Egyptian Journal of Radiology and Nuclear Medicine

RESEARCH

Open Access

Diagnostic value of contrast-enhanced mammography in the characterization of breast asymmetry

Bassant Mahmoud Dawoud[1*], Abdelmonem Nooman Darweesh[1], Mohamed Mohamed Hefeda[1], Rasha Mohamed Kamal[2] and Rasha Lotfy Younis[1]

Abstract

Background: Breast asymmetry is a prevalent mammographic finding described in BI-RADS atlas as asymmetry, focal asymmetry, global asymmetry, and developing asymmetry. Mammography has a limited role in discrimination between benign and malignant asymmetry, and digital mammography can overlook up to 15–30% of breast tumors. The purpose of our study was to assess the role of contrast-enhanced mammography (CEM) in distinction between benign and malignant asymmetries.

Results: Out of the studied 540 indeterminate and suspicious asymmetries, and according to final histopathological results, 97/540 (17.9%) asymmetries were benign, 395/540(73%) asymmetries were malignant, 48/540 (8.9%) asymmetries were normal with no underlying pathology. After comparing results of sonomammography and CEM, CEM showed higher sensitivity (96.5% vs. 85.8), specificity (77.1% vs. 64.4%), NPV (88.8% vs. 62.7%), PPV (92.04% vs. 86.7%) and accuracy (91.3% vs. 80%).

Conclusions: CEM has proven to be a valuable and beneficial imaging technicality for patients and radiologists, with breast cancer detection sensitivities superior to that of full-field digital mammography (FFDM) with ultrasonography (US).

Keywords: Asymmetry, Breast cancer, Contrast-enhanced mammography (CEM), Mammography

Background

The breasts have similar mammographic densities attributing to nearly symmetric internal structures in spite of variable size and parenchymal pattern. However, screening mammography frequently reveals asymmetric breast findings [1]. Breast asymmetry may reflect a variation in normal breast tissue, developing mass, postoperative or post-biopsy changes, hormone replacement therapy or even poor positioning [1, 2].

In the third edition of Breast Imaging-Reporting and Data System (BI-RADS), three types of asymmetries were described: a single projection asymmetry, asymmetric breast tissue, and focal asymmetric density. In the fourth edition "asymmetric breast tissue" was replaced with "global asymmetry," "density seen in only a single projection" was replaced with "asymmetry," and "focal asymmetric density" with "focal asymmetry", no convex margins in all types. The fourth edition of BI-RADS does not include the term "developing asymmetry", only a brief description of "developing density" is included but was introduced by Leung and Sickles [3–5].

Mammography is the standard method of diagnosing breast cancer either in the setting of screening programs or in symptomatic women. It has some limitations,

*Correspondence: dpoussi@rocketmail.com

[1] Faculty of Medicine, Tanta University, El-Geish Street, Tanta, Gharbia Governorate, Egypt
Full list of author information is available at the end of the article

mainly because of reduced contrast between tumors and surrounding tissue especially in dense breasts that leads to a decrease in sensitivity. Thus, complementary imaging methods are needed [6].

The increased parenchymal densities result in a superimposition of dense breast tissue on a two-dimensional (2D) mammographic projection, and this is the main cause of decreased mammographic sensitivity [7, 8].

Contrast-enhanced mammography (CEM) depends on the assessment of the tumor vascularity with the aid of injected non-ionic iodine-based contrast material during mammography. The mammograms are acquired at two energies, below and above the iodine energy K-absorption edge (33.2 kVp) [9].

This morpho-functional nature allows full-field digital mammogram to use a dual-energy subtraction algorithm to depict contrast-enhanced cancers that would be occult on standard unenhanced mammography; it provides exact lesion size and identifies multifocal and multicentric breast cancer, thus contrast mammography is considered a promising modality in characterization of breast asymmetry [10, 11].

Also, CEM is a simple technicality with low cost, widely available in practice and has a high sensitivity as that of MRI [12].

The aim of this study was to assess the diagnostic role of contrast-enhanced mammography in the characterization of breast asymmetries detected on mammograms.

Methods

Study population

The current prospective study included 513 female patients having 540 indeterminate and suspicious asymmetries with and without an ultrasound correlate. Their ages ranged from 19 to 73 years with a mean of 47.9 ± 9.09 years. They were referred to radio-diagnosis department for contrast mammography examination over a period from March 2020 to June 2022. The results were correlated to histopathological analysis by core biopsy or surgical biopsy which was considered the gold standard.

Approval of Research Ethics Committee (REC) and informed consent were obtained from all participants in this study after explanation of the benefits and risks of the procedure. Privacy and confidentiality of all patients' data were guaranteed. All data provision were monitored and used for scientific purpose only.

The inclusion criteria were patients with breast asymmetry associated with distortion, calcifications, newly developed asymmetry or increased in size seen on mammogram, or clinically palpable mass lesion, induration, edema, or shrunken breast. No age predilection.

Exclusion criteria were pregnant patients, patients with contraindications to contrast injection as renal impairment and glomerular filtration rate < 40 mL/min/1.73m2 or previous allergy to the contrast media, and patients with breast lesions other than asymmetry like masses.

All the included subjects were subjected to the following:

Data collection

- Full medical history; personal history, present history, past history of previous breast masses and mode of treatment either surgery, chemotherapy or radiotherapy, history of breast pain, nipple discharge, or axillary lesions, and family history of breast cancer.
- Check of all previous investigations or radiological examination.

Clinical examination

- General examination:—pulse, temperature, blood pressure and general examination to exclude metastasis.
- Local examination:—examination of breast and axilla to detect masses, nipple retraction and axillary lymph nodes.

Laboratory investigations

Recent renal functions tests.

Mammography

- Two standard mammographic views for each breast: craniocaudal and mediolateral oblique views using a KV range of 22–37 and a MA/sec range of 400–600 according to breast size and density.
- Each patient stood with her breast placed horizontally on the film cassette, compression was applied to flatten out the breast to avoid motion and enhance visualization. A craniocaudal film was taken, where the beam was directed 90 degrees. Mediolateral oblique view was done with an angle of 45°.

Breast ultrasound examination

Ultrasound examination was performed for all studied patients using GE S8 ultrasound system with high-frequency linear array L 12–5 transducer connected to a real-time scanner. During examination, the patient was supine with her ipsilateral arm extending over her head and turn slightly toward the contralateral side to allow the breast to lie as flat as possible on the chest wall to

reduce penetration thickness and breast mobility. Glandular tissue was visualized in different imaging planes (transverse, sagittal or radially toward the nipple). Radial plane was helpful for imaging ducts traced as tubular structures to the nipple.

