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FULL PAPER

Qualitative assessments of density and background parenchymal enhancement on contrast-enhanced spectral mammography associated with breast cancer risk in high-risk women

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Objective: To investigate the correlation between the risk of breast cancer for high-risk females and the density and background parenchymal enhancement (BPE) on contrast-enhanced spectral mammography (CESM).
Methods: Females at high-risk, without breast cancer history and received CESM from July 2016 to December 2017 were retrospectively enrolled. The longest follow-up time was 4.5 years, and patients who developed breast cancer with maximized follow-up time were classified as cancer cohort, while females who did not develop breast cancer were categorized as control cohort. These two cohorts were one-to-one matched in age, family and/or genetic history of breast cancer, menopausal status and *BRCA* status. The density and BPE at CESM imaging were assessed. Conditional logistic regression was applied to evaluate the relationship between imaging features and breast cancer risk.
Results: During the follow-up interval, 90 women at high-risk without history of breast cancer were newly diagnosed. Compared with minimal BPE, increasing BPE levels were associated with the risk of breast cancer among high-risk females in a time interval of 4.5 years (mild: odds ratio [OR]=3.2, p = 0.001; moderate: OR = 4.0, p = 0.002; marked: OR = 11.2, p < 0.001). In addition, females with mild, moderate or marked BPE were four times more likely to be diagnosed with breast cancer than females with minimal BPE in a time interval of 4.5 years (OR = 4.0, p < 0.001).
Conclusion: Qualitative CESM BPE assessment may be useful in the prediction of breast cancer risk among high-risk females.
Advances in knowledge: • Qualitative CESM BPE assessment may be useful in the prediction of breast cancer risk among high-risk women during the follow-up period of 4.5 years.
• The significance of breast density as an independent risk factor is not fully established for high-risk women during the follow-up period of 4.5 years.

INTRODUCTION

Breast cancer is one of the most common malignant tumors among females, Its incidence has slightly increased by 0.3% annually for the past years,[1,2] and the age of onset tends to be younger.[3] Therefore, early detection, diagnosis, and treatment of breast cancer are important factors to reduce mortality, improve cure rate and prognosis, especially for high-risk population. Unfortunately, traditional risk prediction models, including Tyrer–Cuzick and Gail models, are not satisfactory.[4]

Research on breast density and breast cancer risk is still an endless stream. Most findings confirmed that dense breasts are associated with a high risk of breast cancer.[5–7] Boyd et al conducted three nested case–control studies on 1112 matched cases in the census population. The results confirmed that the "masking effect" may not fully explain the fivefold breast cancer risk caused by dense breasts.[8] Breast density is accepted as an independent risk factor, but role of density measurement and risk assessment in screening setting are not fully established. Therefore, studying the relationship between breast density and breast cancer risk is necessary.

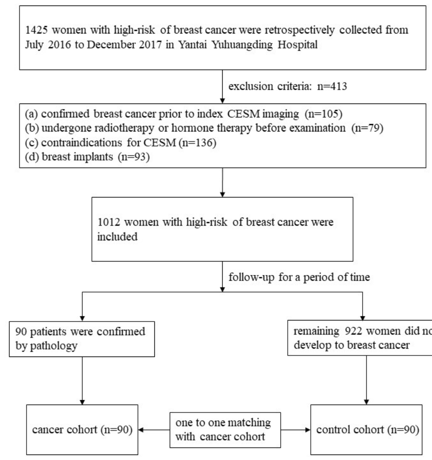
Background parenchymal enhancement (BPE) is the enhancement of normal fibroglandular tissue in the breast after contrast medium injection.[9–11] Many researchers started studying breast BPE, paid attention to the degree, scope, and probability of BPE in various populations, and explored whether BPE is related to breast cancer. The results showed that BPE is an independent predictor of breast cancer risk, particularly in high-risk population.[12–15] Most studies evaluated breast BPE through MRI.

