7 Use of Contrast-Enhanced Mammography in Breast Cancer Screening

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7.1 Introduction

Breast cancer is the leading cause of cancer death among women throughout the world. Breast cancer survival has improved, in part because of a wide variety of new and improved treatments. However, it remains clear that even with these superior treatments, outcomes are better in women with smaller, node-negative cancers and the detection of these smaller cancers is the result of breast cancer screening.

Screening mammography and physical examination remain the mainstay of breast cancer screening programs. Multiple randomized studies have demonstrated that screening mammography reduces breast cancer mortality by approximately 30% [1–4]. However, mammography has its limitations. The sensitivity of mammography overall is 70–85%, but this drops significantly in high-risk women with dense breasts in whom it is no higher than 50% [5, 6]. Specificity of mammography is approximately 89% [7]. Women are frequently called back for additional imaging after they have had their screening mammogram which leads to additional radiation, cost, and patient anxiety. Call backs may occur in up to 20% of women at baseline mammogram [8] and slightly less frequently on subsequent examinations. Biopsies are also frequently recommended after screening with a positive predictive value (PPV) of only approximately 28.6% [7]. Additionally, some believe there is a great deal of "overdiagnosis" by screening mammography.

These limitations are frequently cited as a reason to decrease or avoid screening altogether [9, 10]. With these limitations, improved imaging techniques are needed, both to detect a greater number of cancers when screening and decrease the number of women called back from screening and the number of benign biopsies. As was so aptly stated by Oeffinger et al. at the publication of the most recent American Cancer Society Guidelines, "Given the weight of the evidence that mammography

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screening is associated with a significant reduction in the risk of dying from breast cancer after age 40 year, a more productive discussion would be focused on how to improve the performance of mammographic screening" [11].

To elaborate on Dr. Oeffinger's apt statement, this chapter will discuss various options for improved screening with a focus on contrast-enhanced mammography (CEM). The ideal new or supplemental screening examination needs to improve cancer detection, reduce recall rates, improve the PPV of recommended biopsies, be inexpensive, be widely available, and not add significant radiation.

7.2 Improved Screening: Purely Anatomic Techniques

7.2.1 Digital Breast Tomosynthesis

Digital breast tomosynthesis (DBT), while used occasionally as a supplemental imaging tool, is increasingly being used as a primary screening examination. It uses multiple low-dose projections of the compressed breast obtained with a moveable X-ray source—essentially like a computed tomography scan of the breast. The image slices are reconstructed in a plane parallel to the detector. Using DBT allows overlying breast tissue to be peeled away, enabling easier detection of primarily soft tissue lesions. This leads to an improvement in detection rates over full-field digital mammography (FFDM), sometimes also detecting additional lesions over those seen on FFDM. While DBT is sometimes incorrectly referred to as 3D imaging, it does lead to better lesion localization. Margin analysis is also improved with DBT. Using DBT through an area of a suspected mass may also clarify that the apparent mass is merely overlapping breast tissue. The latter two improvements over FFDM improve specificity and reduce the number of patients called back. PPV is also improved as a result.

Every study comparing the use of DBT to routine mammography has demonstrated slight improvement in cancer detection in addition to a reduction in the rate of call backs. DBT allows detection of approximately 1.5 additional cancers per 1000 women over FFDM: Skaane et al. performed a prospective trial involving nearly 13,000 women and demonstrated that adding DBT to FFDM improved cancer detection rates from 6.1/1000 to 8.0/1000 examinations with a 15% decrease in false-positive findings. The additional cancers detected were invasive cancers [12]. In a multicenter retrospective study that included both academic and private practices, Friedenwald et al. also showed a similar improvement in detection rate from 4.2/1000 to 5.4/1000 examinations and signwificant decrease in recall rates [13]. Improvement in cancer detection with DBT has been demonstrated with all breast densities except in the 10% of women with extremely dense breasts. Kim et al. found that DBT compared favorably to screening ultrasound except in women with extremely dense breasts [14].

While the slight increase in detection rate is certainly an advantage, the real advantage of DBT is in the reduction of call backs. Rafferty et al. demonstrated that

using DBT + FFDM significantly reduced call back rates in patients with nonmalignant findings without a significant change in those women subsequently found to have cancer [15]. McDonald et al. evaluated 25,000 women having baseline mammography and showed a significant reduction in call back rates from 20.5% to 16.0% [8].

In the United States, DBT is increasingly replacing FFDM as a primary screening modality because of the combination of improved detection and decreased call back rates. In countries where call backs are less frequent, DBT may not be used as much. Its limitations include high costs, increased need for data storage, and significant increase in reading time. Since 2D images remain important for an overview of the breast, doing DBT and FFDM doubles the radiation dose to the breast. Vendors have developed synthetic views to replace the FFDM which will lower the radiation dose of DBT back to that of a FFDM alone, but synthetic view software carries a high additional cost. Additionally, DBT does not improve breast cancer detection in women with extremely dense breasts, a population who are at particularly higher risk of developing cancer [16] and in whom cancers are masked and therefore missed on mammography.

