be influenced by many factors.
Objective: To investigate the correlation between potential influencing factors, namely Age and Breast Density, on BPE. Additionally, the study aims to assess the correlation of BPE patterns, Age, and Breast Density among malignant and non-malignant breast lesions.
Methods: The age of the participant, Breast Density in DBT, and BPE pattern in CEM wereobtained for 802 (Malignant-327 vs Non-Malignant -475) histo-pathologically proven lesions. Participants were segregated into 2 groups: Malignant and Non Malignant. The differences in Mean Age, Breast Density, and BPE between the 2 groups were evaluated. Independent samples t-test was used to compare the mean between 2 groups and to compare the distribution of qualitative variables between the groups, chi-square test was used. A P value of less than 0.05 was considered to be statistically significant.To estimate the adjusted odds ratio, Multivariate logistic regression analysis was performed.
Results: In non-dense breasts, the proportion of malignant lesions (40.7%) was higher than the non-malignant lesions (29.3%), whereas in dense breasts, the proportion of non-malignant lesions(70.7%) was higher than the malignant lesions(59.3%). The prevalence of non-dense breasts and, mean age were higher in individuals with malignant lesions compared to those with non-malignant lesions, with a statistically significant P value of less than 0.05.Among the participants with malignant lesions, 77.3% had minimal and mild BPE while fornon-malignant lesions.The pattern of distribution of BPE was similar between malignant and non-malignant lesions with a P value of more than 0.05.The mean age was higher among those with non-dense breastsand those with minimal and mild BPE than those with dense breasts and those with moderate and marked BPE with a P value of less than 0.05.
Conclusion: High mean age and non-dense breast showed a higher proportion of minimal and mild BPE than moderate to marked BPE. The pattern of BPE among malignant and non–malignant groups was similar while high mean age and non-dense breast showed a high proportion of malignancy.

KEYWORDS: Background Parenchymal Enhancement, Contrast Enhanced Mammogram, Digital Breast Tomosynthesis, Contrast-Enhanced Magnetic Resonance Imaging,Breast Density, Breast Malignancy.

Abbreviations: BPE-Background Parenchymal Enhancement, CEM-Contrast Enhanced Mammogram, DBT-Digital Breast Tomosynthesis, CEMRI-Contrast Enhanced Magnetic Resonance Imaging, CC – Cranio-caudal, MLO – Medio Lateral Oblique.

I. INTRODUCTION:

Contrast-enhanced mammography (CEM) emerges as a promising breast imaging modality, integrating the advantages of digital mammography with the application of intravenous contrast agents[1-3]. The contrast agents utilized in CEM, similar to Contrast-enhanced Magnetic Resonance Imaging (CEMRI), effectively highlight areas of neo-angiogenesis in malignant lesions. By providing functional imaging, both CEM and CEMRI demonstrate 100 percent sensitivity and higher

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specificity compared to the anatomical imaging offered by plain mammograms or ultrasound[1-3]. CEM has superior diagnostic accuracy than CEMRI due to less false positive rates.

While CEMRI presents challenges such as high false positive rates, limited availability of dedicated breast coils, and elevated costs[1-3], it also imposes restrictions on individuals with severe claustrophobia, morbid obesity (due to table weight limitations), pacemakers, metallic foreign bodies, or aneurysmal clips. In contrast, CEM emerges as a patient-friendly and cost-effective alternative to CEMRI, offering quicker imaging and interpretation times.

In accordance with the American College of Radiology Lexicon for Contrast-Enhanced Magnetic Resonance Imaging (CEMRI) (5th edition, 2013) and Contrast-Enhanced Mammography (CEM) (Supplementary Atlas, 2022), it is imperative to describe aboutlevel and symmetry of Background Parenchymal Enhancement (BPE)in normal breast parenchymawith subtracted images.

Both CEMRI and CEM involve the use of intravenous contrast, leading to normal enhancement in fibroglandular breast parenchyma. It is crucial to describe BPE relative to the amount of fibroglandular tissue, rather than the entire breast volume, as BPE is not directly correlated with the quantity of fibroglandular tissue[5]. The degree of BPE should be categorized as minimal, mild, moderate, or marked. Additionally, BPE can be characterized as symmetric or asymmetric. Symmetric BPE indicates similar levels and distribution between both breasts, while asymmetric BPE suggests a more extensive distribution of enhancement in one breast compared to the other. Asymmetric BPE may arise post-radiation therapy, with the radiated breast exhibiting less BPE. In cases of unexplained asymmetric BPE, further evaluation is recommended, as it could signify a pathological condition such as diffuse inflammation or malignancy in the breast with higher asymmetric BPE[5].