Contrast-enhanced spectral mammography (CESM) is a new technique of digital mammography that reflects the uptake of iodine contrast agent in breast lesions to a certain extent and indirectly reflects blood supply. CESM includes low-energy and recombined contrast-enhanced image. This technique enhance the detection and diagnosis of breast cancer, thus bringing a new breakthrough for the diagnosis of breast tumor.[16] The sensitivity and specificity of CESM are also higher than those of conventional mammography.[17] Its sensitivity for breast cancer detection is comparable with that of MRI.[18,19] Same with MRI,[20] CESM is also the recommended examination method for breast cancer screening. According to American College of Radiology,[21] the indications for CESM include determination of extent of disease in newly diagnosed breast cancer, response to neoadjuvant chemotherapy, problem solving, intermediate and high-risk screening, and alternative examination when MRI examination is not applicable.

However, to our knowledge, only few studies focused on BPE based on CESM. Sogani et al[22] reported substantial agreement between readers for BPE as detected on CESM and MRI images. Savaridas et al[23] found that CESM BPE has better inter-radiologist agreement than MRI. Sorin, Vera et al[24] found that females with increased BPE had increased odds for breast cancer. However, Yu, Liangliang et al[25] found that CESM BPE was not correlated with benign or malignant breast lesions for non-high-risk females. Therefore, further research of BPE on CESM images is necessary.

In this study, we attempted to investigate whether breast cancer risk in high-risk females is related to CESM density and BPE. Because breast density and BPE levels are associated with hormone, we also compared imaging characteristics between patients diagnosed with ER-positive and ER-negative cancers.

Figure 1. Study profile. CESM, contrast-enhanced spectral mammography.



METHODS AND MATERIALS

Patients

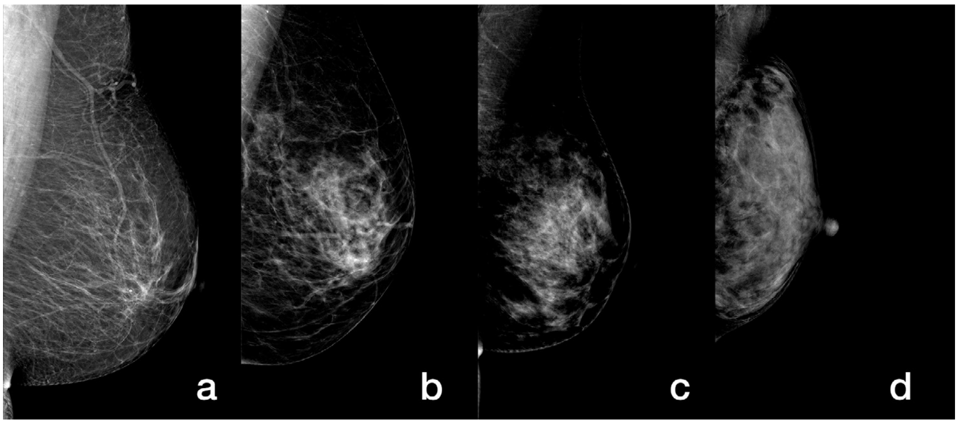
This retrospective study was approved by the Institutional Review Board of Yantai Yuhuangding Hospital, and patient informed consent was waived. Females with high-risk of breast cancer were collected from July 1, 2016 to December 31, 2017 using the Hospital Information System. According to the Tyrer–Cuzick risk model, females with a lifetime risk of breast cancer ≥20% are defined as high-risk. The inclusion criteria were as follows: (a) all females 18 years of age or older, (b) no history of breast cancer prior to index CESM imaging, (c) examination time is the second week of menstrual cycle and menstrual cycle is regular, and (d) has not undergone radiotherapy or hormone therapy before examination. The exclusion criteria were as follows: (a) confirmed breast cancer prior to index CESM imaging, (b) has undergone radiotherapy or hormone therapy before examination, (c) contraindications for CESM (including pregnancy, contrast medium allergy, and renal impairment), and (d) breast implants (the subtraction algorithm is not suitable). The study profile is displayed in Figure 1.