7.2.2 Screening Whole-Breast Ultrasound

The most commonly used method of supplemental breast imaging, particularly in women with dense breasts, is screening whole-breast ultrasound. It is relatively inexpensive, does not expose the patient to additional radiation, and is widely available. Multiple investigators have demonstrated additional detection rates of approximately 3.5 cancers/1000 women [17–19]. The cancers detected are more frequently early-stage invasive cancers and therefore less likely to be considered "overdiagnosis." While there is no arguing that this additional detection is a substantial improvement, ultrasound also has its limitations. The ACRIN 6666 trial was a prospective trial to evaluate the utility of ultrasound screening in a population of 2637 women with normal mammograms, dense breasts, and at least one other risk factor. In the process of detecting the additional cancers, 8% of the women received a biopsy recommendation, and only 7.4% of those biopsies were malignant. An additional 9% of women were recommended to return for 6-month follow-up examinations. In the J-START study involving 72,998 Japanese women from 40 to 49 years old, ultrasound added to mammography improved the sensitivity of mammography alone but decreased its specificity significantly [20]. It should be noted that in patients who are screened for several years, there are fewer unnecessary biopsies with an improvement of PPV from approximately 7% to 20% [21].

This lack of specificity of screening whole-breast ultrasound defeats one of the main purposes of supplemental screening, i.e., to reduce call backs, and adds to the cost of ultrasound screening. With the increasing use of screening ultrasound in women with dense breasts, two studies determined that due to the large number of additional biopsies, the cost of detecting one cancer was $50,000–60,000.00 [19, 22].

Interim results of a prospective trial (ASTOUND trial) comparing DBT with screening ultrasound were performed in 3231 women with dense breasts and negative FFDM. Twenty-four additional cancers were detected; 13/24 (54%) were detected by DBT corresponding to 4/1000 screens. Ultrasound detected 23/24 (96%) or 7.1/1000 screens [23]. Kim et al. compared the performance of these two examinations in a population of 698 women with dense breasts who had 140 cancers. They demonstrated comparable performance of the two except in women with extremely dense breasts in whom DBT was inferior [14].

However, additional results from the ACRIN trial follow-up demonstrate further limitations of supplemental imaging with whole-breast screening ultrasound. At the end of the trial, 612 women who had had three rounds of negative screening mammography and ultrasound were offered a screening MRI. There were 16 cancers detected, 9 of which (56%) were seen only on MRI. MRI added 14.7 additional cancers per 1000 women screened; 75% of these cancers were invasive [24]. Kuhl et al. demonstrated similar findings with the EVA trial [25]. These latter studies suggest that performing only purely anatomic studies such as FFDM, DBT, and ultrasound remains limited for cancer detection and in fact negative examinations may give women a false sense of security when they receive negative results.

7.3 Imaging of Neovascularity

7.3.1 Contrast-Enhanced Breast MRI

Breast MRI has long been acknowledged to be the most sensitive screening examination for the detection of breast cancer. By using contrast to enhance tumor neovascularity, the sensitivity of MRI approaches 97%, sometimes detecting early cancers before a discrete mass can be detected. Specificity was initially poor but over the years has improved to be comparable to that of mammography. Because of the high sensitivity of MRI, in 2007 the American Cancer Society provided guidelines for the annual use of breast MRI for women who are at greater than 20% lifetime risk for development of breast cancer. As a result, not only has it been shown that cancers detected by MRI in the patient population are smaller and less likely to be node positive [26], but there is also a survival benefit in mutation carriers who are screened with annual MRI [27, 28].

In a review of 18,064 screening MRIs and mammography in 7519 women at high risk for developing breast cancer, Sung et al. demonstrated that cancers detected by MRI are more likely to be invasive cancers, whereas those detected by mammography are more likely to be ductal carcinomas in situ. Additionally, they showed that interval cancers which account for more than 20% of all breast cancers are reduced to 5% with screening MRI [29].

With these superb results with screening MRI, it would be ideal to offer MRI to a larger population of women or even all women. There is a large population of women at intermediate risk for developing breast cancer (15–20% lifetime risk) including in the United States alone over three million breast cancer survivors and approximately 15,000 women with high-risk lesions and 25 million women with

dense breasts. However, the cost of this would be prohibitive, and it is not realistic to think there is enough availability of MRI to accommodate these women.