Contrast-enhanced mammography

Fuji Film AMULET innovality digital mammography system was used; model name FDR MS-3500 with some specific software and hardware adaptations for acquisition and image processing, where standard two projections (CC and MLO) views were obtained.

Patient preparation

A cannula was inserted in the ante-cubital fossa on the opposite side of the affected breast. All patients were injected intravenously with iodinated contrast agent (Omnipaque, 300 mg/ml; 1–1.5 ml/kg) just before patient positioning and breast compression to the seated breast; to avoid interference with the normal vascular dynamics of the breast. The cannula was left within the vein to provide a quick intravenous access in case of any reaction.

Image acquisition

- Bilateral craniocaudal (CC) and mediolateral oblique (MLO) views were acquired 2 min after injection of contrast medium; CC view of the unaffected breast followed by CC and MLO views of the affected breast, then MLO view of the unaffected breast.
- Low-energy images at 26 to 31 (kVp), and high-energy images at 45 to 49 (kVp) were obtained. Recombined images are created by subtracting the low-energy images from high-energy images, allowing signal from background breast tissue to be canceled out and areas of contrast uptake to be highlighted. Total duration time from start of injection till the end of examination was about 7–10 min.
- Bilateral breast contrast mammography was performed for each patient in the same sitting.
- Patients were classified into two groups:

Group 1: CEM to confirm diagnosis included (351/540, 65%).

Group 2: CEM to verify extension included (189/540, 35%).

Image analysis

- All CEM images were analyzed by two radiologists with 25 and 15 years of mammography experience, blinded to the clinical data and laboratory indicators, and final decisions reached by consensus were reported.
- The images were reviewed to estimate the morphological findings and enhancement characteristics.
- The presence or absence of contrast enhancement was mainly assessed on the recombined images and based on contrast enhancement and morphology like those described in the breast imaging-reporting and data system (BI-RADS) MRI lexicon developed by the American College of Radiology (ACR).
- The morphological characteristics of the enhancing lesions were assessed, and its maximum size was measured. The enhancement was described as follow: -
- Focus enhancement; single or multiple, unilateral, or bilateral, faint or intense enhancement.
- Mass enhancement; its shape: oval, rounded and irregular, its margin: circumscribed and non-circumscribed (irregular or spiculated), and internal enhancement characteristics: homogeneous, heterogeneous, rim enhancement and dark internal septations.
- Non-mass enhancement; its internal enhancement pattern: homogeneous, heterogeneous, clumped, and clustered ring and distribution: focal, linear, segmental, regional, multiple regions and diffuse.
- Finally, based on the morphological and enhancement features, the lesion was given one of the American College of Radiology (ACR), Breast Imaging-Reporting and Data System BI-RADS categories.

Statistical analysis

- Data were coded and entered using the SPSS (Statistical Package for Social Sciences) version 25 for Windows® (IBM SPSS Inc, Chicago, IL, USA).
- Data were tested for normal distribution using the Shapiro–Wilk test. Qualitative data were represented as frequencies (count) and relative percentages. For comparing categorical data, Chi square test ($\chi 2$) was used. Monte Carlo Exact test was used instead of chi square when expected frequency is less than 5. Quantitative data were expressed as mean ± SD (Standard deviation), median, minimum, maximum and range.
- Spearman's correlation (r) was used to test the correlation between two variables with nonparametric quantitative data.
- Standard diagnostic indices including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic efficacy were calculated as described by Galen RS.

- Probability (P value): P value ˂0.05 was considered significant.

Results

This study was carried on 513 females' patients having 540 indeterminate and suspicious asymmetries with and without an ultrasound correlate. Twenty-seven patients had multiple lesions: Seven patients had two asymmetries in the same breast, and 20 patients had bilateral asymmetries. Patients were either asymptomatic attending for annual screening mammography or were symptomatic presenting clinically by palpable mass lesion, induration, edema, and shrunken breast. Fifteen cases had previous breast surgery. The results were compared to core or surgical biopsy results. None of the patients showed any sign of a reaction to the contrast media.

The patients' age ranged from 19 to 73 years with a mean age of 7.9 ± 9.09. Out of the patients included in this study, 25% had a first degree relative with history of breast cancer. The symptomatic cases were 403/513 (78.5%) and the most common clinical presentation was breast mass (217/513; 42.3%), while nipple discharge was the least complaint (5/513; 1%). Some of our studied patients had presented by more than one complaint. There was a significant correlation between symptoms and malignancy (P < 0.001). Breast mass presentation was more in malignant cases; out of 395 pathologically proven malignant asymmetry, 201 cases presented with breast mass complaint (50.8%).

The breast density was classified according to the American College of Radiology Breast Imaging-Reporting and Data System (ACR-BI-RADS) lexicon into ACR A, B, C and D. Mammographic density was rated as fatty (ACR density A or B) in 189/513 patients (36.8%) and dense (ACR density C or D) in 324/513 patients (63.2%). In this study, 256/324 patients (79%) were histopathologically proven malignant. There was no significant correlation between breast density and malignant pathology (P value 0.156).

Regarding the type of asymmetry

21/540 (3.9%) cases were single view asymmetries (Fig. 1), 356/540 (65.9%) cases were focal asymmetries, 157/540 (29.1%) cases global asymmetry, and 6/540 (1.1%) cases developing asymmetry (Fig. 2).

Ten cases having single view asymmetry (47.6%) were malignant, four cases (19%) were benign, and seven cases (33.3%) were normal. We had 269 cases (75.6%) of focal asymmetry were malignant, 58 (16.3%) were benign and 29 cases (8.1%) were normal. Out of 157 (70%) cases of global asymmetry, 110 were malignant, 35/157 (22.3%) were benign and 12/157 cases (7.7%) were normal. The six cases of developing asymmetry were malignant (100%). Developing asymmetry was more commonly associated with malignant pathology 6/6 cases. The presence of a developing, focal, or global asymmetry strongly correlated with an underlying malignant pathology (P value 0.004) as shown in Table 1.

Associated findings were identified in 214/ 540 (39.6%) asymmetries. Skin and nipple changes were identified in 106/214 (49.5%) and suspicious calcification in 54/214 (25.3%) (Fig. 1). The percentage of associated pathological axillary lymph nodes and distortion were equal 12.6%.

There was a significant correlation between asymmetry associated with suspicious calcification, pathological axillary lymph nodes, skin/nipple changes, distortion, and malignancy (rs = 0.416 and P value < 0.001). Correlation of mammography associated findings with final outcome is illustrated at Table 2.

On performing a targeted ultrasound examination, no ultrasound correlate was seen in 150/540 (27.8%) asymmetries, an indeterminate and a probably malignant ultrasound correlate was identified in 390/540 (72.2%). There was a significant correlation between presence of ultrasound findings and malignancy (rs = 0.387 and P value < 0.001).