A total of 1012 women were identified. According to pathology, the 90 enrolled females developed breast cancer within the maximized follow-up time and thus were classified as cancer cohorts. Remaining 922 women did not develop breast cancer within the maximized follow-up time. 90 women were randomly selected from the 922 women and were classified as control cohorts. The randomly selected was conducted by using R 3.5.1. The two cohorts have corresponding age, family and/or genetic history of breast cancer, menopausal status and *BRCA* gene according to one-to-one matching.

CESM image acquisition protocol

All breast examinations were performed using CESM (GE Healthcare, Senographe DS Senobright) and the imaging protocols were consistent. Since the iodine contrast agent needed to be injected intravenously, all patients were evaluated the risks for contrast reaction before the official injection. After confirming that there was no contrast reaction to iodine contrast agent, the Omnipaque 350 (GE

Figure 2. Mediolateral oblique low-energy images of CESM demonstrate different breasts with (a) A, (b) B, (c) C, and (d) D density. CESM, contrast-enhanced spectral mammography.



Healthcare, Inc., Princeton, NJ) at a dose of 1.5 ml/kg was injected into the upper arm vein by using a high-pressure syringe at a flow rate of 3 mls^{-1}. The unilateral mammary gland was compressed to take the mediolateral oblique view and the craniocaudal view images for high-low energy exposure after the injection was completed for approximately 2 min. In the same manner, the mediolateral oblique view and the craniocaudal view images of the other side of the breast were acquired. Imaging for each patient was completed within 7 min. Low and high energy exposures were continuously obtained within 1.5 s of one compression. Each image was acquired on the workstation with two image types, namely, a low-energy image and a recombined image. The low-energy exposure images were used to determine breast density, and the recombined images were used to determine BPE.

Image interpretation

All images were reviewed by two radiologists with at least 10 years of experience in breast imaging diagnosis who assessed breast density and BPE of CESM images according to the BI-RADS system.[26] Prior to image review, the radiologists examined a standardized set of 25 cases that demonstrated density and BPE categories on CESM images. All four views were used for image interpretation. The breast density on the low energy CESM image and the amount of BPE on the recombined CESM image were assessed. The radiologists were blinded as to which cases were cancers and which were controls. Breast density was classified into four categories: A (the breasts are almost entirely fatty), B (there are scattered areas of fibroglandular density), C (the breasts are heterogeneously dense), and D (the breasts are extremely dense) (Figure 2). BPE amount was sorted into four categories: minimal (<25%), mild (25%–50%), moderate (51%–75%), and marked (>75%) (Figure 3). For the same patient, when there was asymmetry in density or BPE in the four views, the radiologists retained the highest category. All disagreements were resolved through consultation. Agreement of breast density and BPE of CESM images from two reviewers was assessed using Kendall's W coefficient of concordance. If no agreement could be reached, it would be reviewed by a radiologist with 20 years of experience in breast imaging diagnosis.

Statistical analysis

All statistical tests were conducted using SPSS 20.0. In the matched study, conditional logistic regression analysis was used to compare the CESM density and amount of BPE. Odds ratios (OR) value and 95% confidence interval (CI) were calculated. OR >1 was used as risk factor, and its high value indicates a high risk degree. Factors that significantly differ across patients and control subjects were further

Figure 3. Mediolateral oblique recombined images of CESM demonstrate different breasts with (a) minimal, (b) mild, (c) moderate, and (d) marked BPE. BPE, background parenchymal enhancement; CESM, contrast-enhanced spectral mammography.