The characterization of BPE becomes crucial as it has the potential to impact the diagnostic efficacy of these imaging modalities. While numerous studies have explored BPE in the context of CEMRI, there exists only a meagre data on BPE in CEM.

This study aims to address this gap by systematically examining the potential influencing factors of BPE in CEM, specifically focusing on variables such as Age and Breast Density. Additionally, the study endeavors to establish correlations between BPE patterns and the occurrence of Malignant versus Non-malignant lesions. Through a comprehensive analysis, we aim to contribute valuable insights into the understanding of BPE in the context of CEM, thereby enhancing the overall understanding of factors influencing diagnostic outcomes in this modality.

II. PATIENTS AND METHODS:

Study Population: We secured approval from the Institutional Ethical Committee before initiating the study. Before conducting a CEM scan, informed written consent was obtained from all participants. Patient selection for this retrospective study encompassed individuals who underwent CEM between July 2019 and January 2022

Inclusion Criteria: Comprised patients with a pathologically confirmed diagnosis of breast lesions who underwent CEM before surgery or biopsy.

Exclusion Criteria: Encompassed lesions lacking a pathological report, cases undergoing hormonal treatment (including hormonal replacement therapy or hormonal contraceptives), instances of bilateral breast lesions, previous history of radiotherapy to the breast and patients with a single breast. Ultimately, after applying these criteria, 802 lesions met the inclusion criteria

Imaging workup and interpretation:CEM was performed using the Hologic–Selenia Dimensions 3D Tomosynthesis unit. Ultrasound of both breasts were done for all patients before CEM and second look USG after CEM in a few cases. Digital Breast Tomosynthesis (DBT) was done for almost all patients for screening/diagnostic purposes, followed by CEM in indicated patients. With DBT and USG, the diseased side and the view in which the lesion was better identified, were noted before CEM.

For CEM, a peripheral intra-venous cannula was placed in the antecubital or forearm vein preferably with a 22G needle[1-3]. The position was checked with 10 ml of saline bolus. Using a Medradplus single head pressure injector, 1.5ml/kg body weight of low osmolar, nonionic, iodinated contrast [Iohexol or omnipaque 300 to 350mg of iodine/ml] was injected at a rate of 3ml/sec with the patient in a sitting position[1-3] . The patient was also monitored for contrast reaction. After 120 seconds, imaging was started with a CC view of the diseased breast followed by a CC view of the opposite breast, MLO of the diseased breast, and MLO of the opposite breast, which was completed within 6 minutes of contrast injection. A delayed CC view

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of the diseased breast was obtained at 8 minutes in cases of enhancing lesions[1-3].

The CEM mode automatically collected 2 images in each view, one with a low-energy (LE) acquisition at 28-32 kVp and a high-energy acquisition at 45–49 kVp, depending on breast thickness and density[1,3,5]. For each low and high-energy pair, subtraction was performed automatically, generating a recombinant (RC) image. It maximized the conspicuity of iodine contrast agent uptake in the lesion. The low-energy and RC images were sent to the workstation for image interpretation[1,3,5]. Density of the breast in DBT and BPE of the breast in CEM(RC image) were analyzed qualitatively in the non-diseased breast.

ACR BI-RADS Mammographic Breast Density(5th edition) (Figure.1)

The breasts are almost entirely fatty

B. There are scattered areas of fibroglandular density

C. The breasts are heterogeneously dense, which may obscure small masses.

D.The breasts are extremely dense, which lowers the sensitivity of mammography.

ACR BI-RADS CEM LEXICON on level of BPE(2022 supplementary edition):

1.Minimal (Figure 2.)
2.Mild (Figure 3.)
3.Moderate (Figure 4.)
4.Marked (Figure 5.)

