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ORIGINAL RESEARCH

Factors Influencing Background Parenchymal Enhancement in Breast Contrast-Enhanced Mammography: A Retrospective Study

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Objective: To evaluate the association between background parenchymal enhancement (BPE) level and extent on contrast-enhanced mammography (CEM) with age, menopausal status, breast density, and menstrual cycle phase in women. Additionally, to characterize the dynamic changes in BPE during CEM.

Methods: This retrospective study included 103 women who underwent CEM at a single institution between September 2019 and November 2021 for screening or diagnostic purposes. Menopausal status and menstrual cycle phase were recorded for all patients. BPE on subtracted CEM images was assessed quantitatively (region of interest [ROI] analysis of pixel values) and qualitatively (subjective classification). Statistical analysis was performed to determine the relationship between BPE (level and extent) and age, menopausal status, breast density, and menstrual cycle phase. Dynamic changes in BPE level over time were also analyzed.

Results: Both BPE level and extent were negatively correlated with age ($P=0.004$, $r=-0.280$; $P=0.001$, $r=-0.318$). Postmenopausal women exhibited lower BPE level and extent compared to premenopausal women ($P=0.003$, $Z=-2.958$; $P=0.042$, $2=4.123$). No significant association was observed between BPE and breast density or menstrual cycle phase ($P>0.05$). BPE level increased significantly from 3 to 9 minutes post-contrast injection ($P<0.001$, $t=-10.7$).

Conclusion: BPE in CEM is significantly associated with age and menopausal status. Further research is needed to clarify the relationship between BPE and breast density and menstrual cycle phase. BPE demonstrates a dynamic increase in level over time, this relates to post-contrast injection, rather than to the age of the woman.

Keywords: Mammography, Breast, Female Patients

Introduction

Breast cancer remains a leading cause of cancer-related death in women, accounting for approximately 31% of new female cancer cases annually.[1] While mammography is a cornerstone of breast cancer screening, its sensitivity is limited, leading to breast cancer cases being missed.[2] Contrast-enhanced mammography (CEM) is supplemental to screening mammography. CEM is an emerging technology that addresses this limitation. By utilizing an intravenous iodine-based contrast agent and specialized image processing, CEM provides both morphological and vascular information about breast lesions. Compared to contrast-enhanced magnetic resonance imaging (CE-MRI), CEM offers advantages such as shorter examination times, lower cost, and increased patient comfort, particularly for those with claustrophobia or implanted cardiac pacemakers.[3,4] Moreover, studies have demonstrated that CEM exhibits comparable sensitivity and diagnostic accuracy to CE-MRI,with potentially superior specificity.[5–8] Consequently, CEM may serve as a valuable alternative for women who cannot undergo CE-MRI.[9,10]

Background parenchymal enhancement (BPE) is a key feature evaluated on subtracted CEM images, reflecting the enhancement of normal fibroglandular tissue following contrast administration.[11] Previous studies have suggested BPE level on CE-CBBCT was significantly associated with menstrual status, breast density and previously treated breast cancer.[12]

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Furthermore, the influence of breast density on BPE is controversial, with conflicting reports regarding its impact.[13–15] MRI recommendations for BPE since BPE is a factor in that examination as well. For example, most recent ACR guidelines do not recommend scheduling MRI during a certain phase of the menstrual cycle, though previously they did recommend scanning during week 2 of the cycle.[16] Similarly, there is a lack of consensus on whether BPE fluctuates with the menstrual cycle. Some researchers advocate for performing CEM during specific phases of the menstrual cycle (eg, days 8–14) to minimize the potential confounding effect of BPE on lesion detection.[17] However, others have reported minimal variation in BPE throughout the menstrual cycle.[18,19] In addition, the dynamic changes of pixel values of BPE during CEM inspection have not been reported.

This study aimed to investigate the relationship between BPE in CEM and various factors, including age, menopausal status, breast density, and menstrual cycle phase, to identify potential determinants of BPE and enhance the diagnostic accuracy of CEM in breast disease. Additionally, we sought to characterize the dynamic changes in BPE levels during the CEM examination, which could aid in differentiating benign BPE from malignant lesion enhancement.