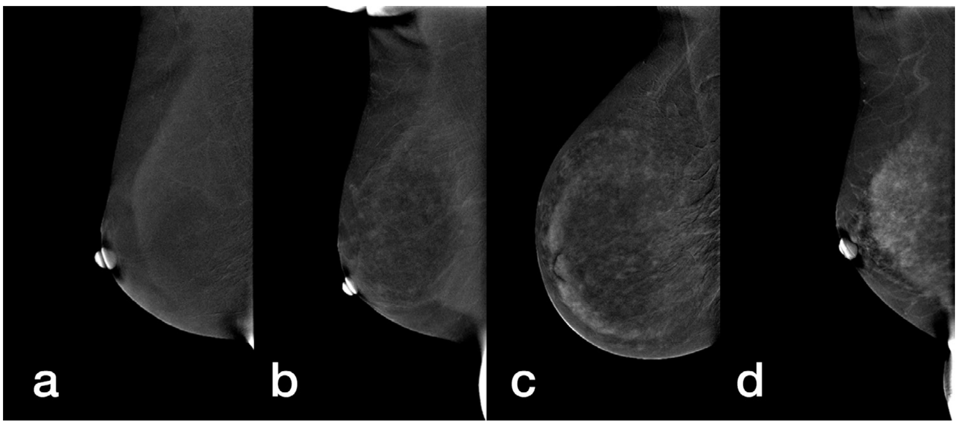


Table 1. Patient characteristics and indications of the cancer cohort and matched control cohort

Variable	Cancer cohort (n = 90)	Control cohort (n = 90)	p-value
Age (y)a	48.1 ± 9.9	47.8 ± 9.7	0.923
Follow-up interval (y)[ab]	3.8 ± 0.6	3.9 ± 0.5	0.879
Indication for high-risk screening CESM			1
BRCA1 mutation	12(14)	12(14)	
BRCA2 mutation	14(16)	14(16)	
Family and/or genetic history of breast cancer	64(70)	64(70)	
Menopausal status			0.766
Pre-menopausal	48(53)	45(50)	
Post-menopausal	42(47)	45(50)	
DCIS	44(49)	NA	
ER positive	22(50)	NA	
ER negative	22(50)	NA	
Invasive breast cancer	46(51)	NA	
ER positive	26(57)	NA	
ER negative	20(43)	NA	

CESM, contrast-enhanced spectral mammography; DCIS, ductal carcinoma in situ; NA, not applicable.
Note: Unless otherwise indicated, data are numbers of patients and data in parentheses are percentages. All patients were matched for age and BRCA mutation status.
[a] Data are mean ± standard deviation.
[b]Data are period between CESM and cancer diagnosis in the cancer cohort and follow-up time in control cohort.

analyzed using receiver operating characteristic (ROC) curve to identify optimal thresholds to maximize both sensitivity and specificity. Logistic regression and Fisher's exact test were used to evaluate the difference in breast tissue imaging characteristics between ER positive and ER negative patients with breast cancer. $p < 0.05$ was considered significant.

RESULTS

Patient characteristics

The longest follow-up time was 4.5 years. Table 1 exhibits the patients' characteristics between the two cohorts. 90 patients were enrolled in the cancer cohort, including 46 invasive cancers and 44 ductal carcinoma *in situ*. The mean follow-up time, age, family and/or genetic history of breast cancer, menopausal status and *BRCA* status of the two cohorts were matched.

Association between qualitative imaging features and developing breast cancer

Overall agreement (Kendall's W) values between the readers were 0.788 for breast density and 0.819 for BPE. In the cancer cohort, no significant association was observed between breast cancer risk and breast density ($p > 0.05$; Table 2) during the follow-up period of 4.5 years. However, the amount of BPE was significantly associated with breast cancer risk ($p < 0.05$) during the follow-up period of 4.5 years. ROC curve showed an optimal threshold of BPE greater than minimal can maximize sensitivity and specificity at 72 and 71%, respectively, in discriminating patients with cancer and control subjects (Figure 4). By using this threshold, we found that a significantly higher percentage of females in the cancer cohort had either mild, moderate, or marked BPE (78% [70 of 90 women]) than did females in the control cohort (47% [42 of 90 women], $p = 0.003$).