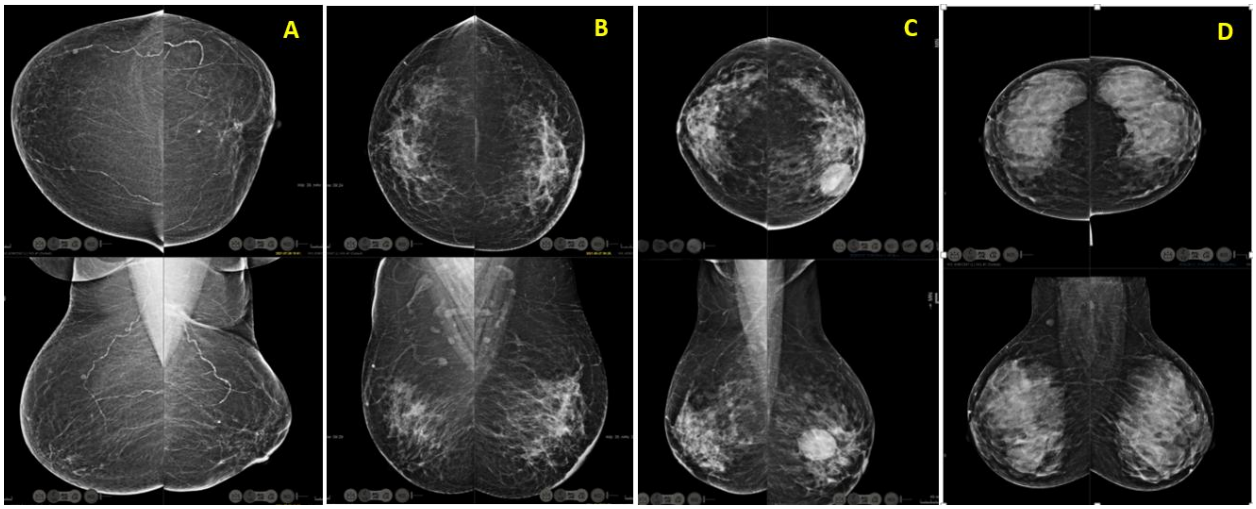

Figure 1. DBT images of Breast Density.

A. CC (Top row) and MLO (Bottom row) views of the same patient showing Type A breast density;
B. CC (Top row) and MLO (Bottom row) views of the same patient showing Type B breast density;
C. CC (Top row) and MLO (Bottom row) views of the same patient showing Type C breast density;
D. CC (Top row) and MLO (Bottom row) views of the same patient showing Type D breast density

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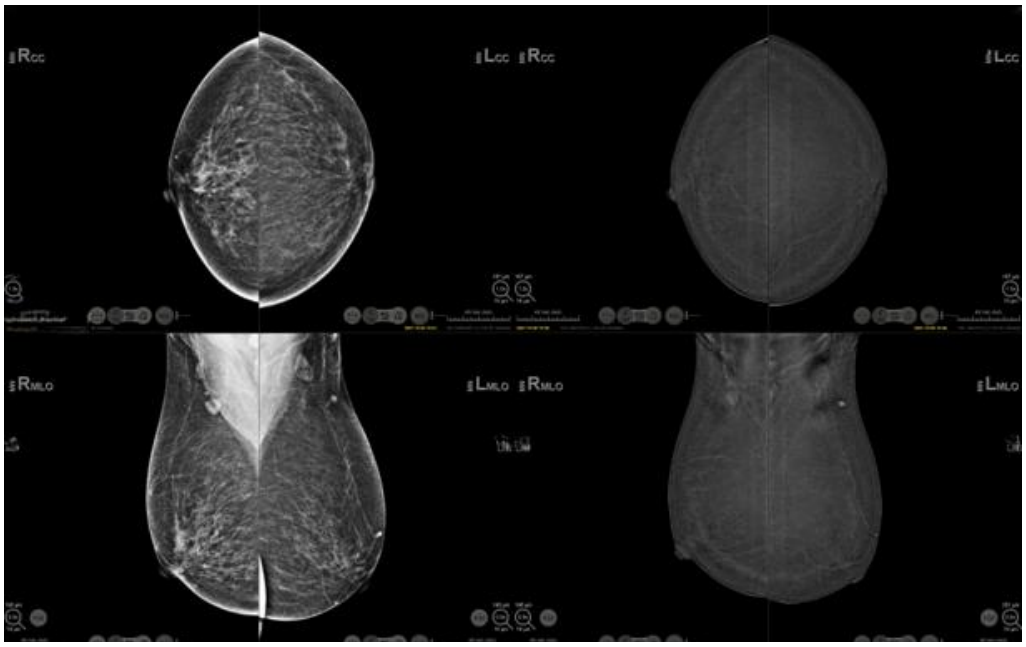

Figure 2. Column 1 shows DBT images; column 2 shows CC (Top row) and MLO (bottom row) views of the same patient with minimal BPE.

