Qualitative Assessments of Density and Background Parenchymal Enhancement on Contrast-Enhanced Spectral Mammography Associated with Breast Cancer Risk of High-Risk Women

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Research

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Abstract

Background: To investigate the correlation between the risk of developing breast cancer for high-risk women and the density and background parenchymal enhancement (BPE) on contrast-enhanced spectral mammography (CESM).

Methods: This retrospective study was approved by the Institutional Review Board of our hospital. Women at high risk, without breast cancer history and received CESM examination from July 2016 to December 2017 were retrospectively enrolled. Patients who developed breast cancer after CESM examination were classified as cancer cohorts, and women who did not develop breast cancer with maximized follow-up time were categorized as control cohorts. These two cohorts were one-to-one matched in age, family and/or genetic history of breast cancer, and BRCA status. The density and amount of 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 with no history of breast cancer were diagnosed with breast cancer (invasive, $n = 46$; in situ, $n = 44$). During follow-up, women with mild, moderate or significant BPE were seven times more likely to be diagnosed with breast cancer than women with minimal BPE [$P = 0.005$; odds ratio (OR) = 7.0; 95% confidence interval(CI): 1.1-71.1]. Breast density was not significantly different between the two cohorts ($P = 0.5$).

Conclusions: Increased BPE levels increase the risk of breast cancer among high-risk women.

Background

Breast cancer is one of the most common malignant tumors among women, and 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 less effective [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]. Although breast density as an independent risk factor of breast cancer is still immature in the health care system, its monitoring has certain clinical importance in some areas. Therefore, studying the relationship between breast density and breast cancer risk is necessary.

Background parenchymal enhancement (BPE) is the enhancement of normal fibrous glands 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 magnetic resonance imaging (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 removes normal breast tissues, especially dense glands, and only shows abnormal tumor tissues, thereby enhancing the detection and diagnosis of breast cancer. The negative predictive value of CESM is remarkably high, thus bringing a new breakthrough for the diagnosis of breast tumor. The sensitivity and specificity of CESM are also higher than those of conventional mammography [16]. Its sensitivity for breast cancer detection is comparable with that of MRI [17, 18]. However, to our knowledge, only few studies focused on BPE based on CESM. Sogani J, et al. [19] reported substantial agreement between readers for BPE as detected on CESM and MRI images. Therefore, evaluating BPE on CESM images is necessary. In this study, we attempted to investigate whether breast cancer risk in high-risk women is related to CESM density and BPE.

Methods

Patients

This retrospective study was approved by the Institutional Review Board of Yantai Yuhuangding hospital, and patient informed consent was waived. Data were collected from July 1, 2016 to December 31, 2017 using the Hospital Information System. According to the Tyrer–Cuzick risk model, women with a lifetime risk of breast cancer $\geq 20\%$ are defined as high-risk. The inclusion criteria were as follows: (a) all women 18 years of age or older, (b) no history of breast cancer prior to index CESM imaging, (c) examination time is the 2nd week of menstrual cycle and menstrual cycle is regular, and (d) has not undergone radiotherapy or hormone therapy before examination.

A total of 1012 women were identified. According to pathology, the 90 enrolled women developed breast cancer after CESM examination and thus were classified as cancer cohorts. Meanwhile, women who did not develop breast cancer within the maximized follow-up time were categorized as control cohorts. The two groups have corresponding age, family and/or genetic history of breast cancer, and BRCA gene according to one-to-one matching conducted by randomly selecting cases from the control cohorts.

CESM image acquisition protocol

All breast examinations were performed using CESM (GE Healthcare, Senographe DS Senobright). The contrast agent Omnipaque 350 (GE 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 mL/s. The contralateral mammary gland was compressed to take the mediolateral oblique view, and the craniocaudal view imaged 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 image of the suspected 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 imaging diagnosis who assessed breast density and BPE of CESM images according to the BI-RADS system [20]. The breast density using 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 4 (the breasts are extremely dense) (Fig. 1). BPE amount was sorted into four categories: minimal (< 25%), mild (25–50%), moderate (51–75%), and marked (> 75%) (Fig. 2). All disagreements were resolved through consultation.

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 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 value < 0.05 was considered significant.

Results

Patient characteristics

Table 1 exhibits the patients' characteristics between the two cohorts. Forty-five patients were 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, and BRCA status of the two cohorts were matched.

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

Variable	Cancer Cohort (n = 90)	Control Cohort (n = 90)
Age (y)*	48.1 ± 9.9	47.8 ± 9.7
Follow-up interval (y)*†	2.2 ± 1.5	2.7 ± 1.2
Indication for high-risk screening CESM		
BRCA1 mutation	12(14)	12(14)
BRCA2 mutation	14(16)	14(16)
Family and/or genetic history of breast cancer	64(70)	64(70)
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
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. NA = not applicable. * Data are mean ± standard deviation. † Data are time to diagnosis in the cancer cohort and follow-up time in control cohort. DCIS = ductal carcinoma in situ.		

Association of qualitative imaging features with developing breast cancer

In the cancer cohort, no significant association was observed between breast cancer risk and breast density ($P = 0.5$; Table 2). However, the amount of BPE was significantly associated with breast cancer risk ($P = 0.03$). 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 (Fig. 3). By using this threshold, we found that a significantly higher percentage of women in the cancer cohort had either mild, moderate, or marked BPE (78% [70 of 90 women]) than did women in the control cohort (47% [42 of 90 women], $P = 0.003$).