Abridged (or abbreviated) MRI is a technique that has been proposed to lower costs and increase available time on MRI scanners by reducing the number of sequences performed. This technique was first performed by Kuhl et al. who prospectively evaluated results of screening MRI with only three sequences which would take 3 min to perform compared with their routine 17 min for 606 screening MRIs in 443 women at intermediate or slightly increased risk for developing breast cancer. Reading the full number of sequences required 28 s per examination and yielded a sensitivity of 100% and specificity of 94.3%. Reading a single maximum intensity projection image required 2.8 s with a sensitivity of 90.9% with a negative predictive value of 99.8% [30]. Mango et al. retrospectively reviewed three sequences from a complete MRI in 100 women with known breast cancer to include the first post-contrast, subtraction, and maximum intensity projection images. Over 95% of the cancers were visualized on a single (first post-contrast) image when read without prior examinations or history. Once prior examinations and history were available, the sensitivity of these abridged examinations was 100% [31]. Harvey et al. reviewed both abbreviated and full MRI protocols in 568 women and demonstrated no difference in cancer detection, while the abbreviated protocol reduced scan times by 18.8 min per examination and interpretation times by 4.9 min per interpretation [32]. Van Zelst et al. also demonstrated non-inferiority of MRI scans performed in 2 min compared with full diagnostic MRI scans [33].

The premise of abbreviated MRI has been so well accepted that there is currently an ECOG-ACRIN trial comparing it with DBT where the primary goal is to compare invasive cancer detection rates between the two techniques and secondary goals are to compare tumor biology, PPV of biopsies, call back rates and short-term follow-up rates, and interval cancer rates and to undertake a comparative cost analysis.

However, despite the promise of abbreviated MRI, it is still not likely that we can accommodate such large populations of women for breast MRI. Additionally, women who are claustrophobic and have certain metallic implants or allergy to gadolinium are unable to undergo MRI.

The success of MRI for the detection of early breast cancers is large because of its ability to image the neovascularity associated with most invasive breast cancers. Contrast-enhanced mammography (CEM) is a relatively new technique which was developed to utilize enhancement of neovascularity in a fashion like MRI for the earlier detection of breast cancer using an upgraded platform of digital mammography. The remainder of this chapter will focus on CEM and its potential for use in the screening setting.

7.3.2 Contrast-Enhanced Mammography

As has been described previously, CEM is performed after bolus injection of iodinated contrast material at a dose of 1.5 ml/kg. Imaging begins approximately 2.5–3 min after the injection is complete. Standard craniocaudal and mediolateral oblique views

are obtained within 5 min, and additional views can also be obtained since the contrast remains present for up to 10 min. Two nearly simultaneous images are performed with each exposure: a low-energy image below the *k*-edge of iodine (33 keV) and a high-energy image above the *k*-edge of iodine. Post-processing subtracts out non-enhancing tissue, yielding an image of any enhancing lesions. Since there is only one image done per view, kinetic information is not obtained. The low-energy images are the equivalent of a routine mammogram [34–36]. The radiation dose is of course increased with CEM, with the range of increase quoted between 20% and 80% depending on the breast thickness and vendors [37, 38]. Nevertheless, even with the additional radiation, the dose falls within the Mammography Quality Standards Act guidelines.

The report of a CEM combines the results of the low-energy images with the post-contrast images to provide a single Breast Imaging Reporting and Data System (BI-RADS) classification. Early experience utilizing CEM has been in the diagnostic setting where it has consistently been shown to be superior to digital mammography. In patients called back from abnormal screening mammography or in patients with clinical symptoms, Dromain et al. evaluated 120 women with unilateral CEM and demonstrated significantly improved sensitivity: 93% for CEM compared with 78% for FFDM and a trend toward improved sensitivity when compared with FFDM plus ultrasound [39]. In a similar population of 113 women called back from screening, Lobbes et al. showed sensitivity of 100% vs. 96.9% (all patients had mammographic abnormalities to begin with) and significantly improved specificity and PPV with CEM compared with FFDM [40].

In 52 women with known cancers, Jochelson et al. demonstrated significant superiority of CEM compared with FFDM in the detection of the index lesion (96% vs. 81%) and similar detection compared to MRI [41]. Fallenberg et al. did a similar comparison of these three techniques in 80 women with breast cancer and demonstrated significantly better sensitivity of CEM compared with mammography. They also found that of the 14 patients whose cancers were not detected on FFDM, ten women had extremely dense breasts and three had heterogeneously dense breasts [42].

CEM has been shown to be superior to FFDM in women with dense breasts (Fig. 7.1) in multiple other studies. In a multireader trial using temporal technique to perform contrast mammography in 70 women with dense breasts and at least 1 suspicious lesion on mammography, Diekmann et al. showed sensitivity improving from 35% to 59% [43]. In Taiwan, Cheung et al. prospectively evaluated CEM compared with FFDM in 89 women with 100 lesions and dense breasts. The low-energy images were read blinded to the post-contrast images. Sensitivity improved from 71.5% to 92.7%, and specificity improved from 51.8% to 67.9% with the use of contrast [44].