Materials and Methods

Patient Selection

This retrospective study was approved by the Biomedical Research Ethics Committee of The Fourth Hospital of Hebei Medical University, and the requirement for informed consent was waived. The study adhered to the principles of the Declaration of Helsinki, and all data were anonymized prior to analysis.

Between September 2019 and November 2021, 103 female patients who underwent CEM examination at The Fourth Hospital of Hebei Medical University were retrospectively included in this study. This study was approved by the Hospital Ethics Committee (Approval Number 2021KY228). Patients were referred for CEM due to clinical concerns such as a palpable mass, nipple discharge, or as part of a routine screening supplement program. Inclusion criteria were: 1) Documented menopausal status and menstrual cycle phase. 2) Availability of both 3-minute and 9-minute craniocaudal (CC) view CEM images of the diseased breast. Exclusion criteria were: 1) Lesions encompassing the entire breast, precluding accurate BPE assessment. 2) Patients are currently taking hormone replacement therapy or have taken hormone replacement therapy at any time in the past. During the study period, a total of 406 patients were enrolled, including 201 cases of breast hyperplasia, 11 cases of lost follow-up, 57 cases of neoadjuvant chemotherapy, 34 cases after surgery,finally 103 cases were enrolled.

CEM Examination

Contrast-enhanced mammography (CEM) examinations were conducted using a GE Senographe Essential digital mammography system equipped with dual-energy acquisition technology. This system enables the acquisition of low-energy images, comparable to conventional mammograms, using a standard X-ray beam spectrum (26–31 kVp). Simultaneously, high-energy images (45–49 kVp) are acquired for post-processing and image subtraction purposes.

Patients were advised to fast for 4–6 hours prior to the examination. During the examination, patients were positioned to ensure complete exposure of their upper body, with any metallic objects removed to avoid artifact. Intravenous access was established, and an iodinated contrast agent (iopromide 370 mgI/mL, Shanghai Boleko Xinyi Pharmaceutical Company) was administered at a dose of 1.22 mL/kg with an injection rate of 3 mL/s.

Image acquisition commenced 2 minutes after contrast administration. The imaging sequence consisted of cranio-caudal (CC) views of both the unaffected and affected breasts, followed by mediolateral oblique (MLO) views of both breasts. Additional imaging was performed at 9 minutes as needed. Low-energy and subtracted images were automatically transferred to the picture archiving and communication system (PACS) for interpretation.

Image Information

Two experienced radiologists (over 5 years of expertise) independently evaluated the anonymized CEM images. To ensure unbiased assessment, the radiologists were blinded to patient clinical information and histopathological findings. In cases of discrepancy between the two readers, a third radiologist with over 10 years of experience was consulted to reach a consensus.

Classification Method of Breast Density

Breast density was categorized according to the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) fifth edition criteria (2013), using the four standard density categories: (a) almost entirely fatty, (b) scattered areas of fibroglandular density, (c) heterogeneously dense, and (d) extremely dense. For this analysis, breast density was dichotomized by combining categories (a) and (b) into a "non-dense mammary glands group" and categories (c) and (d) into a "dense mammary glands group" (Figure 1).

Evaluation Method of BPE Range

The American College of Radiology recommends assessing BPE in the following way,[20] and include a reference: The background of normal breast tissue should be described when the substance is enhanced. Because CEM is performed by intravenous contrast agents, the fibroglandular parenchyma of the breast shows normal enhancement. As is the case with MRI, BPE should be described relative to the amount of fibroglandular tissue and not the volume of the entire breast,BPE is not necessarily directly related to the amount of fibroglandular tissue and should be described as: a. Minimal b. Mild c. Moderate d. Marked.Similarly breast density, BPE was dichotomized into "low" and "high" categories by combining the minimal and mild BPE categories and the moderate and marked BPE categories, respectively (Figure 2).

Measurement of BPE Enhancement Level

Using ROI of about 0.01–0.1cm^2, the enhancement degree of BPE was measured in 3-minute and 9-minute subtraction images of the affected breast respectively. Quantitative analysis of BPE, measured as pixel value within the ROI,three places with obvious BPE enhancement were selected for each position to be measured and recorded. The measurement position was more than 1cm away from the lesion, as recommended, while avoiding blood vessels and pectoralis major[21] (Figure 3).