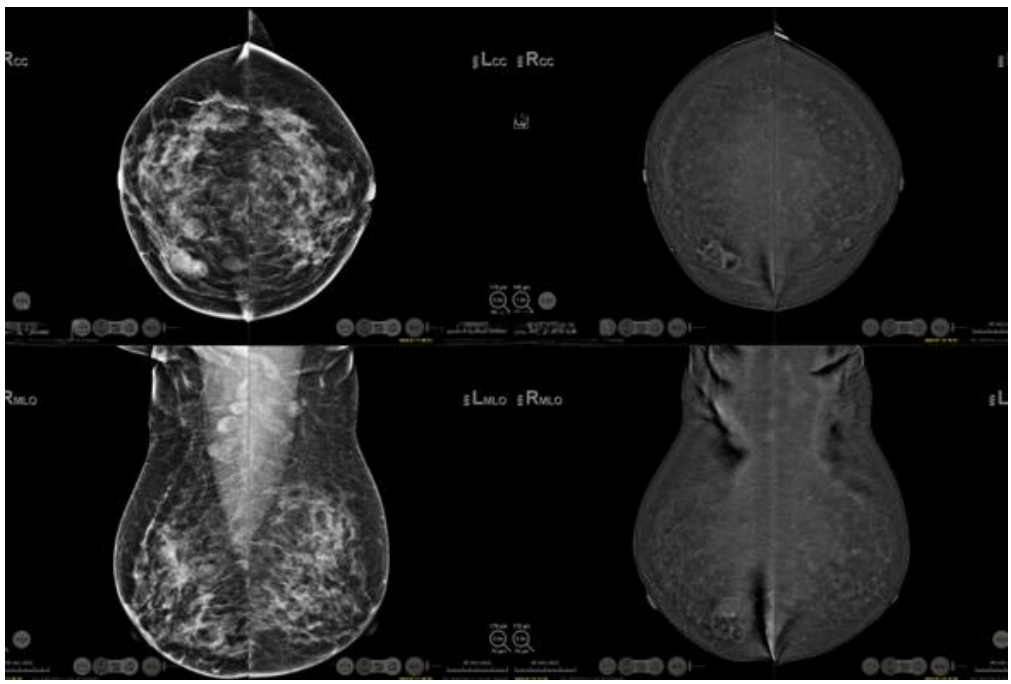

Figure 3. Column 1 shows DBT images; column 2 shows CC (Top row) and MLO (bottom row) views of the same patient with mild BPE.

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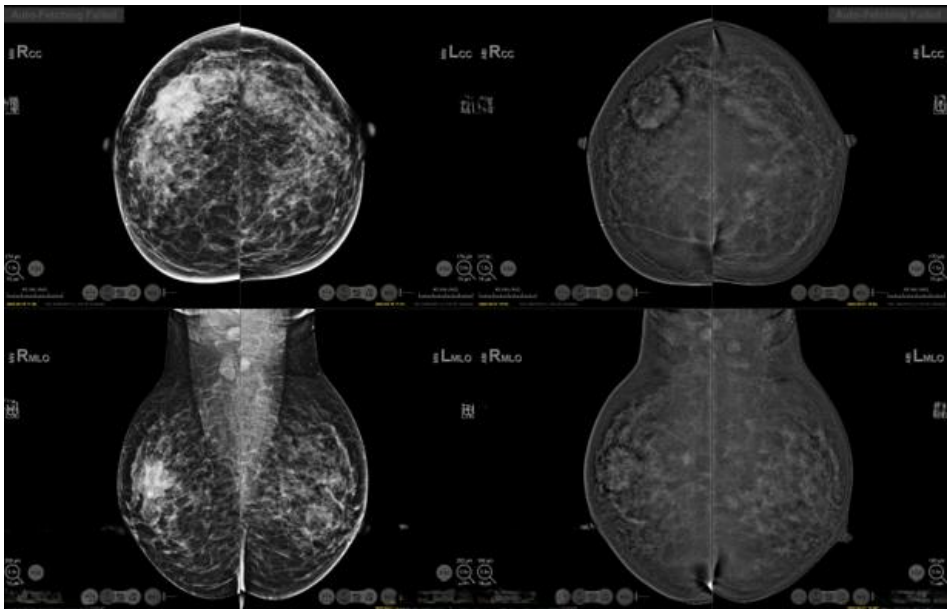

Figure 4. Column 1 shows DBT images; column 2 shows CC (Top row) and MLO (bottom row) views of the same patient with moderate BPE.