Cheung et al. also showed that the one area in which CEM was not as reliable was in women presenting with suspicious microcalcifications. They reported results in 59 women with suspicious calcifications in whom the negative predictive value of contrast mammography was only 93.9% which is comparable to MRI in the same setting [45] (Fig. 7.2).

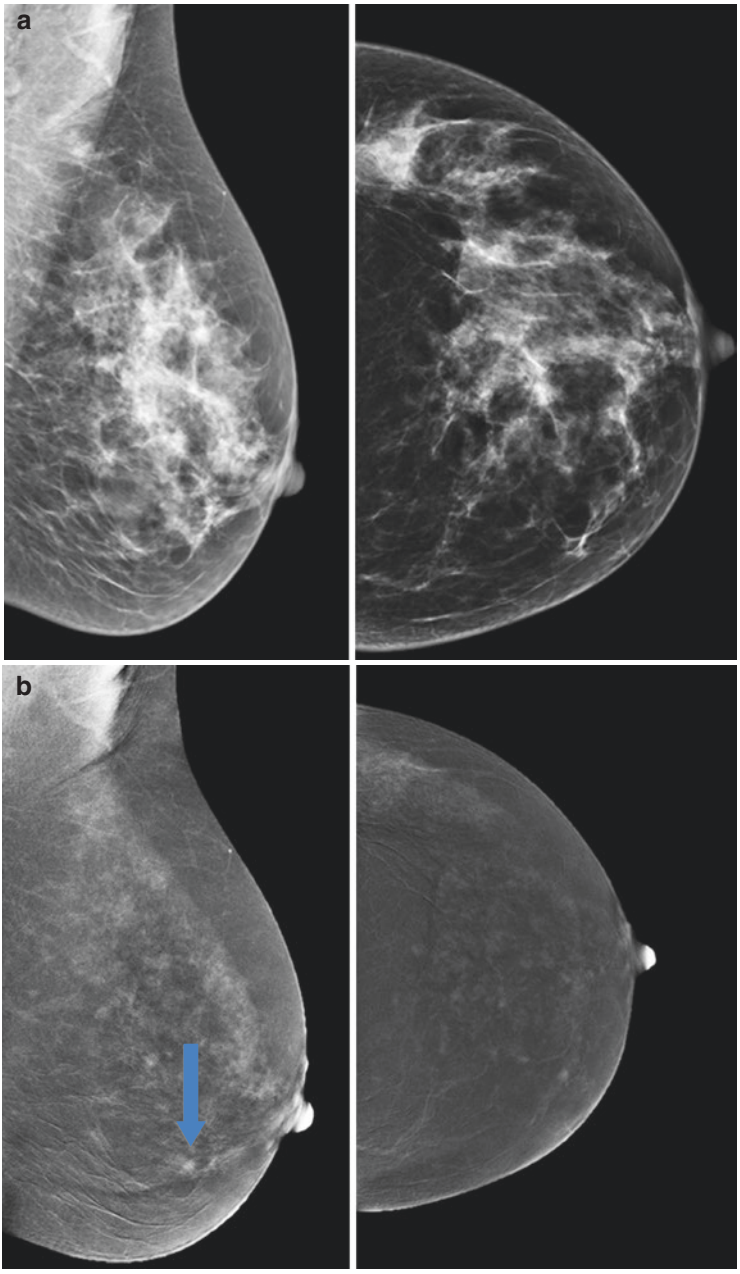

Fig. 7.1 A 62-year-old woman with a family history of breast cancer and dense breasts. (**a**) Low-energy images of the left breast demonstrate no suspicious abnormalities. (**b**) Post-contrast images demonstrate a 5 mm irregular mass in the lower inner quadrant of the left breast. (**c**) Targeted ultrasound demonstrates 5 mm mass left breast corresponding to CEM finding. Biopsy demonstrated infiltrating ductal carcinoma

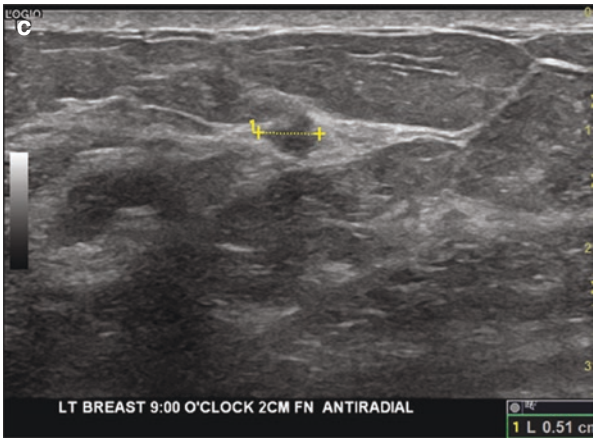

Fig. 7.1 (continued)

Considering the success of CEM in the diagnostic setting, it appears that it could have potential to improve cancer detection in the screening setting, potentially filling the need for better supplemental imaging for those patients at increased risk for breast cancer who do not meet the American Cancer Society criteria for annual breast MRI. This concept has been met with some resistance primarily due to fear of contrast reactions in healthy women. Therefore, only a small number of papers have been published on this topic.