Menstrual Cycle Grouping

Information regarding menopausal status, date of the last menstrual period, and history of hormone replacement therapy was collected from each patient prior to the CEM examination. Premenopausal women were further classified into four

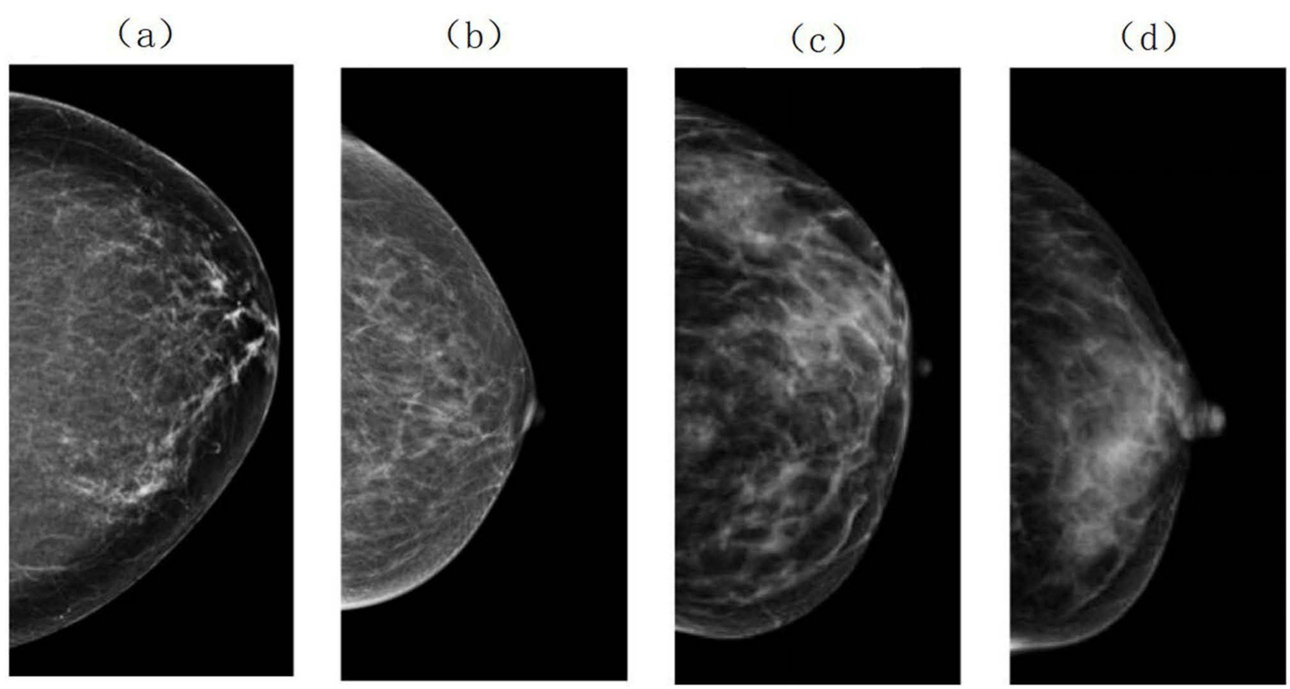

Figure 1 Breast density classification in low-energy images.

Notes: According to the ACR BI-RADS fifth edition criteria (2013), using the four standard density categories: (**a**) almost entirely fatty, (**b**) scattered areas of fibroglandular density, (**c**) heterogeneously dense, and (**d**) extremely dense.