Patients were classified into two groups: Group 1: (351/540; 65%) in whom CEM was done to confirm a previous ultrasound and mammographic suspicious findings, and Group 2: (189/540; 35%) in whom CEM was done to assess malignancy extension in patients previously diagnosed with malignancy.

CEM characterized 215/540 (39.8%) as malignant asymmetries, 90/540 (16.6%) as benign asymmetries, and 46 /540 (8.5%) as normal with no underlying pathology (Fig. 3).

CEM was performed to evaluate the extent of disease and staging as regards size, multiplicity and bilaterality in 189/540 (35%) asymmetry, it added extension in 118/540 (21.8%) as follows: added wider extension in 91 cases, additional enhancing lesion in contralateral breast in 20 case and additional enhancing lesions in the same breast (multifocal/multicentric) in seven cases (Fig. 4).

The background parenchymal enhancement was assessed on the recombined images of the study: 461/513 cases (89.9%) showed minimal and mild background enhancement and 52/ 513 cases (10.2%) showed moderate and marked background parenchymal enhancement.

The pattern of contrast mammography findings was no-enhancement in 71/540 asymmetry (13.1%), enhancing mass in 248/540 asymmetries (45.9%), enhancing foci in 20/540 asymmetries (3.7%) and non-mass enhancement in 201/540 asymmetries (37.2%) (Fig. 2).

On contrast-enhanced mammography, non-enhancing asymmetries represented 71/540 asymmetries (13.1%).

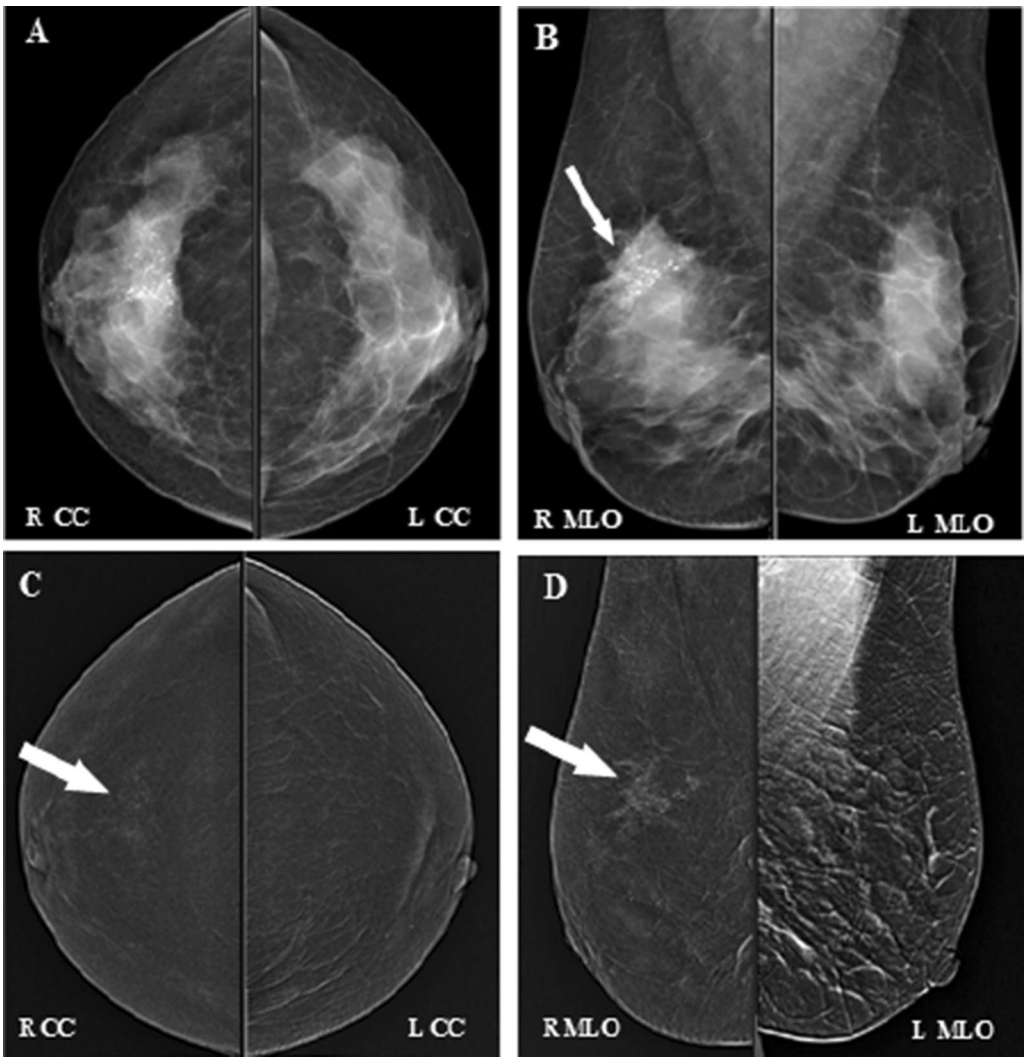

Fig. 1 A 42-year-old female, complaining of right breast pain. **(A)** Craniocaudal mammographic view of both breasts, and **(B)** Mediolateral mammographic views of both breasts revealed right upper quadrant single view asymmetry (arrow) seen at right MLO view associated with right upper outer quadrant segmental fine pleomorphic calcifications. **(C)** Craniocaudal CEM view of both breasts, and **(D)** Mediolateral CEM views of both breasts revealed right upper outer quadrant clumped segmental non-mass enhancement. Pathology revealed low-grade DCIS. CEM confirmed the malignant nature of right upper outer quadrant lesion and showed its actual extension

(See figure on next page.)