Jochelson et al. performed the first prospective trial comparing CEM with FFDM and screening MRI in women at increased risk for developing breast cancer. Three hundred and seven heavily prescreened patients with increased breast cancer risk underwent CEM and MRI within 30 days of each other. No cancers were detected by FFDM (the low-energy images). MRI and CEM each detected two invasive lobular cancers. One patient had a sub-centimeter area of enhancement on MRI not seen on CEM which was upgraded to DCIS when she returned 9 months later with a new contralateral invasive cancer as well. At 1-year follow-up, there were no interval cancers but two screen-detected cancers. Specificity of CEM was equal to that of MRI. However, the patients had all had multiple prior MRIs, while only one patient had a prior CEM. It is well known that having prior examinations for comparison improves specificity. Therefore, it is expected that CEM will ultimately be more specific than MRI [46] as was demonstrated in earlier diagnostic trials [40, 41] (Fig. 7.3).

After this study, CEM has been used routinely in women at increased risk due to either family history with lifetime risk under 20% or personal history especially in women with dense breasts (Fig. 7.4); women with a history of high-risk lesions diagnosed at biopsy (Fig. 7.5); women receiving high-risk screening with yearly MRI as the alternating mammographic study; and women who cannot undergo MRI due to severe claustrophobia, gadolinium allergy, or metallic implants. There are

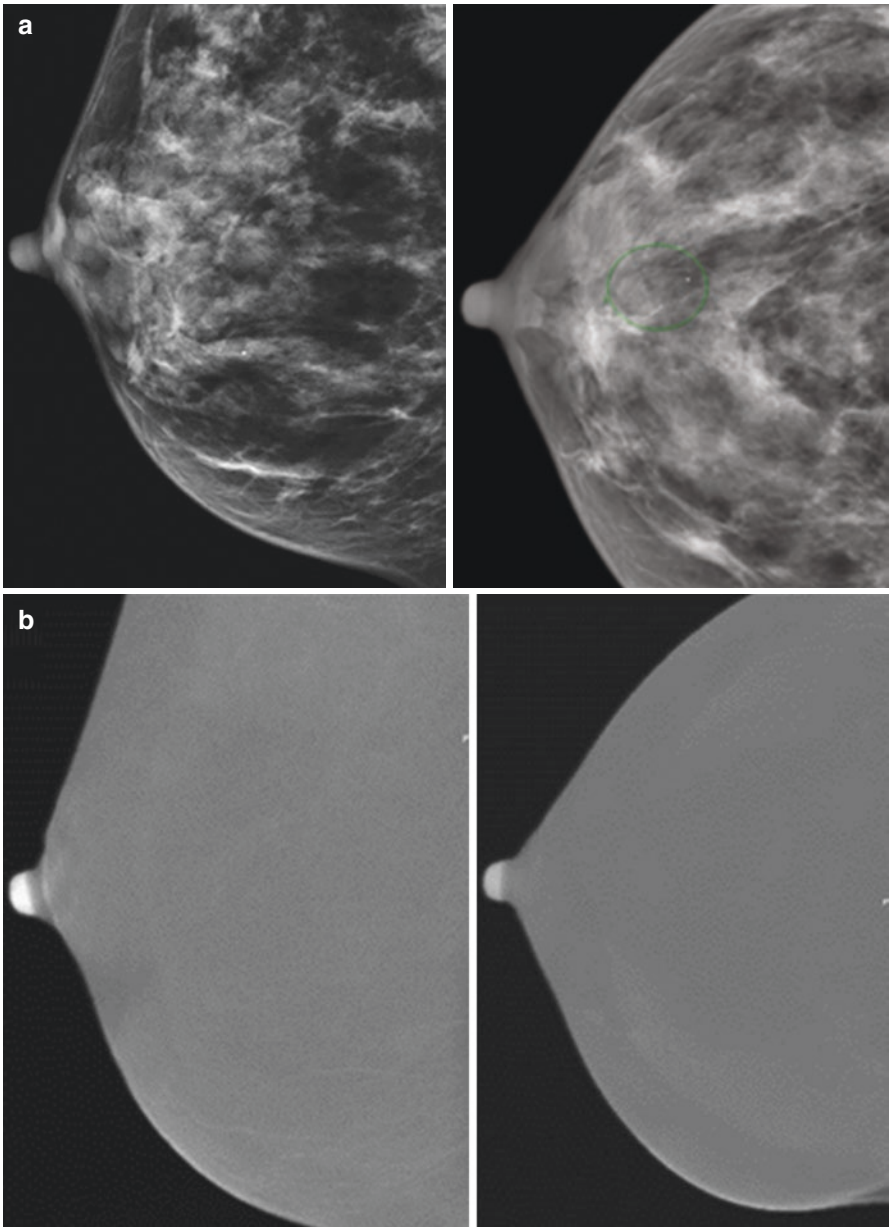

Fig. 7.2 False-negative CEM. A 51-year-old woman with a family history of breast cancer and dense breasts for screening. (**a**) Low-energy images demonstrate a new 0.9 cm group of pleomorphic calcifications, suspicious for malignancy. (**b**) Contrast images demonstrate minimal background parenchymal enhancement. No abnormal enhancement was seen in the area of microcalcifications or elsewhere. Calcifications were biopsied and yielded intermediate-grade ductal carcinoma in situ with necrosis