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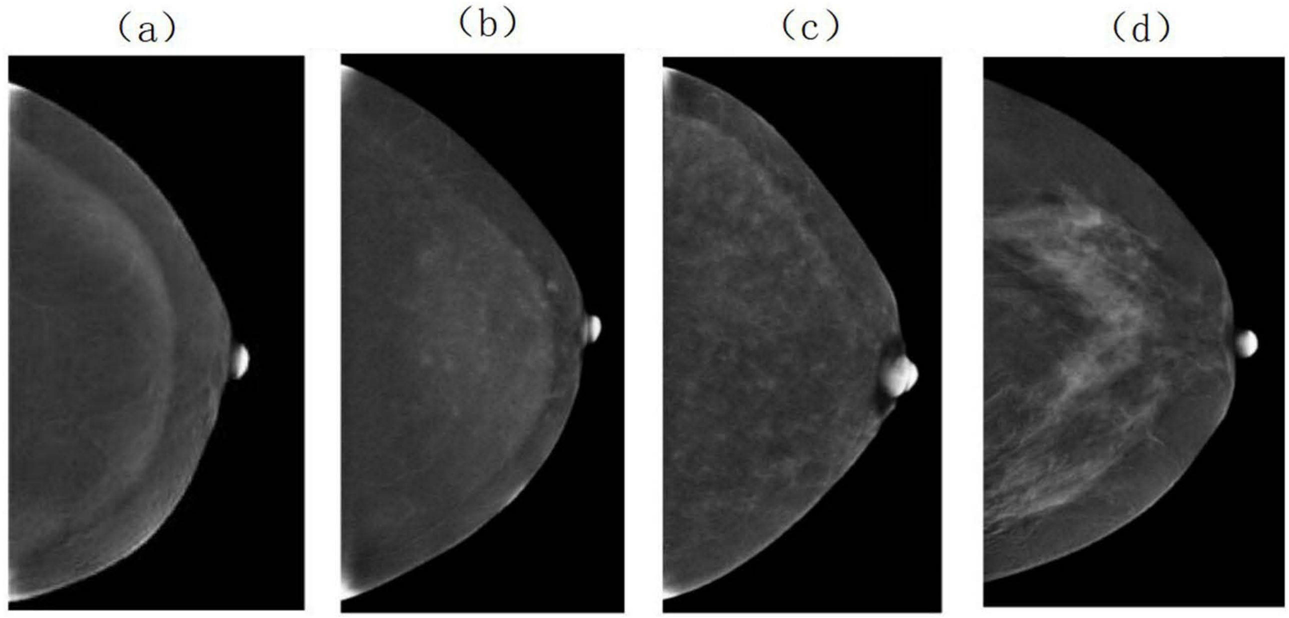

Figure 2 Classification of BPE extent in subtraction images.
Notes: As is the case with MRI, BPE should be described as: (**a**) Minimal, (**b**) Mild, (**c**) Moderate, and (**d**) Marked.

groups based on their menstrual cycle phase: day 1–7 (menstrual period), day 8–14 (follicular phase), day 15–21 (ovulation phase) and day 22–28 (luteal phase).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 21.0. Spearman's rank correlation coefficient was used to assess the correlation between BPE level (pixel value) and age, as well as between BPE extent and age. The Wilcoxon rank-sum test was employed to compare BPE level between premenopausal and postmenopausal women and between low and high breast density groups. The Kruskal–Wallis *H*-test was used to analyze the relationship between BPE level and menstrual cycle phase. The chi-square test was used to compare BPE extent across menopausal status, breast density categories, and menstrual cycle phases. Paired *t*-tests were used to compare BPE levels between the 3-minute and 9-minute imaging time points. Statistical significance was defined as $P < 0.05$. Kappa consistency test was used to evaluate inter-observer consistency.

Results

Patient Demographics and Clinical Characteristics

There are 14 patients aged 30–39, 37 patients aged 40–49, 32 patients aged 50–59, 15 patients aged 60–69 and 5 patients aged 70–79. The mean age of the participants was 49.9 ± 10.5 years. There were 15 cases of A (Almost entirely fatty) and B (Scattered areas of fibroglandular density), 88 cases of C (Heterogeneously dense) and D (Extremely dense). There were 52 premenopausal patients and 51 postmenopausal patients. There were 11 patients in the subgroup on the 1st–7th day (menstrual period), 14 patients in the subgroup on the 8–14th day (follicular phase), 17 patients in the subgroup on the 15–21st day (ovulation phase) and 10 patients in the subgroup on the 22–28th day (luteal phase). Among them, 47 cases were benign and 56 cases were malignant. There were 47 benign lesions and 56 malignant lesions. The detailed case classification is shown in Table 1. Good agreement between the two observers (Kappa=0.807, $p<0.001$).