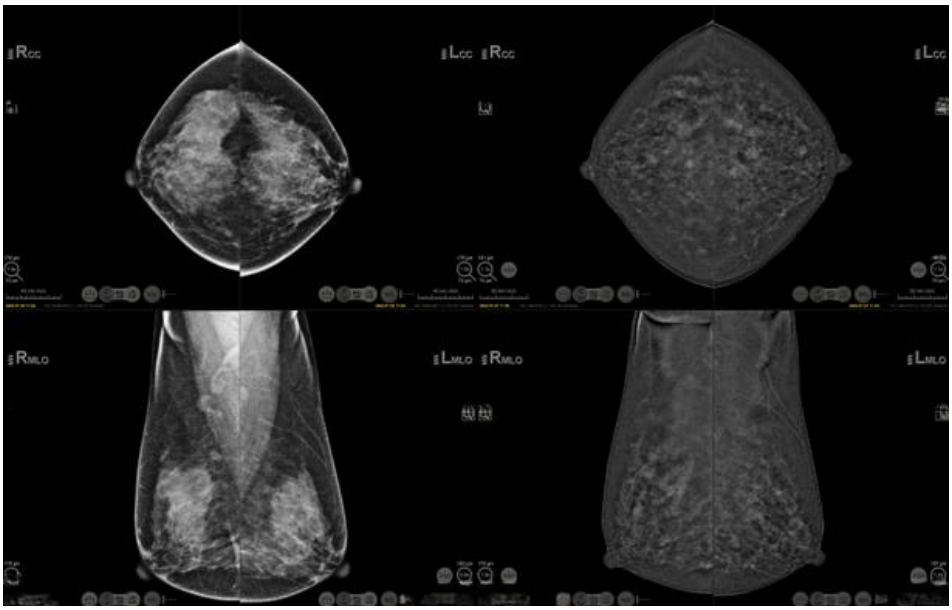

Figure 5. Column 1 shows DBT images; column 2 shows CC (Top row) and MLO (bottom row) views of the same patient with marked BPE.

Data collection and Statistical analysis :

The age of the patient, Breast Density, and laterality of the breast lesion was collected from our electronic records. Background parenchymal enhancement on the non-diseased side was recorded. Based on the histopathological results obtained from the FNAB/core biopsy or excision biopsy, the lesions were segregated into malignant or non-malignant categories. All non-malignant cases had imaging or clinical follow-up for at least one year.

The data collected were made into a master chart using Microsoft Excel 2019 and then loaded onto SPSS version 26 for statistical analysis. Both quantitative and qualitative variables were collected. Age was treated as both quantitative and qualitative while HPE findings, BPE, and breast density were qualitative variables. To compare the mean between the two groups, the independent samples t-test was used and to compare the distribution of qualitative variables between the groups, the chi-square test was used. A P value of

less than 0.05 was considered to be statistically significant.

To estimate the adjusted odds ratio,Multivariate logistic regression analysis was performed with the enter method. The dependent variable for the model was the malignant status of the lesion while age, breast density, and BPE findings were the covariates used in the model.

III. RESULTS:

Table 1: Distribution according to breast density (non-dense/ dense breast) measured by DBT between the malignant and non-malignant lesions

Breast density	Malignant on HPE (n=327)		Non-malignant on HPE/Cytology/Follow up (n=475)		X^2	P value
	N	%	N	%		
Non-dense (Type A &B)	133	40.7	139	29.3	11.24	0.001
Dense (Type C &D)	194	59.3	336	70.7		

In non-dense breasts, the proportion of malignant lesions is higher than the non-malignant lesions, whereas in dense breasts, the proportion of non-malignant lesions is higher than the malignant lesions.
In individuals with a malignant lesion, 40.7% had non-dense breasts, while among those with a non-malignant lesion, 29.3% had non-dense breasts. The prevalence of non-dense breasts was higher in individuals with malignant lesions compared to those with non-malignant lesions, with a statistically significant P value of less than 0.05.