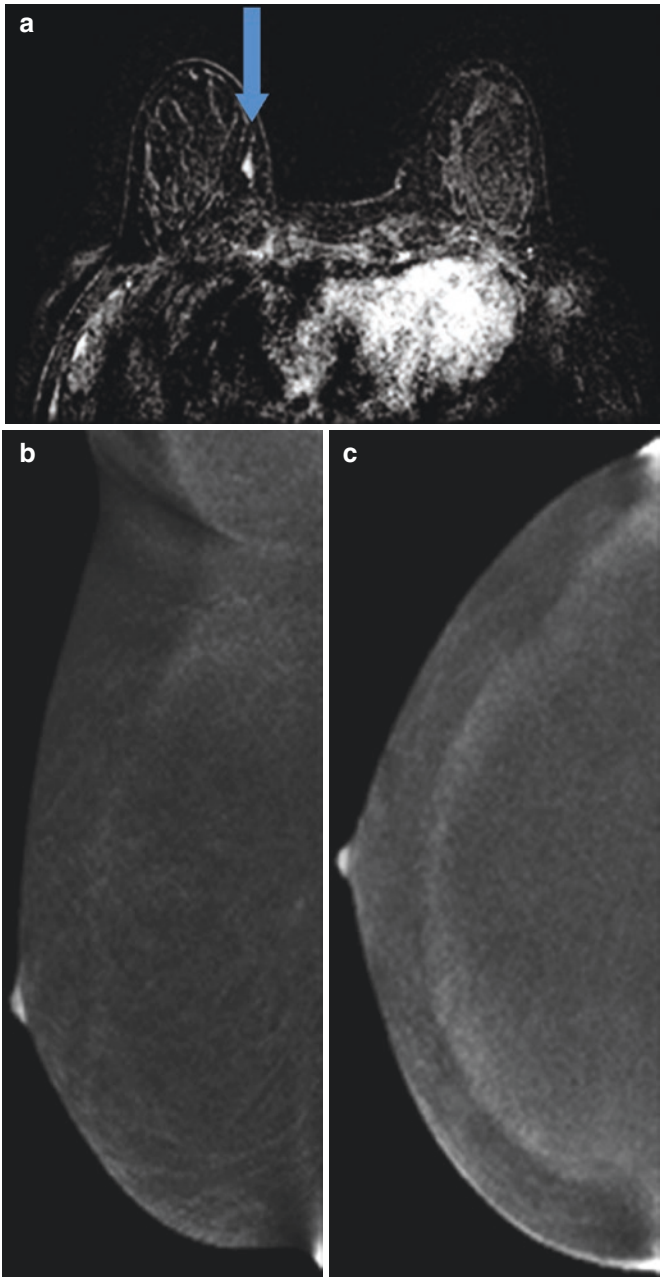

Fig. 7.3 False-positive MRI/true negative CEM. A 28-year-old with a strong family history of breast cancer and dense breasts. (**a**) Axial subtraction images from MRI demonstrate 1.2 cm area of linear non-mass enhancement in the lower inner quadrant. (**b**, **c**) Contrast-enhanced mammography shows mild background parenchymal enhancement with no suspicious enhancement. MRI-guided biopsy yielded stromal fibrosis and fibroadenomatoid changes with no evidence for malignancy