Relationship Between BPE Level and Clinical Parameters of Patients

A total of 103 patients were included in this study. Revealed a weak negative correlation between BPE level and patient age (Spearman's rank correlation coefficient, $r = -0.318$, $P = 0.001$). Postmenopausal women exhibited significantly

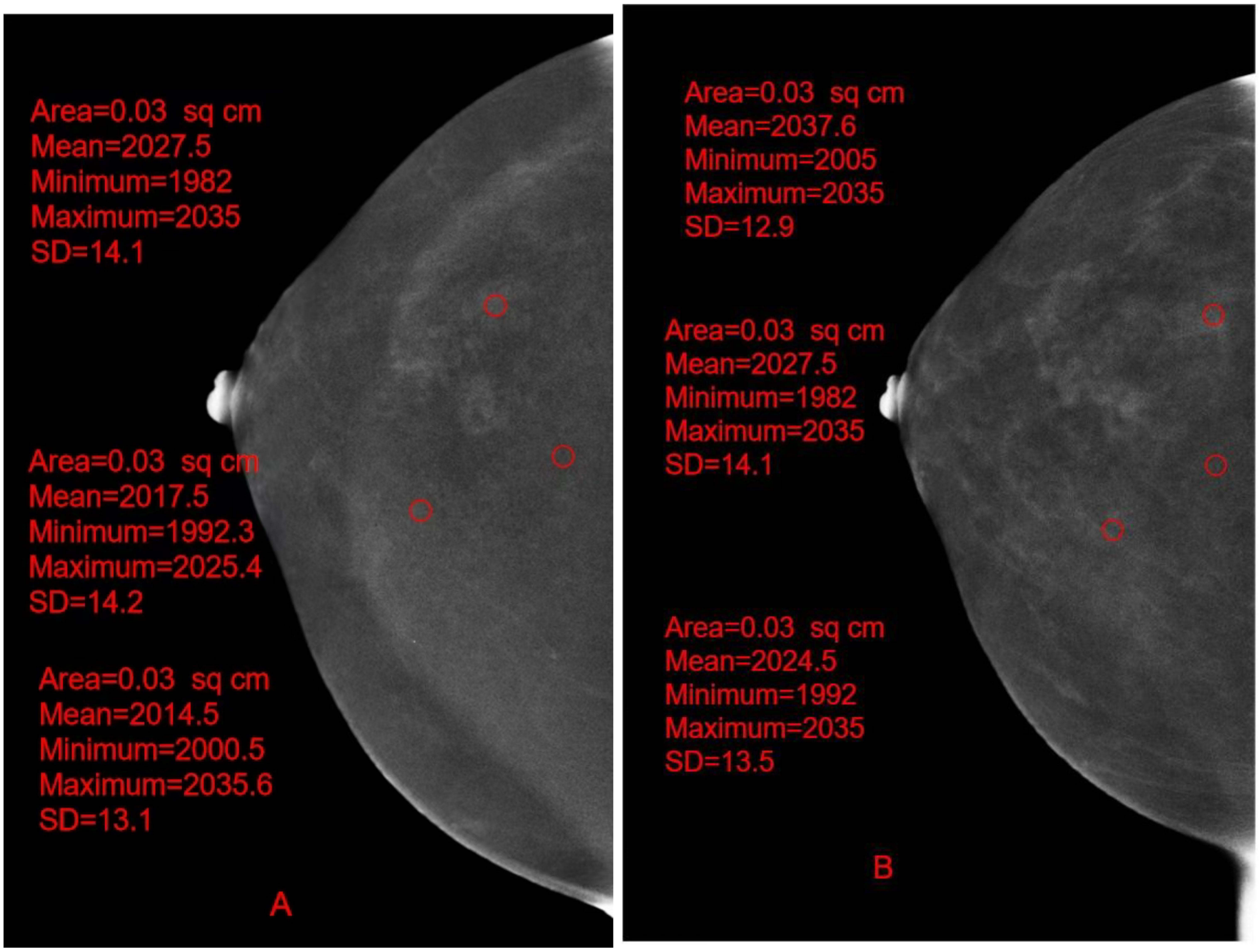

Figure 3 Measurement of BPE levels in subtraction images.
Notes: The patient is a 54-year-old female. The enhancement of BPE was measured by ROI on 3-minute and 9-minute subtraction images on the affected side, respectively. Plot 3 ROI regions at 3 minutes and 9 minutes, respectively, and measure the BPE value. (**A**) Measurement of BPE values at different 3 points at 3 minutes of subtraction; (**B**) 9-minute subtraction measurements for different 3-point BPE values.
Abbreviations: SD, standard deviation.

lower BPE level compared to premenopausal women (Wilcoxon rank-sum test, P = 0.003). No significant differences in BPE level were observed between different breast density categories (Wilcoxon rank-sum test, P = 0.101) or across menstrual cycle phases in premenopausal women (Kruskal–Wallis *H*-test, P = 0.564) (Table 2).