Fig. 2 A 45-year-old female, complaining of left breast pain. **(A)** Craniocaudal mammographic view of both breasts, and **(B)** Mediolateral mammographic views of both breasts in 2020 revealed no abnormality. **(C)** Craniocaudal mammographic view of both breasts, and **(D)** Mediolateral mammographic views of both breasts in 2021 revealed left axillary tail focal asymmetry (arrows). **(E)** Craniocaudal mammographic view of both breasts, and **(F)** Mediolateral mammographic views of both breasts in 2022 revealed increased size of the left axillary tail focal asymmetry (developing asymmetry) (arrows). **(G)** Ultrasound image showing left axillary tail irregular hypoechoic soft tissue mass with posterior attenuation, and vertical orientation and color flow on color Doppler examination. **(H)** Craniocaudal CEM view of both breasts, and **(I)** Mediolateral CEM views of both breasts revealed left axillary tail mass lesion with homogenous enhancement (arrows). Pathology revealed invasive lobular carcinoma. CEM confirmed the malignant nature of left breast lesion

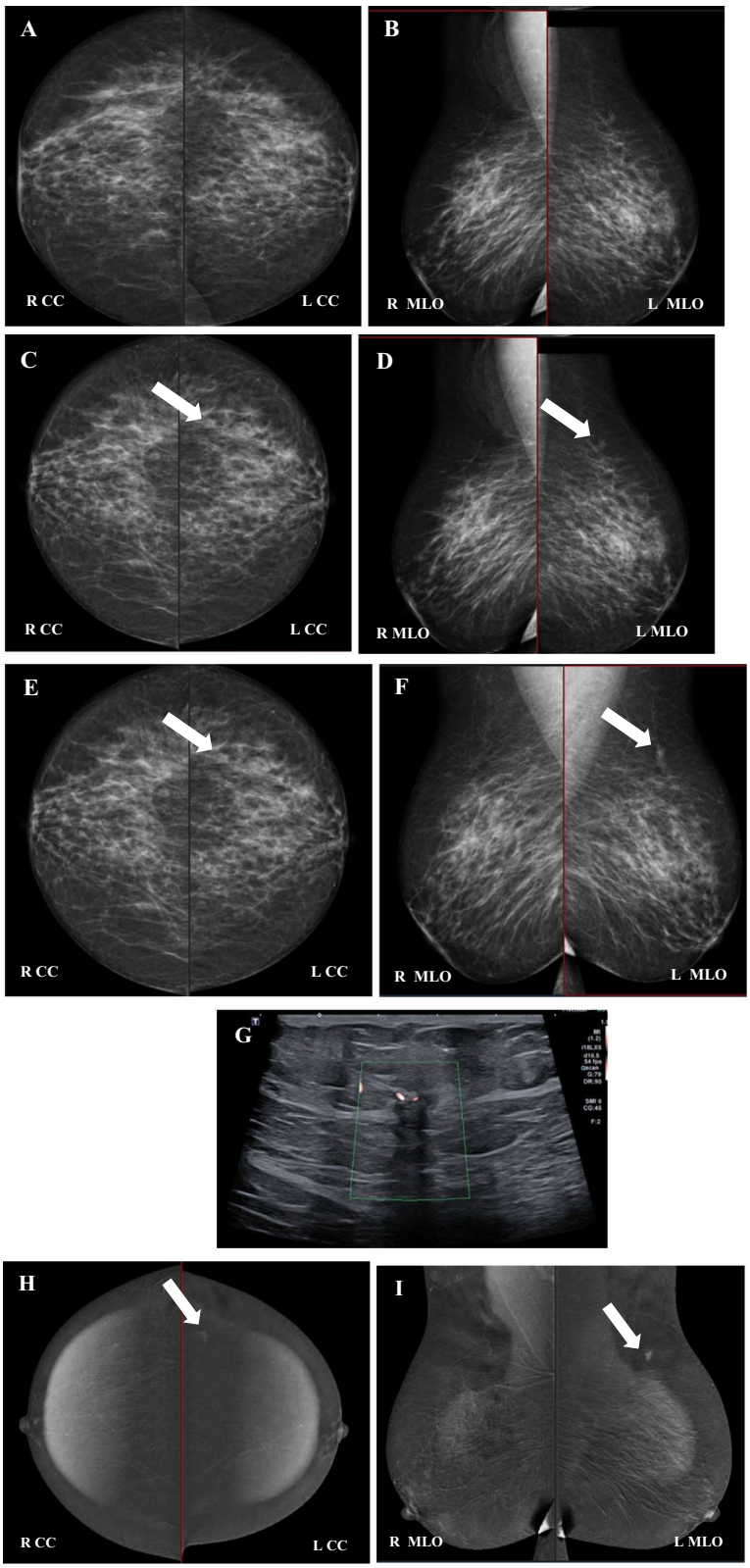

Fig. 2 (See legend on previous page.)

Table 1 Breast asymmetry and their correlation to their final diagnosis by histopathology (n = 540)

	Histopathology			Total
	Normal	Benign	Malignant	
Asymmetry				
Single view	7	4	10	21
	33.3%	19%	47.6%	100%
Focal	29	58	269	356
	8.1%	16.3%	75.6%	100%
Global	12	35	110	157
	7.7%	22.3%	70%	100%
Developing	0	0	6	6
	0.0%	0.0%	100%	100%
Total	48	97	395	540

Out of the cases with asymmetry, 45.9% (248/540) showed mass enhancement, 37 asymmetries (14.9%) of which were benign and 211 asymmetries (85%) of which were malignant. In addition, 201/540 asymmetries (37.2%) showed non-mass enhancement, 29 asymmetries (14.4%) of which were benign and 171 asymmetries (85.1%) of which were malignant. Any enhancing asymmetry showing a mass or non-mass enhancement was significantly correlated with malignant pathology with ($rs = 0.416$ and P value < 0.001). The enhancement pattern of breast asymmetries and their correlation to a final diagnosis are shown in Table 3.

Pathological specimens of the 540 patients included in our study were obtained by core or surgical biopsy. Histopathological findings are illustrated in Table 4.

In the examined patients included in this study, 97/540 asymmetries (17.9%) were pathologically proved benign, 395/540 asymmetries (73%) were pathologically proved malignant, 48/540 asymmetries (8.9%) were normal with no underlying pathology.

The commonest cause of false-positive asymmetries is the inflammatory breast lesion (13/33; 39.4%) as shown in Table 5.

According to the final outcome of the studied patients depending on histopathological findings which were accepted as a standard reference, contrast mammography recorded 382 patients (70.7%) as true positive cases, 111 patients (20.6%) as true negative cases, 33 patients (6.1%) as false-positive cases, and 14 patients (2.6%) as false-negative cases with a sensitivity of 96.5%, a specificity of 77.1%, an accuracy of 91.3%, a positive predictive value of 92.04%, and a negative predictive value of 88.8%, while sonomammography had a sensitivity of 85.8%, a specificity of 64.4%, an accuracy of 80%, a positive predictive value of 86.7%, and a negative predictive value of 62.7% as shown in Table 6.

Discussion

Breast cancer is the most common cancer among females, and a substantial reason for women misery and precocious death. It is estimated that 2.3 million new patients are diagnosed with breast cancer annually all over the world [13, 14].

The asymmetry is a mammographic area of increased breast density compared to the corresponding area in the contralateral breast. Most asymmetries are benign or because of summation artifacts due to superimposition of breast tissue during mammography, but an asymmetry may suggest breast cancer. Estimation and diagnosis of asymmetries are challenging as they often are superfine and mimic typical fibro glandular tissue [15].