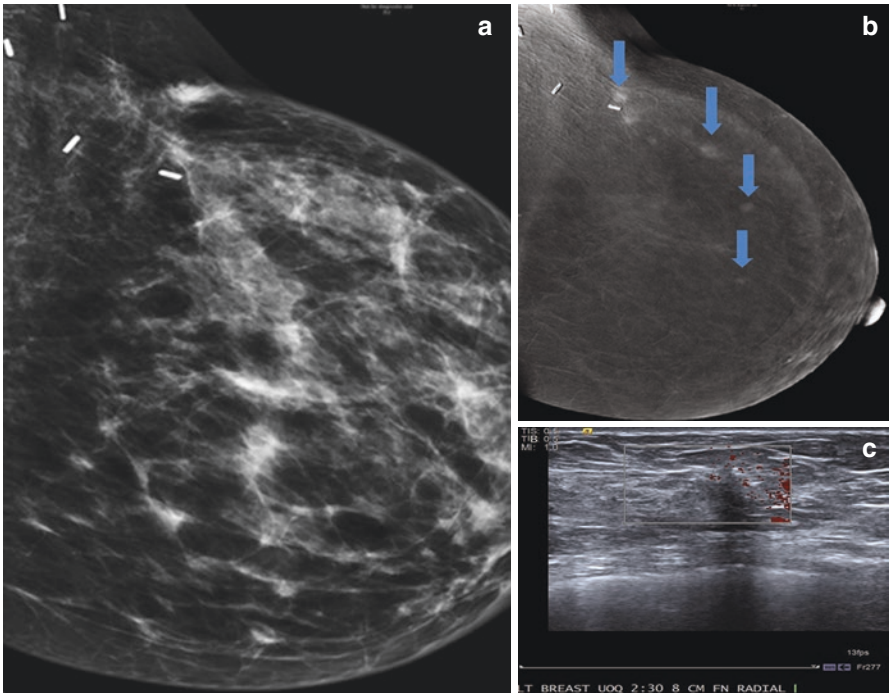

Fig. 7.4 A 45-year-old woman 1 year after lumpectomy with clear margins, radiation therapy, and 1 year of tamoxifen for routine follow-up: (**a**) heterogeneously dense breast showing post-lumpectomy change but no other abnormality. (**b**) Multiple enhancing masses at the lumpectomy site and extending toward the nipple. (**c**) Targeted ultrasound of a representative mass demonstrating an irregular hypoechoic lesion. Biopsy demonstrated infiltrating ductal carcinoma

also a growing number of patients who are concerned about gadolinium deposits in the brain who are choosing not to undergo MRI and are therefore having CEM.

Sung et al. have prospectively compared CEM with whole-breast screening ultrasound. Preliminary results are available in 250 intermediate-risk patients. Five cancers were detected: one by FFDM, two on ultrasound, and five on CEM [47]. If these early results hold, CEM may be more sensitive than whole-breast ultrasound in the screening setting (Fig. 7.6). Klang et al. have reported their experience comparing CEM to ultrasound in a retrospective study of 953 women who underwent 87 biopsies, 43% of which were malignant. CEM sensitivity was 97% compared to 92% for ultrasound. CEM specificity was 40% compared to 8% for ultrasound [48].

Sumkin et al. compared MRI with CEM and molecular breast imaging in 79 women with 80 breast cancers. They demonstrated that while MRI was slightly more sensitive than CEM, MRI had significantly more false positives [49]. It should be noted that at this time, MBI does not meet the American College of Radiology appropriateness criteria for breast cancer screening due to its high total body radiation dose.

In a retrospective review of screening CEM compared with FFDM, Sung et al reported the results of 904 screening contrast mammograms, 77% in women with dense breasts and over 90% had other risk factors including family history or personal history of breast cancer. Fourteen cancers were detected corresponding to a