Correlation Between BPE Range and Age

A weak negative correlation was observed between BPE extent and patient age (Spearman's rank correlation coefficient, $r = -0.280$, P = 0.004).

Relationship Between BPE Range and Menstrual Status

A greater proportion of postmenopausal women (90.2%, 46/51) exhibited low BPE extent compared to premenopausal women (75.0%, 39/52).This difference in BPE extent distribution between menopausal groups was statistically significant ($\chi^2 = 4.123$, P = 0.042) (Table 3).

Relationship Between BPE Range and Breast Density

Low reinforcement accounted for 93.3% (14/15) of non-dense mammary glands (fatty and scattered fibroadenoid mammary glands) and 80.7% (71/88) of dense mammary glands (inhomogeneous dense and dense mammary glands). High reinforcement of non-dense breast accounted for 6.7% (1/15) and high reinforcement of dense breast accounted for

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Table 1 Clinical Parameters of Patients

Clinical Parameters	Number	Percentage
Age		
30–39 years old	14	13.6%
40–49 years old	37	35.9%
50–59 years old	32	31.1%
60–69 years old	15	14.6%
70–79 years old	5	4.8%
Breast density		
Almost entirely fatty	1	1%
Scattered areas of fibroglandular density	14	13.6%
Heterogeneously dense	86	83.4%
Extremely dense	2	2%
Menstrual state		
Premenopause	52	50.5%
Postmenopausal period	51	49.5%
Menstrual cycle		
Day 1–7	11	21.2%
Day 8–14	14	26.9%
Day 15–21	17	32.7%
Day 22–28	10	19.2%

Notes: Baseline table of clinical information and pathological findings.

Table 2 The Relationship Between BPE and Clinical Parameters of Patients

Clinical Parameters of Patients	Statistics (r/Z/H value)	BPE (P value)
Age	−0.318	0.001*
Menstrual state	−2.958	0.003*
Breast density	−1.641	0.101
Menstrual cycle	2.041	0.564

Notes: *Represents a P <0.05, with a statistical difference.
Abbreviation: BPE, background parenchymal enhancement.

Table 3 Correlation Between BPE Level and Menopausal Status

Menstruation Status	Low Reinforcement (n=85)	High Reinforcement (n=18)
Premenopause	39(75.0%)	13(25.0%)
Postmenopausal	46(90.2%)	5(9.8%)
χ2	4.123	
P	0.042	

Notes: Represents a P <0.05, with a statistical difference.
Abbreviations: χ^2, Chi-Square Value; P, p-value.

19.3% (17/88). No significant difference in BPE extent distribution was observed between low and high breast density groups (χ^2 = 0.409, P = 0.680) (Table 4).

Relationship Between BPE Range and Menstrual Cycle

No significant association was found between BPE extent and menstrual cycle phase in premenopausal women (χ^2 = 0.438, P = 0.932) (Table 5).

Table 4 Correlation Between BPE Range and Mammography Density

Mammary Gland Density	Low Reinforcement (n=85)	High Reinforcement (n=18)
Non-dense mammary glands group	14(93.3%)	1(6.7%)
Dense mammary glands group	71(80.7%)	17(19.3%)
χ2	0.409	
P	0.680	

Notes: Represents a P <0.05, with a statistical difference.
Abbreviations: χ2, Chi-Square Value; P, p-value.

Table 5 Relationship Between BPE Range and Menstrual Cycle

Menstruation Cycle	Low Reinforcement (n=39)	High Reinforcement (n=13)
Days 1–7	8(72.7%)	3(27.3%)
Days 8–14	11(78.6%)	3(21.4%)
Days 15–21	12(70.6%)	5(29.4%)
Days 22–28	8(80.0%)	2(20.0%)
χ2	0.438	
P	0.932	

Notes: Represents a P <0.05, with a statistical difference.
Abbreviations: χ^2, Chi-Square Value; P, p-value.