Contrast-enhanced mammography has a superiority in explaining both anatomic changes and local perfusion changes caused by tumor angiogenesis [17].

CEM is beneficial in settling vague findings detected at conventional breast imaging, preoperative staging of breast cancer to assess the extent of disease, detection

Table 2 Mammography associated findings and their correlation to the final diagnosis

Associated mammographic findings	Asymmetries							
	Single		Focal		Global		Developing	
	Benign	Malignant	Benign	Malignant	Benign	Malignant	Benign	Malignant
Pathological axillary LN	0	0	0	23	0	4	0	0
	0.0%	0.0%	0.0%	100.0%	0.0%	100.0%	0%	0%
Suspicious calcification	0	1	2	38	0	12	0	1
	0.0%	100.0%	5.0%	95.0%	0.0%	100.0%	0%	100%
Distortion	0	2	1	15	2	2	0	0
	0.0%	100.0%	4.8%	71.4%	50.0%	50.0%	0%	0%
Skin and nipple changes	1	1	13	21	15	53	0	1
	50.0%	50.0%	38.2%	61.8%	21.7%	76.8%	0%	100%

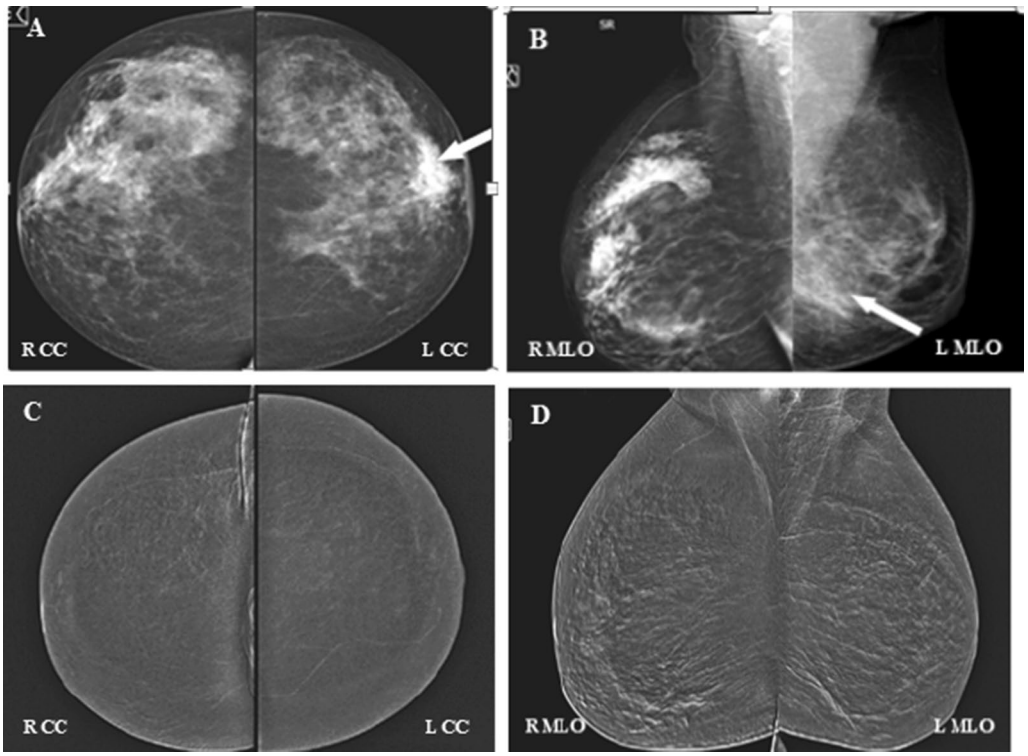

Fig. 3 A 36-year-old female performed a follow-up examination after left conservative breast surgery for breast cancer one year ago. **(A)** Craniocaudal mammographic view of both breasts, and **(B)** Mediolateral mammographic views of both breasts revealed left breast lower outer quadrant focal asymmetry (arrows) associated with skin thickening, asymmetric left breast size and densities (postoperative sequalae)**. (C)** Craniocaudal CEM view of both breasts, and **(D)** Mediolateral CEM views of both breasts revealed no enhancement; no underlying pathology. Pathology revealed normal tissue

of tumor multiplicity, and assessment of treatment response. It is used as an alternative to breast MRI in women who are at an increased risk of developing breast cancer. Also, it may detect ductal carcinoma in situ (DCIS); mostly associated with microcalcification detected in low-dose images [16, 17].

The aim of this work is to evaluate the diagnostic role of CEM in the differentiation between benign and malignant breast architectural asymmetries detected on mammograms.

This study included 513 females' patients presented with 540 indeterminate and suspicious asymmetries. The age of the patients ranged from 19 to 73 years, with a median age of 47 years and a mean age of 47.9 years ± 9.09.

In this study, symptomatic cases were 403/513 (78.5%) and the most common clinical presentation was breast mass 217/513 (42.3%). There was a significant correlation between symptoms and malignancy ($P < 0.001$). Breast mass presentation was more in malignant cases, out of 395 pathologically proven malignant asymmetry, 201 cases presented with breast mass complaint (201/395) 50.8%.

In keeping with this study, Tennant et al. [18] stated that CEM supplies immediate and clinically useful information in patients with suspicious palpable abnormalities.

The breast density was classified according to the American College of Radiology Breast Imaging-Reporting and Data System (ACR-BI-RADS) lexicon into ACR A, B, C and D. In this study, there was no significant correlation between breast density and malignant pathology with p value = 0.156. This disagrees with Gordon, 2021[19] who realized that dense breast tissue is an independent risk factor for developing cancer.

CEM has several indications in this study; most cases 65% had performed it for better assessment of abnormal imaging findings on sonomammography to set diagnosis (benign, malignant nor no abnormal underlying findings), 35% of them had performed it to evaluate disease extent and staging as regards size, multiplicity and bilaterality. CEM added extension in 118/540 (21.8%) as follows: added wider extension in 91 cases, additional enhancing lesion in contralateral breast in 20 case and additional enhancing lesions in the same breast (multifocal/multicentric) in seven cases.