Table 2: Distribution according to BPE types in CEM between malignant and non-malignantlesions

Findings	Malignant on HPE (n=327)		Non-malignant on HPE/Cytology/Follow up (n=475)		X^2	P value
	N	%	N	%		
Minimal & Mild	253	77.3	344	72.4	2.49	0.114
Moderate & Marked	74	22.6	131	27.6		

Among the participants with malignant lesions, 77.3% had minimal and mild BPE while among those with non-malignant lesions, the proportion was 72.4%. The BPE distribution pattern was similar between malignant and non-malignant lesions with a P value of more than 0.05.

Table 3: Comparison of mean age among the participants with malignant and non-malignant lesions.

HPE	Age (in years)		T value	P value
	Mean	SD		
Malignant (n=327)	52.68	10.61	5.39	0.001
Non-Malignant (n=475)	48.78	9.64		

The mean age among the participants with malignancy was 52.68 ± 10.60 years and for those with non-malignant lesions was 48.78 ± 9.64 years. The mean age was more among those with malignant lesions than those with non-malignant lesions and the difference was statistically significant with a P value of less than 0.05.

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Table 4: Comparison of age of the patients with density of breast in DBT

BPE in CEM	Total	Age in years		T value	P value
		Mean	SD		
Non-dense	272	54.42	10.63	8.38	0.001
Dense	530	48.29	9.35		

The mean age was higher among those with non-dense breast than those with dense breast with P value of less than 0.05.

Table 5: Comparison of age of the patients with BPE in CEM

BPE in CEM	Total	Age in years		T value	P value
		Mean	SD		
Minimal & Mild	597	51.86	10.45	8.21	0.001
Moderate& marked	205	46.03	8.10		

The mean age was higher among those with minimal and mild BPE than those with moderate and marked BPE with P value of less than 0.05.

Table 6 : Comparison of Breast Density in DBT with BPE in CEM

Breast density	Minimal & Mild (n=597)		Moderate& marked (n=205)		X^2	P value
	N	%	N	%		
Non-dense (Type A &B)	257	43	15	7.3	86.92	0.001
Dense (Type C &D)	340	57	190	92.7		

Among the participants with minimal and mild BPE, 43% had non-densebreasts and among those with moderate and marked BPE, the proportion of non-dense breastswas 7.3% only. Non-dense breast was associated with minimal and mild BPE with a P value of less than 0.05.

Table 7: Logistic regression analysis of influencing factors of malignant lesions.

Factor		B	SE	Wald x^2	P value	AOR	95% CI
Breast density	Dense					1	
	Non dense	0.336	0.157	4.569	0.033	1.4	1.1-1.9
BPE in CEM	Minimal & Mild					1	
	Moderate& marked	0.005	0.181	0.001	0.977	1.01	0.70-1.4
Age group (in years)	≤ 40			20.02	0.001	1	
	41-60	1.207	0.270	20.02	0.001	3.34	1.97-5.67
	>60	0.571	0.205	7.79	0.005	1.77	1.18-2.64

Those with non-dense breasts were at a 1.4 times increased risk of having malignant lesions than those with dense breasts.

Those in the age group 41 to 60 years were 3.34 times increased risk of having malignant lesions in comparison to those aged less than or equal to 40 years. For those aged more than 60 years, the risk was 1.77 times in comparison to those aged less than or equal to 40 years.

BPE was not as significant as Age and Breast Density in prediction of malignancy

IV. DISCUSSION:

CEM, akin to CEMRI, provides functional imaging through the utilization of intravenous contrast agents. It has been demonstrated as a cost-effective and patient-friendly modality within the breast imaging armamentarium. Numerous investigations have affirmed that the sensitivity of CEM is comparable to that of CEMRI, with a specificity surpassing that of CEMRI. The evaluation of the morphology of enhancing lesions in reconstructed contrast images, correlated with

low-energy images, facilitates the characterization of breast lesions.

According to prior research in MRI and CEM, it is crucial to address BPE as it can impact diagnostic effectiveness and potentially serve as an independent predictor of breast cancer in high-risk populations. In our analysis, we examined potential influencing factors in CEM, including age and breast density, and assessed their relationship with BPE. Additionally, we investigated the prevalence of malignancy concerning breast density (dense/non-dense), age (young/old), and BPE levels (lower/higher).