Compared with minimal BPE, increasing BPE levels were associated with the risk of developing breast cancer among high-risk females during the follow-up period of 4.5 years (mild: OR = 3.2, $p = 0.001$; moderate: OR = 4.0, $p = 0.002$; and marked: OR = 11.2, $p < 0.001$). In addition, females with mild, moderate or marked BPE were four times more likely to be diagnosed with breast cancer than females with minimal BPE during the follow-up period of 4.5 years (OR = 4.0; $p < 0.001$). As shown in Figure 5, a female with moderate BPE has developed breast cancer.

When the breast density was divided into the fatty breasts (density A and B) and the dense breast (density C and D), there was no significant difference between increasing breast density level and the risk of developing breast cancer among high-risk females during the follow-up period of 4.5 years (OR = 1.8; p = 0.059).

Associations of imaging parameters with ER status of breast cancer

In the cancer cohort, breast density and BPE were not significantly associated with ER status ($p > 0.05$; Table 3).

DISCUSSION

In this study, we investigated the correlation of breast density and BPE on CESM and the risk of developing breast cancer in a high-risk group with the longest follow-up time of 4.5 years. Our

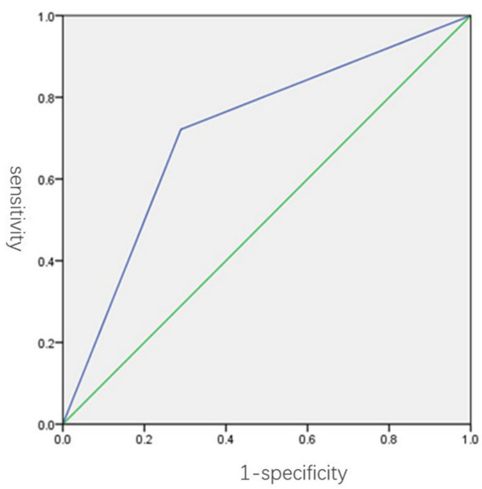
Table 2. Comparison of imaging characteristics between the cancer and control cohorts

Characteristic	Cancer cohort (n = 90)	Control cohort (n = 90)	Odds ratioa	p-value
BPE				
Minimal	20 (22)	48 (53)	Reference	
Mild	36 (40)	27 (30)	3.2 (1.55, 6.59)	0.001
Moderate	20 (22)	12 (13)	4.0 (1.65, 9.70)	0.002
Marked	14 (16)	3 (4)	11.2 (2.90, 43.27)	< 0.001
BPE (dichotomous)				
Minimal	20 (22)	48 (53)	Reference	
Mild, moderate, or marked	70 (78)	42 (47)	4 (2.09, 7.64)	< 0.001
Density				
A	2 (2)	4 (4)	Reference	
B	22 (25)	32 (36)	1.4 (0.23, 8.17)	0.726
C	48 (53)	44 (49)	2.2 (0.38, 12.51)	0.381
D	18 (20)	10 (11)	3.6 (0.56, 23.24)	0.178
Density				
A, B	24 (27)	36 (40)	Reference	
C, D	66 (73)	54 (60)	1.8 (0.98, 3.44)	0.059

BPE, background parenchymal enhancement.
Note.Unless otherwise indicated, data are numbers of subjects, with percentages in parentheses.
[a]Data in parentheses are 95% confidence intervals.

results suggest that females with mild, moderate or marked BPE were four times more likely to be diagnosed with breast cancer than females with minimal BPE during the follow-up period of 4.5 years. However, the significance of breast density as an independent risk factor is not fully established for high-risk females during the same follow-up period. Our research has an advantage. The *BRCA* gene and family and/or genetic history of breast cancer, two independent biomarkers of breast cancer risk, were matched between the cancer and control cohorts. This experimental design increases the reliability of the results.