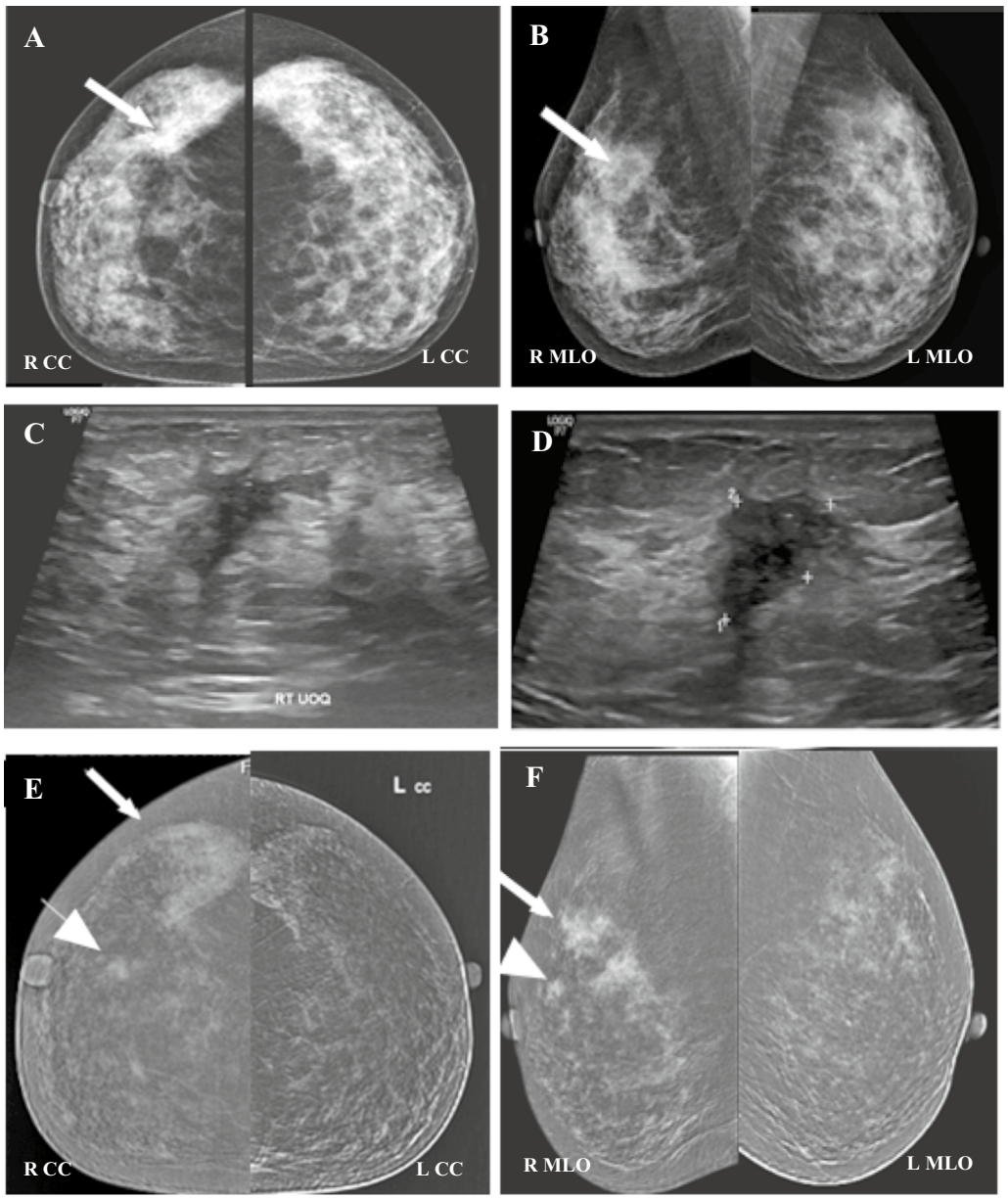

Fig. 4 A 29-year-old female, complaining of palpable right breast swelling and induration. **(A)** Craniocaudal mammographic view of both breasts, and **B** Mediolateral mammographic views of both breasts revealed right upper outer quadrant breast focal asymmetry (arrows). **(C& D)** Ultrasound images showing right upper outer quadrant irregular hypoechoic two soft tissue masses with spiculated margin, posterior attenuation, and vertical orientation. **(E)** Craniocaudal CEM view of both breasts, and **(F)** Mediolateral CEM views of both breasts revealed right upper outer quadrant heterogenous focal (arrow heads) and segmental (arrows) non-mass enhancement. Pathology revealed invasive ductal carcinoma. CEM confirmed the malignant nature of right breast lesion and proved lesion multiplicity (two malignant lesions)

Regarding histopathological diagnosis of the 97 benign lesions (17.9%) included in the study, 6.9% were mammary adenosis, 3.7% were mastitis, 2% were fibrocystic disease, 0.6% were fat necrosis and 4.8% were other benign lesions.

Regarding histopathological diagnosis of the 395 malignant lesions (73%) included in the study, 57.8% were IDC, 7% were ILC, 3.3% were DCIS, 2.6% were IDC with DCIS, 1.5% were invasive mixed carcinoma and 0.9% were other malignant lesions. Kamal et al. [20] goes with this study who reported that according to histopathology results and outcomes of follow-up studies, 35/380 (9.2%) asymmetries were

Table 3 The enhancement pattern of breast asymmetries and its correlation to the final diagnosis

Associated mammographic findings	Asymmetries							
	Single		Focal		Global		Developing	
	Benign	Malignant	Benign	Malignant	Benign	Malignant	Benign	Malignant
No enhancement	1	0	17	0	7	0	0	0
	12.5%	0.0%	37.0%	0.0%	41.2%	0.0%	0%	0%
Focal enhancement	0	0	5	12	1	1	0	0
	0.0%	0.0%	29.4%	70.6%	33.3%	33.3%	0%	0%
Mass enhancement	3	8	26	171	8	30	0	2
	27.3%	72.7%	13.2%	86.8%	21.1%	78.9%	0%	100%
Non-mass enhancement	0	2	10	86	19	79	0	4
	0.0%	100.0%	10.4%	89.6%	19.2%	79.8%	0%	100%

Table 4 Histopathological results (n = 540)

Pathological results		No	%
Normal		48	8.9
Malignant lesions (n = 395)	IDC	313	57.8
	ILC	38	7.0
	DCIS	18	3.3
	IDC with DCIS	14	2.6
	Invasive mixed carcinoma	8	1.5
	Other malignant	5	0.9
Benign lesions (n = 97)	Fibrocystic	11	2
	Mammary adenosis	37	6.9
	Mastitis	20	3.7
	Fat necrosis	3	0.6
	other benign	26	4.8

IDC Intraductal Carcinoma, *ILC* Invasive Lobular Carcinoma, *DCIS* Ductal Cell carcinoma In Situ

Table 5 Histopathology of CEM false-positive cases (N = 33)

	No	%
Fibrocystic	2	6.1
Mammary adenosis	8	24.2
Mastitis	13	39.4
Fat necrosis	1	3.0
Benign enhancing lesions	9	27.3
Total	33	100.0%

overlapping tissues, 88/380 (23.2%) were benign lesions, and 257/380 (67.6%) were malignant lesions.