In non-dense breasts, the proportion of malignant lesions (40.7%) was higher than the non-malignant lesions (29.3%), whereas in dense breasts, the proportion of non-malignant lesions (70.7%) was higher than the malignant lesions (59.3%). The prevalence of non-dense breasts and,mean age were higher in individuals with malignant lesions compared to those with non-malignant lesions, with a statistically significant P value of less than 0.05. Among the participants with malignant lesions, 77.3% had minimal and mild BPE while fornon-malignant lesions. The BPE distribution pattern was similar between malignant and non-malignant lesions with a P value of more than 0.05.The mean age was higher among those with non-dense breasts and those with minimal and mild BPE than those with dense breasts and those with moderate and marked BPE with a P value of less than 0.05.

Individuals exhibiting non-dense breast composition demonstrated a 1.4-fold elevated risk of harboring malignant lesions in comparison to their counterparts with dense breast tissue. Moreover, those within the age bracket of 41 to 60 years exhibited a notable 3.34-fold increased risk of possessing malignant lesions compared to individuals aged less than or equal to 40 years. In the demographic aged over 60 years, the risk was 1.77 times higher relative to those aged less than or equal to 40 years. Notably, breast parenchymal enhancement (BPE) emerged as a less significant predictor of malignancy compared to age and breast density in our investigation

In the study conducted by Arkani et al, a noteworthy correlation was identified between mammographic density and BPE[6]. Conversely, Cubuk et al and Hansen et al did not observe a significant correlation between breast density and BPE in their respective studies[7]. In our investigation, participants with non-dense breasts had a higher proportion of minimal and mild BPE than those with dense breasts.

DeMartini et al investigated the influence of BPE on MRI diagnostic performance in a cohort of 736 women. They observed a significantly higher prevalence of moderate or marked background parenchymal enhancement in patients younger than 50 years compared to those aged 50 and older (39.7% vs. 18.9%; $p < 0.0001$)[8]. Our study aligns with these findings, revealing a higher mean age in individuals with minimal and mild BPE compared to those with moderate and marked BPE.

Sogani et al conducted a comparison of BPE between CESM and MRI, examining its correlation with clinical factors. Their findings indicated that the menstrual cycle did not exhibit a distinct pattern of variation in BPE for both CESM and MRI. As a result, they proposed that scheduling examinations with menstrual cycle timing to evaluate BPE was not necessary. Additionally, the research highlighted that women undergoing hormonal therapy for breast cancer, those in a post-radiation status, and postmenopausal women exhibited consistently lower BPE compared to their counterparts[9].

Luczynska et al conducted an analysis of BPE on CESM, comparing it to MRI. They concluded that quantitatively assessing the level of enhancement of lesions in CESM provides better results compared to qualitative assessment without comparison, particularly in relation to BPE[10].

Meucci et al emphasized the significance of scoring BPE in CESM and recommended that future radiologists actively engage with CESM and utilize its tools, such as BPE[11]. Our study aligns with and follows this guidance.

According to Cong Xu et al, in high-risk females for breast cancer, evaluating CESM, BPE could be valuable in predicting breast cancer, whereas breast density in mammograms was not identified as an independent risk factor[12].

Wang et al conducted an analysis involving 207 patients to examine the connection between clinical factors and the degree of BPE on CEM. Their findings indicated that the timing of the menstrual cycle was independently linked to the degree of BPE in premenopausal patients, with the lowest degree observed on menstrual days 8–14[13]. Due to the lack of a consistent association with the menstrual cycle in other studies, we have not incorporated menstrual cycle scheduling into our CEM protocols.

In contrast to previous studies, our research is distinguished by its larger sample size, contributing to enhanced reliability and reduced margin of error. Our study relied on qualitative assessment due to the limited availability of

quantitative software. The limitation of this study is that the observations were made by a single observer which may have subjective bias. The correlation of BPE with menstrual status was not done.

V. CONCLUSION :

In our study**,** high mean age and non-dense breasts showed a higher proportion of minimal and mild BPE than moderate to marked BPE. The pattern of BPE among malignant and non–malignant groups was similar while high mean age and non-dense breast showed a high proportion of malignancy.Those with non-dense breasts were at 1.4 times increased risk of having malignant lesions than those with dense breasts. Those in the age group 41 to 60 years were 3.34 times increased risk of having malignant lesions in comparison to those aged less than or equal to 40 years. For those aged more than 60 years, the risk was 1.77 times in comparison to those aged less than or equal to 40 years.BPE was not as significant as Age and Breast Density in the prediction of malignancy.

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