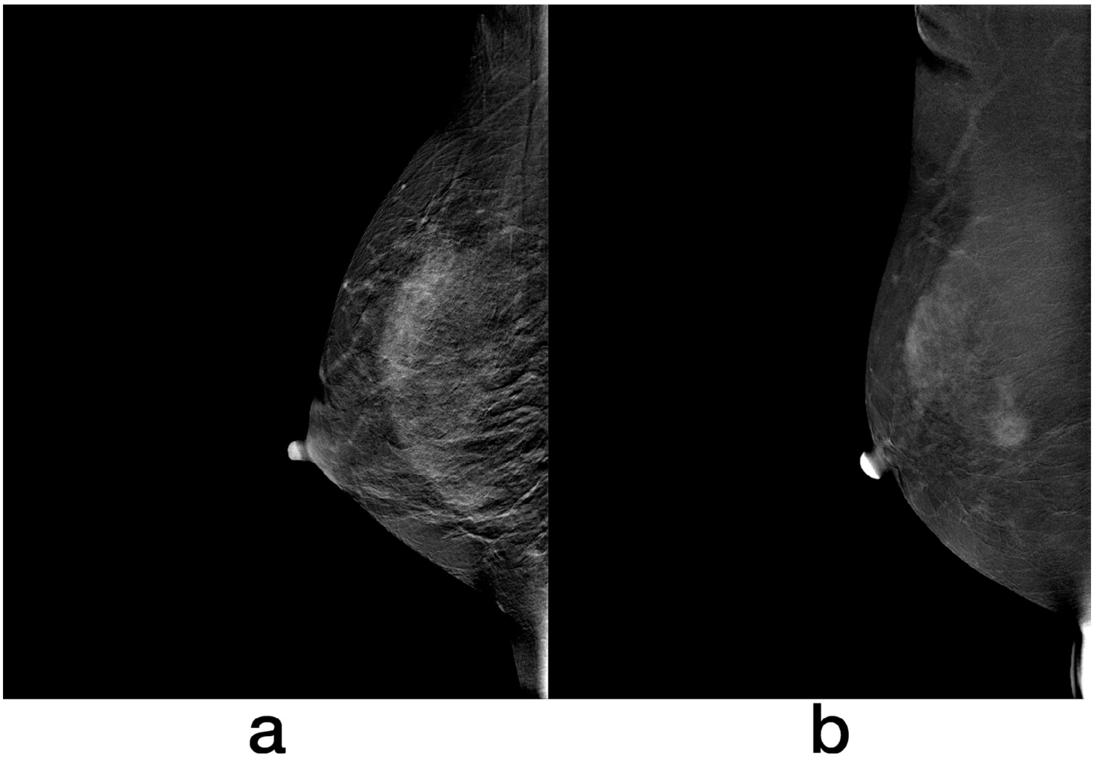
Figure 4. ROC curve shows accuracy of BPE assessment in the discrimination of patients with cancer (n = 90) and control subjects (n = 90). The AUC was 0.72 (95% confidence interval: 0.61, 0.82). An optimal BPE threshold of greater than minimal was identified to maximize sensitivity and specificity, with a resulting diagnostic performance of 72% sensitivity and 71%, specificity. AUC, area under the curve; BPE, background parenchymal enhancement; ROC, receiver operating characteristic.



Previous studies showed that the increased BPE levels on MR or CESM images were associated with an increased risk of breast cancer.[13,23,24] In the present work, we reported similar results that the increased BPE levels on CESM images were associated with an increased risk of breast cancer. Unlike the previous studies, the subjects in this study were high-risk females. This finding may improve the effectiveness of breast cancer risk models.