Focal asymmetry was the most prevalent asymmetrical density in the present study (356/540) 65.9%. Harvey et al. [21] considered focal asymmetry more suspicious than global asymmetry, especially if accompanied with parenchymal distortion. In fact, most of our

Table 6 Diagnostic indices of sonomammography and contrast-enhanced mammography compared to pathology in the assessment of breast asymmetry (n = 540)

	Sonomammography	Contrast-enhanced Mammography
Sensitivity	85.8%	96.5%
Specificity	64.4%	77.1%
Positive predictive value	86.7%	92.04%
Negative predictive value	62.7%	88.8%
Positive likelihood ratio	2.4	4.2
Negative likelihood ratio	0.22	0.05
Accuracy	80%	91.3%

focal asymmetry cases were malignant (269/356) 75.6%, especially in instances when the focal asymmetry was associated with suspicious mammographic findings like distortion, pathological axillary lymph nodes, suspicious calcifications, skin, and nipple changes (97/269) 36% (P value < 0.001).

On the contrary, focal asymmetry cases were more likely to be associated with a benign pathology if they did not present with other suspicious findings (16/269) 6%.

In this study, all non-enhancing focal asymmetries were benign. Most of the patients in the study with malignant focal asymmetry showed mass enhancement 171 case, 86 malignant cases of focal asymmetry showed non-mass enhancement, the extension and size of those non-mass enhancement were better delineated by CEM when compared to sonomammography, this agrees with Wessam et al. [22] that stated that focal and global asymmetries associated with other suspicious mammographic findings were statistically significant with malignancy and CEM played a great role in delineation of tumor size and extension. Any non-enhancing asymmetries of benign nature have no associated suspicious imaging findings.

Global asymmetry was the second most frequently represented asymmetrical density in this study (157/540) 29%; if it was not associated with other mammographic suspicious findings, it was statistically correlated with benign findings; this agrees with Youk et al. [4]; they found that global asymmetry is almost benign and needs no additional evaluation if there are no corresponding palpable abnormalities, architectural distortions, significant calcifications, or masses (BI-RADS Category 2).

Single view asymmetry was the third most frequently represented asymmetrical density in our study (21/540) 3.9%, ten cases of single view asymmetry (47.6%) were malignant, four cases (19%) were benign, and seven cases were normal (33%) with no underlying pathology. This matches with the result of the study of Kamal et al. [20] who found that 45% of one view asymmetry were malignant, 20% were benign and 35% were normal.

A developing asymmetry should be viewed with suspicion because it is an uncommon manifestation of breast cancer [4]. It was the least asymmetry represented in this study (6/540) 1.1%. Six cases were pathologically proven to be malignant; three cases were invasive ductal carcinoma and the other three were invasive lobular carcinoma. Chesebro et al. [23] reported that the growth pattern of ILC makes it represent a high percentage of developing asymmetries.

In terms of lesion detection in this study, 324/513 (63.2%) were heterogeneously dense breasts and extremely dense breast, which are the main causes of false-negative and false-positive cases in mammography. Adding contrast mammography provides additional information in dense breasts as underlying lesion enhancement, extension, and multiplicity. The heterogeneous dense parenchyma did not correlate with a corresponding degree of background parenchymal enhancement (BPE). In keeping with this study, several studies including Fallenberg et al. [24], Cheung et al. [25], Dromain et al. [26] proved that CEM is superior to mammography in the identification of multiplicity, extent, and size of malignant lesions especially in the dense breast parenchyma.

The commonest causes of false-positive asymmetries in this study are the inflammatory breast lesions (13/33, 39.4%). Wessam et al. [22] found that inflammatory breast lesions are the commonest cause of false-positive asymmetries in their study (8/15, 53.3%).

When compared to sonomammography, CEM showed higher sensitivity (96.5% vs. 85.8), specificity (77.1% vs. 64.4%), NPV (88.8% vs. 62.7%), PPV (92.04% vs. 86.7%) and accuracy (91.3% vs. 80%). Our study agrees with Kamal et al. [20] who compared CEM and sonomammography in terms of accuracy (88.4% vs. 80.53%).

Wessam et al. [22] reported CEM sensitivity of 100% (vs. 97.8% for sonomammography), and positive and negative predictive values of 85.85 and 100% (vs. 93.7 and 93% for sonomammography, respectively). Dromain et al. [26] also proved that CEM had better sensitivity than FFDM plus US (93% versus 90%), as well as better specificity (63% versus 47%). The study of Tardivel et al. [27] concluded that the high NPV of CEM was valuable in resolving cases with indeterminate lesions (i.e., BI-RADS 3 or 4a) by averting the need for biopsy.

The main limitation in using CEM is the shortage in availability of biopsy capability [27]. If a finding is found on recombined images only, it can be sampled by finding either a low-energy correlate to target with stereotactic/tomosynthesis-guided core biopsy, an ultrasound correlates to target for ultrasound-guided biopsy, or an MRI correlate to target for MRI-guided biopsy [28]. If no mammographic or ultrasound correlate is seen, CEM may result in diagnostic MRI examinations for these patients [27].

Like conventional mammography, areas along the chest wall, far medial breast, or in the axilla may be a cause for a false-negative study as they may not be well-imaged. This can be avoided by performing breast MRI for better assessment [27].

Radiation exposure is another disadvantage of CEM in comparison with FFDM because the average glandular dose of CEM is typically 1.2–1.5 times greater than that of FFDM [24]. Also, CEM has a risk for contrast reaction and the diagnosis of inflammatory breast lesions is challenging due the similarity of enhancement patterns between malignant and inflammatory lesions [29].

Our study was limited by the fact that cases deemed to be benign or negative on histopathology did not undergo follow-up period to determine the true negative disease status.

Conclusions

Contrast-enhanced mammography is the imaging modality of choice for better identification and accurate diagnosis of breast cancer with better sensitivity than FFDM with US.

CEM is a valuable tool in the setting of characterization of asymmetry and local staging especially in mammographic dense breast.

CEM has a limited role in diagnosing inflammatory breast lesions, and therefore, it is not recommended to use it in evaluating breast asymmetries with clinical signs of mastitis.

We recommend using contrast-enhanced mammography as a routine examination especially for women with dense breasts that may be able to detect lesions

that would otherwise go unnoticed due to breast asymmetry for early diagnosis of the disease and thus better outcome.

Abbreviations
ACR: American College of Radiology; BI-RADS: Breast Imaging-Reporting and Data System; CEM: Contrast-enhanced mammography; CC: Craniocaudal; DCIS: Ductal carcinoma in situ; FFDM: Full-field digital mammography; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; MLO: Mediolateral oblique; MRI: Magnetic resonance imaging; 2D: Two-dimensional; US: Ultrasound.

Acknowledgements
The authors would like to acknowledge all the participants for their cooperation and patience.