Dynamic Changes in BPE Levels Over Time

The mean BPE pixel values of 3 minutes and 9 minutes were 2021.6±17.7 and 2026.4±17.0 respectively (see Figure 4).

Discussion

This study retrospectively analyzed the relevant factors affecting BPE, and through quantitative BPE analysis, the age of all patients showed a weak negative correlation with the BPE pixel value. The pixel value of BPE in postmenopausal patients was lower than that in premenopausal patients, and there was a statistical difference. There was statistical difference between 3-minute and 9-minute BPE. There was no significant difference between breast density, menstrual cycle time and BPE level. These results are in part consistent with previous studies, where we made a relatively different observation with 9-minute delayed photography, which helps provide the best time to observe lesions.

Through quantitative analysis, this study showed that the BPE level and range of CEM were weakly negatively correlated with patient age, which was consistent with the previous findings.[22] There were differences in breast BPE premenopause and postmenopause, which was consistent with the findings of Fallenberg et al.[23] BPE decreases as women get older, which is caused by lower levels of estrogen. Because with age, the ovaries undergo degenerative changes, resulting in lower estrogen levels, which in turn lead to lower BPE. In fact, women over 35 years old have a state of reduced ovarian reserve function, that is, the gradual decline of ovarian function and estrogen level,[24,25] which may be the reason for the weak correlation between age and the level and range of BPE. The level of estrogen in premenopausal patients is high, and the histamine-like effect of estrogen can induce vasodilation and proliferation of epithelial cells, and increase the permeability of microvessels. Hormones can promote mitosis, leading to accelerated metabolism and increased blood perfusion.[26,27] Postmenopausal patients are also typically older, with reduced hormone levels, loss of epithelial cell proliferation, gradual atrophy of glands, and increased duct and fat composition, which in turn leads to lower BPE.

In this study, the proportion of high BPE in dense breast was higher than that in non-dense breast (6.7%vs 19.3%).In contrast to Savaridas et al, whose study participants were part of a cancer staging study approved by an institutional

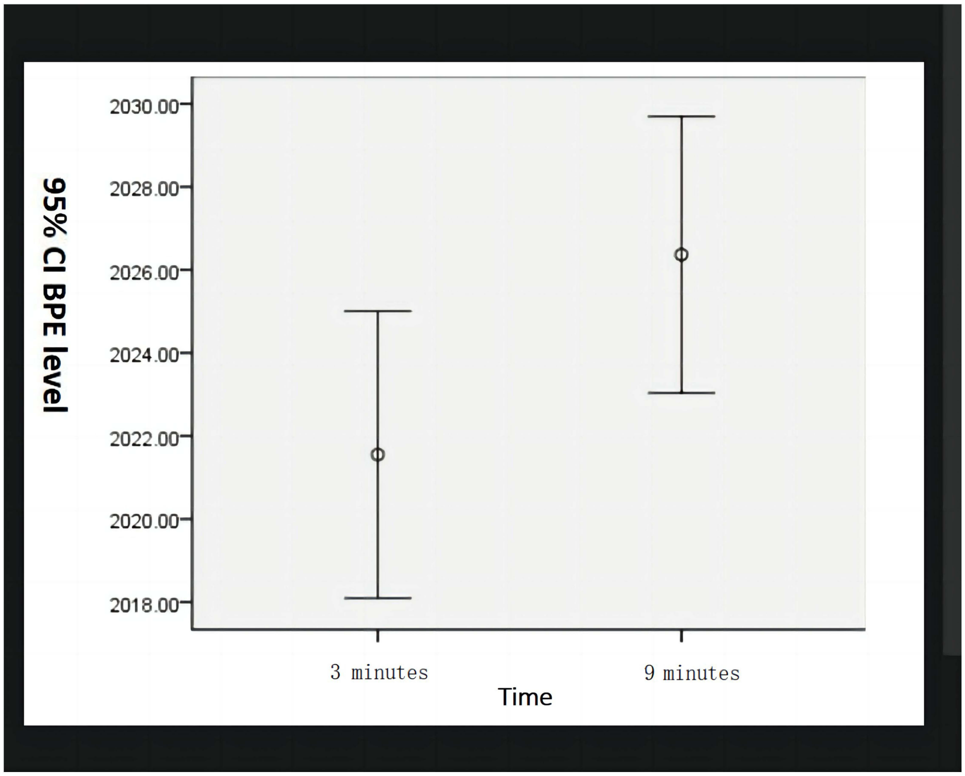

Figure 4 Error bars at BPE level.
Notes: The average BPE pixel value had a 95% confidence interval from 3 to 9 minutes after injection of contrast medium.
Abbreviations: CI, confidence internal; BPE, background parenchymal enhancement.