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

Characteristic	Cancer cohort (n = 90)	Control cohort (n = 90)	Odds Ratio*	P value
BPE	20(22)	51(57)	2.1 (1.0, 4.4)	0.03
Minimal	36(40)	24(27)	7.0 (1.1, 71.1)	0.005
Mild	20(22)	12(13)		
Moderate	14(16)	3 (3)		
Marked				
BPE (dichotomous)				
Minimal	20(22)	48(53)		
Mild, moderate, or marked	70(78)	42(47)		
Density			1.6 (0.8, 3.2)	0.5
A	2(2)	4(4)		
B	22(25)	32(36)		
C	48(53)	44(49)		
D	18(20)	10(11)		
Note.—Unless otherwise indicated, data are numbers of subjects, with percentages in parentheses.				
* Data in parentheses are 95% confidence intervals.				
During follow-up, women with mild, moderate or significant BPE were seven times more likely to be diagnosed with breast cancer than women with minimal BPE (P = 0.005; OR = 7.0; 95% CI: 1.1–71.1). As shown in Fig. 4, a woman with moderate BPE has developed breast cancer.				

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 = 0.6 and P = 0.8, respectively) (Table 3).

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*	P value
BPE			1.0 (0.3, 2.3)	0.8
Minimal	8(17)	8(19)		
Mild	18(37)	16(38)		
Moderate	16(33)	13(31)		
Marked	6(13)	5(12)		
Density			1.2 (0.3, 3.2)	0.6
A	4(8)	3(7)		
B	17(35)	10(24)		
C	20(42)	20(48)		
D	7(15)	9(21)		
Note.—Unless otherwise indicated, data are numbers of subjects, with percentages in parentheses.				
* Data in parentheses are 95% confidence intervals.				

Discussion

In this study, we investigated the correlation of breast density and background parenchymal enhancement on contrast-enhanced spectral mammography and the risk of developing breast cancer in a high-risk group. Our results suggest that women with mild, moderate or significant background parenchymal enhancement were seven times more likely to be diagnosed with breast cancer than women with minimal background parenchymal enhancement. Breast density was not significantly different between the cancer and control cohorts. Previous studies showed that the increased background parenchymal enhancement levels on MR images increase the risk of breast cancer for high-risk women as indicated by background parenchymal enhancement detection on contrast-enhanced spectral mammography and MR images [13, 19, 21]. In the present work, we reported similar results that the increased background parenchymal enhancement levels on contrast-enhanced spectral mammography images increase the risk of breast cancer of high-risk women. This finding may improve the effectiveness of breast cancer risk models.

Previous studies showed that BPE level is affected by hormone level [22–26]. For premenopausal people, the enhancement of mammary gland tissue is the most apparent during the 1st and 4th weeks but the weakest during the 2nd week. Therefore, all participants underwent CESM examination during their 2nd

week of menstrual cycle. BPE is reduced by endocrine therapy (including selective estrogen receptor modulator or aromatase inhibitor). King et al. [27] reported that BPE is substantially reduced in breast cancer patients treated with tamoxifen and cysts. King et al. [28] 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 [29]. 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 risk factor for hormone sensitive and non-hormone sensitive breast cancers.

Our research has another 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.

Many studies indicated the correlation between breast density and breast cancer [30]. 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. Some scholars believe that this phenomenon strongly indicates a biological correlation between dense tissue and breast cancer risk [31]. 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 women with BRCA mutations [32]. This finding is similar to our results. The difference may be attributed to the non-identical research participants. Passaperuma K's research subjects are women with BRCA gene mutation, and our research participants are high-risk women. In addition, integrating breast density as an independent breast cancer risk factor into the health care system is still immature. Further evaluating the relationship between breast density and breast cancer risk is necessary.

Our study has several limitations. First is the small data set. As a new technology, a large sample size is needed to improve research results. Second, this study is single-centered. A multi-centered research is necessary to obtain high-level evidence for clinical applications. Third, the relationship between BPE on CESM and breast cancer risk in the general population of women is still unknown. We will continue our research in future works.

Conclusions

In summary, our study suggests that the increased BPE levels increase the risk of breast cancer among high-risk women. Breast density may be a less effective predictor of breast cancer among high-risk women. Large sample size and multi-centered retrospective study should be performed to improve efficiency and provide high level evidence for clinical application in subsequent studies.

Declarations

Ethics approval and consent to participate

Institutional Review Board approval was obtained.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

All authors have made great contributions to this manuscript and participated in the design of this study and data analysis. All authors read and approved the final manuscript.

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Figures

Figure 1

Mediolateral oblique low-energy images of CESM demonstrate different breasts with (a) A, density.

Figure 2

Mediolateral oblique low-energy images of CESM demonstrate different breasts with (b) B density.

Figure 3

Mediolateral oblique low-energy images of CESM demonstrate different breasts with (c) C, density.

Figure 4

Mediolateral oblique low-energy images of CESM demonstrate different breasts with (d) D density.

Figure 5

Mediolateral oblique recombined images of CESM demonstrate different breasts with (a) minimal,

Figure 6

Mediolateral oblique recombined images of CESM demonstrate different breasts with (b) mild.

Figure 7

Mediolateral oblique recombined images of CESM demonstrate different breasts with (c) moderate.

Figure 8

Mediolateral oblique recombined images of CESM demonstrate different breasts with (d) marked BPE.

Figure 9

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.

Figure 10

Recombined images of CESM in a 41-year-old woman with a family history of breast cancer shows moderate BPE. This patient was found to have invasive ductal carcinoma 171 days after index CESM.