Authors' contributions
AN suggested the research idea, ensured the original figures and data in the work, minimized the obstacles to the team of work, RM correlated the study concept and design and had the major role in analysis, BM collected data in all stages of manuscript, performed data analysis. RL supervised the study with significant contribution to design the methodology, manuscript revision and preparation. MM correlated the clinical data of patient and matched it with the findings, drafted and revised the work. All authors read and approved the final manuscript for submission.

Funding
No funding was obtained for this study.

Availability of data and material
The authors confirm that all data supporting the finding of the study are available within the article and the raw data ad data supporting the findings were generated and available at the corresponding author on request.

Declarations

Ethics approval and consent to participate
Informed written consents were taken from the patients and healthy volunteers, the study was approved by ethical committee of Tanta university hospital, faculty of medicine.
Committee's reference number: 33680/2/20.

Consent for publication
All participants included in the research gave written consent to publish the data included in the study.

Competing interests
The authors declare that they have no competing of interests.

Author details
[1]Faculty of Medicine, Tanta University, El-Geish Street, Tanta, Gharbia Governorate, Egypt. [2]Faculty of Medicine, Cairo University, Cairo Governorate, Egypt.

Received: 21 October 2022 Accepted: 9 December 2022
Published online: 16 December 2022

References

1. Samardar P, de Paredes ES, Grimes MM et al (2002) Focal asymmetric densities seen at mammography: US and pathologic correlation. Radiographics 22(1):19–33
2. Berg WA, Campassi C, Langenberg P et al (2002) Breast Imaging Reporting and Data System: inter-and intraobserver variability in feature analysis and final assessment. Am J Roentgenol 174(6):1769–1777
3. D'Orsi CJ, Sickles EA, Mendelson EB, et al (2014) 2013 ACR BI-RADS Atlas: breast imaging reporting and data system. Published online 2014.
4. Youk JH, Kim EK, Ko KH, et al (2009) Asymmetric mammographic findings based on the fourth edition of BI-RADS: types, evaluation, and management. Radiographics 29(1):e33.
5. Leung JWT, Sickles EA (2007) Developing asymmetry identified on mammography: correlation with imaging outcome and pathologic findings. Am J Roentgenol 188(3):667–675
6. Emaus MJ, Bakker MF, Peeters PHM et al (2015) MR imaging as an additional screening modality for the detection of breast cancer in women aged 50–75 years with extremely dense breasts: the DENSE trial study design. Radiology 277(2):527–537
7. Autier P, Boniol M (2018) Mammography screening: a major issue in medicine. Eur J Cancer 90:34–62
8. Freer PE (2015) Mammographic breast density: impact on breast cancer risk and implications for screening. Radiographics 35(2):302–315
9. del Travieso-Aja M, Maldonado-Saluzzi D, Naranjo-Santana P et al (2019) Diagnostic performance of contrast-enhanced dual-energy spectral mammography (CESM): a retrospective study involving 644 breast lesions. Radiol Med (Torino) 124(10):1006–1017
10. del Mar T-A, Naranjo-Santana P, Fernández-Ruiz C et al (2018) Factors affecting the precision of lesion sizing with contrast-enhanced spectral mammography. Clin Radiol 73(3):296–303
11. Dromain C, Vietti-Violi N, Meuwly JY (2019) Angiomammography: a review of current evidences. Diagn Interv Imaging 100(10):593–605
12. Ali-Mucheru M, Pockaj B, Patel B et al (2016) Contrast-enhanced digital mammography in the surgical management of breast cancer. Ann Surg Oncol 23(5):649–655
13. Łukasiewicz S, Czeczelewski M, Forma A et al (2021) Breast cancer—epidemiology, risk factors, classification, prognostic markers, and current treatment strategies—an updated review. Cancers (Basel) 13(17):4287
14. Coughlin SS (2019) Epidemiology of breast cancer in women. Breast cancer metastasis and drug resistance. Published online 2019:9–29
15. Johnson B (2021) Asymmetries in mammography. Radiol Technol 92(3):281M-298M
16. Tennant SL (2021) CEM as a problem-solving tool: from contrast-enhanced mammography: state of the Art. (93–114). (Marc Lobbes Maxine S. Jochelson, ed.). Springer Nature 2021.
17. Lalji U, Lobbes M (2014) Contrast-enhanced dual-energy mammography: a promising new imaging tool in breast cancer detection. Women's Health 10(3):289–298
18. Tennant SL, James JJ, Cornford EJ et al (2016) Contrast-enhanced spectral mammography improves diagnostic accuracy in the symptomatic setting. Clin Radiol 71(11):1148–1155
19. Gordon PB (2022) Breast density and risk of interval cancers. Can Assoc Radiol J 73(1):19–20
20. Kamal RM, Moustafa AFI, Fakhry S et al (2019) Adding the merits of contrast to the ease of mammography; can we highlight what's behind breast asymmetries? Egypt J Radiol Nuclear Med 50(1):39
21. Harvey JA, Nicholson BT, Cohen MA (2008) Finding early invasive breast cancers: a practical approach. Radiology 248(1):61–76
22. Wessam R, Gomaa MMM, Fouad MA et al (2019) Added value of contrast-enhanced mammography in assessment of breast asymmetries. Br J Radiol 92(1098):20180245
23. Chesebro AL, Winkler NS, Birdwell RL et al (2016) Developing asymmetries at mammography: a multimodality approach to assessment and management. Radiographics 36(2):322–334
24. Fallenberg EM, Dromain C, Diekmann F et al (2014) Contrast-enhanced spectral mammography versus MRI: initial results in the detection of breast cancer and assessment of tumour size. Eur Radiol 24(1):256–264
25. Cheung YC, Lin YC, Wan YL et al (2014) Diagnostic performance of dual-energy contrast-enhanced subtracted mammography in dense breasts compared to mammography alone: interobserver blind-reading analysis. Eur Radiol 24(10):2394–2403
26. Dromain C, Thibault F, Diekmann F et al (2012) Dual-energy contrast-enhanced digital mammography: initial clinical results of a multireader, multicase study. Breast Cancer Res 14(3):1–18

27. Tardivel A, Balleyguier C, Dunant A et al (2016) Added value of contrast-enhanced spectral mammography in postscreening assessment. Breast J 22(5):520–528
28. Phillips J, Fein-Zachary VJ, Slanetz PJ (2019) Pearls and pitfalls of contrast-enhanced mammography. J Breast Imag 1(1):64–72
29. Lewis TC, Pizzitola VJ, Giurescu ME et al (2017) Contrast-enhanced digital mammography: a single-institution experience of the First 208 cases. Breast J 23(1):67–76

Publisher's Note