ethics committee (Australia New Zealand Clinical Trial Registry: ACTRN12613000684729),[28] there were no statistical differences in the level and extent of BPE across breast densities in this study. This may be due to differences in the types of breast glands in the enrolled cases in the two studies. Asian women are more likely to have unevenly dense or dense mammary glands compared to Western women.[29] The difference in results may also be due to differences in the number of enrolled cases between the two studies. BPE represents physiologically active breast tissue with the ability to proliferate and is associated with hormones. Low BPE may indicate inactive breast tissue, while dense breast and low BPE may be due to severe fibrosis of glandular tissue.[30,31]

This study showed that BPE levels and ranges were different at different times of the menstrual cycle, which was consistent with the results of Sogani et al.[32] Zhao et al found that the BPE range was not affected by the menstrual cycle, but the level of BPE was lowest on the 8th to 14th day of the menstrual cycle, and there was a statistical difference compared with other periods of the menstrual cycle.[33] The reason for the difference between this study and the above studies may be the difference in the assessment time and body position of BPE. In addition, the sample size of each menstrual cycle subgroup in this study was small, and the sample size will be expanded in the future to further study the relationship between menstrual cycle and BPE level.

In this study, the difference of BPE pixel value between 3 minutes and 9 minutes was compared. The mean value of BPE pixel value in 3 minutes was 2021.5±17.7, and the mean value of BPE pixel value in 9 minutes was 2026.4±17.0, and there was a statistical difference between them. Our results show that the BPE of CEM increases with time, which is consistent with the results of Sorin et al included 183 patients to study the relationship between BPE range and injection time, and the result showed that the BPE range increased slightly over time.[34] Our results show that the BPE of CEM increases with time, improper BPE evaluation time may mask the lesion and reduce the diagnostic value of CEM. Therefore, it is recommended to evaluate BPE at about 3 minutes of photography.

This study has several limitations. As a retrospective, single-center study with a relatively small sample size, the generalizability of our findings may be limited. Furthermore, we did not analyze all potential factors that could influence

BPE.Our study population primarily consisted of women with breast-related concerns, which may introduce selection bias and limit the applicability of our results to the general population. While conducting BPE research in healthy individuals would be ideal, it is often impractical and raises ethical considerations. Premenopausal women are divided into four groups based on their menstrual cycle: 1–7 days (menstrual period), 8–14 days (follicular period), 15–21 days (ovulation period), and 22–28 days (luteal period), and some women may misremember the time, which is inevitable, which may cause the results of this study to be inconsistent with other studies.Future prospective studies with larger, more diverse cohorts are needed to confirm our findings.

Finally, the manual delineation of ROIs for BPE assessment introduces a degree of subjectivity, which could potentially affect the reproducibility of our measurements. The development of more standardized or automated methods for BPE quantification could improve the objectivity and reliability of future studies.[35]

Conclusions

In this study, the CEM technology was used to analyze the factors affecting BEP on the breast side of the lesion, and a good result was obtained. The 9-minute delayed photography fully demonstrated the change of B over time. In clinical work, the observation of the lesion should be made in the early stage when BPE has little influence on the lesion. In addition, breast density is closely related to the occurrence of breast cancer, and hormone levels in different periods of the menstrual cycle are very closely related to breast density. These close links are ultimately subtle in the occurrence and development of breast diseases, and it is worth exploring the relationship through new technologies to provide more information and value in early clinical diagnosis and treatment.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author on reasonable request.

Ethics Approval

This retrospective study was approved by the Biomedical Research Ethics Committee of The Fourth Hospital of Hebei Medical University. The study adhered to the principles of the Declaration of Helsinki, and all data were anonymized prior to analysis.

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Disclosure

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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