Previous studies showed that BPE level is affected by hormone level.[27–31] For pre-menopausal people, the enhancement of mammary gland tissue is the most apparent during the first and fourth weeks but the weakest during the second week.[32] Therefore, all participants underwent CESM examination during their second week of menstrual cycle. BPE is reduced by endocrine therapy (including selective estrogen receptor modulator or aromatase inhibitor). King et al[33] reported that BPE is substantially reduced in breast cancer patients treated with tamoxifen and cysts. King et al[34] also evaluated the effect of aromatase inhibitors on BPE and reported similar conclusions. According to literature, the decrease in local blood vessels in the breast after radiotherapy also decreases BPE.[35] Therefore, all high-risk patients included in our study did not undergo endocrine therapy or radiotherapy. In addition, no significant associations between BPE and ER status were reported in the cancer cohort. This finding suggests that BPE can be used as a

Figure 5. Recombined images of CESM in a 41-year-old female with a family history of breast cancer shows moderate BPE (a). This patient was found to have invasive ductal carcinoma 171 days after index CESM (b). BPE, background parenchymal enhancement; CESM, contrast-enhanced spectral mammography.



risk factor for hormone sensitive and non-hormone sensitive breast cancers.

Many studies indicated the correlation between breast density and breast cancer.[36] This correlation is not limited to the statistical data of epidemiology and extends to many different research fields, including genetics, tumor etiology, and tumor therapy. In many cases of breast cancer, the tumor tissue is located in the area with high breast density years before the diagnosis. This phenomenon strongly indicates a biological correlation between dense tissue and breast cancer risk.[37] Although most studies showed that breast density is associated with breast cancer risk, previous works on mainstream journals revealed that an increased mammographic breast density is not associated with high breast cancer risk in females with *BRCA* mutations.[38] This finding is similar to our results. The difference may be attributed

Table 3. Comparison of imaging characteristics between patients diagnosed with ER-positive and ER-negative cancers

Characteristic	ER-positive ($n = 48$)	ER-negative ($n = 42$)	Odds ratio[a]	p-value
BPE				
Minimal	10 (21)	10 (24)	Reference	
Mild	19 (39)	17 (40)	1.1 (0.37, 3.34)	0.842
Moderate	11 (23)	9 (21)	1.2 (0.35, 4.24)	0.752
Marked	8 (17)	6 (14)	1.3 (0.34, 5.27)	0.682
Density				
A	1 (2)	1 (2)	Reference	
B	14 (29)	8 (19)	1.8 (0.10, 31.96)	0.706
C	25 (52)	23 (55)	1.1 (0.06, 18.4)	0.954
D	8 (17)	10 (24)	0.8 (0.04, 14.89)	0.881

BPE, background parenchymal enhancement.
Note. Unless otherwise indicated, data are numbers of subjects, with percentages in parentheses.
[a]Data in parentheses are 95% confidence intervals.

to the non-identical research participants. Passaperuma K's research subjects are females with *BRCA* gene mutation, and our research participants are high-risk females. At present, it is controversial to regard breast density as an independent risk factor for breast cancer. Further evaluating the relationship between breast density and breast cancer risk is necessary.

Our study has several limitations. First, this study is single-centered with a small data set. As a new technology, a multi-centered research with a large sample size is necessary to obtain high-level evidence for clinical applications. Second, the proportion of ductal carcinoma *in situ* in the cancer cohort was relatively high, and this situation was inconsistent with the real clinical environment. Future research should try to solve this problem, such as using large sample research. Third, the longest follow-up period was only 4.5 years. If the follow-up time was longer, it was unknown whether the results would be changed. Future studies will be followed up for a longer period of time. Fourth, the relationship between BPE on CESM and breast cancer risk in the general population of females is still unknown. We will continue our research in future works. Fifth, since this study was a retrospective study and the patients' BMI was not recorded in the medical record system, the correlation between breast density and BMI could not be obtained. In the future, a prospective study will be designed to explore whether BMI can affect breast density.

CONCLUSION

In summary, our study suggests that qualitative CESM BPE assessment may be useful in the prediction of breast cancer risk among high-risk females, while the significance of breast density as an independent risk factor is not fully established for high-risk females during the follow-up period of 4.5 years. Large sample size, long follow-up time and multicentered retrospective study should be performed to improve efficiency and provide high level evidence for clinical application in subsequent studies.

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DATA SHARING STATEMENT

Some or all data, models, or code generated or used during the study are available from the corresponding author by request.

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