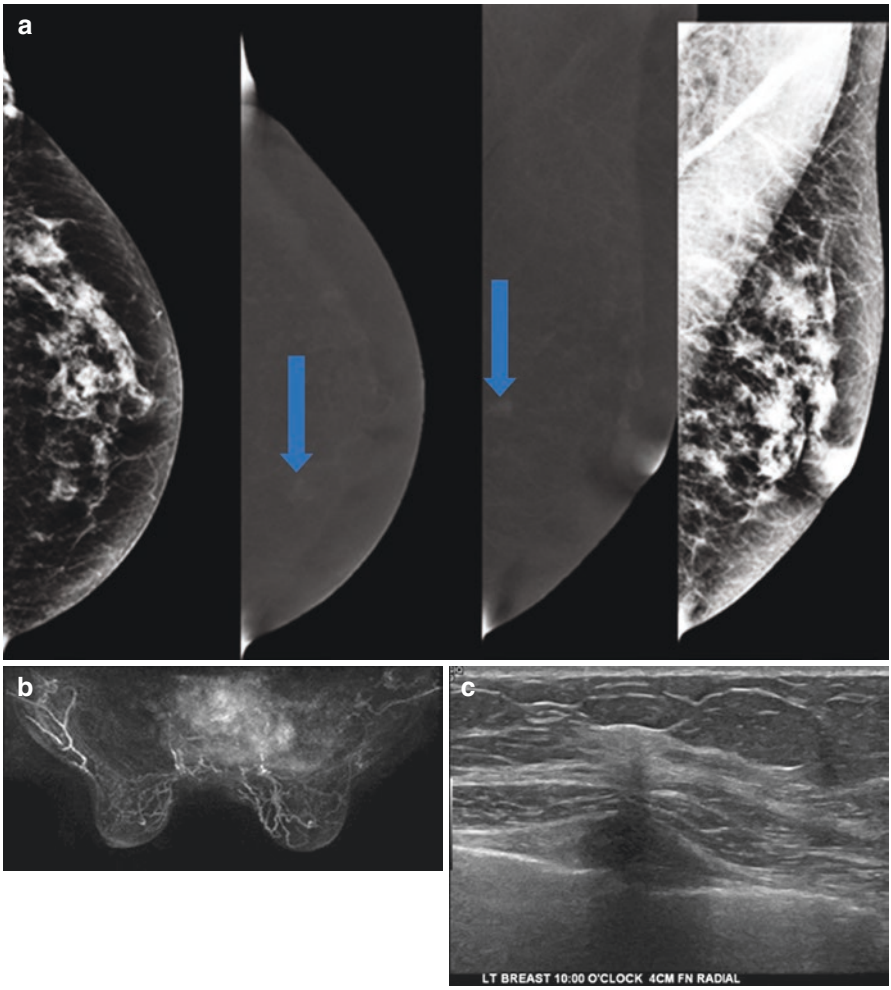

Fig. 7.5 A 61-year-old woman with a history of lobular carcinoma in situ for screening. False-negative MRI (**a**) Left low-energy and contrast images in the mediolateral oblique and craniocaudal projections show heterogeneously dense breast tissue and no abnormalities on the low-energy images. Post-contrast images demonstrate an area of non-mass enhancement in the upper inner breast posterior third. (**b**) Axial subtraction MIP MRI images demonstrated no abnormality. (**c**) Targeted ultrasound was performed and detected a 4 mm hypoechoic mass with posterior shadowing. Ultrasound-guided biopsy yielded invasive lobular carcinoma. (**d**) Post-biopsy mammogram demonstrates a ribbon-shaped marker corresponding to the area of non-mass enhancement

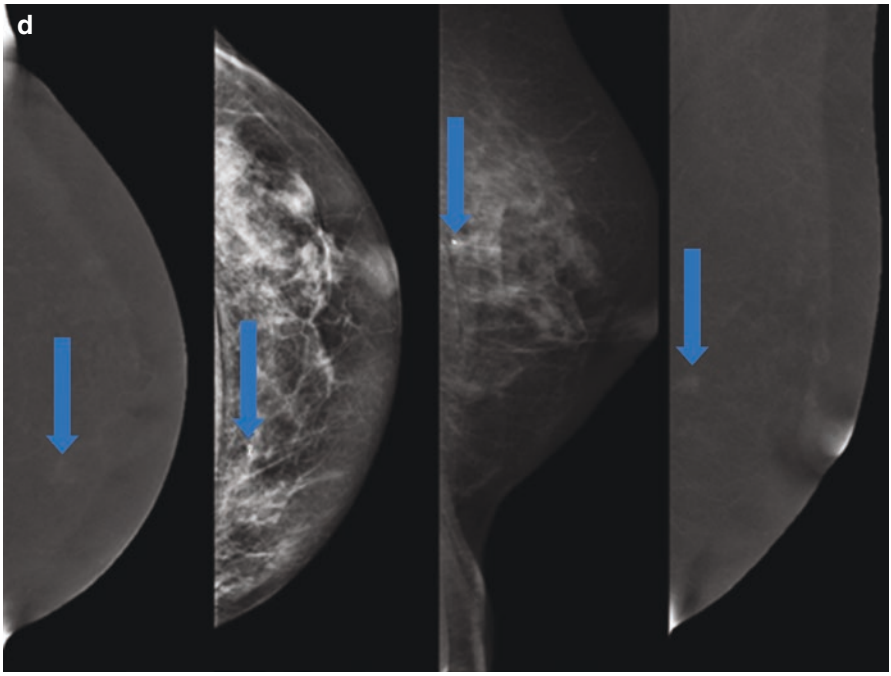

Fig. 7.5 (continued)

cancer detection rate of 15/1000 examinations. Six of the 14 (43%) cancers were detected due to contrast enhancement alone (in review).

Chou et al. performed a study comparing vascular with nonvascular imaging in 185 women with BI-RADS 4 or 5 lesions. In this population there were 81 cancers and 144 benign lesions. Not surprisingly, MRI, contrast mammography, and contrast tomosynthesis were more sensitive than FFDM or non-contrast DBT. The authors found no significant difference between MRI, CEM, and contrast tomosynthesis. Specifically, contrast tomosynthesis was no better than CEM without DBT [50].

CEM is well tolerated by patients. Hobbs et al. interviewed 49 women regarding their preference of CEM compared with MRI. These women significantly preferred CEM because it was faster and more comfortable and there was less noise ($p < 0.001$) [51]. In a prospective screening trial, Phillips et al. reported that 79% of women preferred contrast mammography to MRI if the examinations had equal sensitivity [52].

There are several limitations to the use of CEM. Probably the most significant limitation to adoption of CEM for screening is fear of contrast reaction. As with CT scanning, a small percentage of patients may have contrast reactions, generally mild, but there is the potential for a life-threatening reaction. In the screening study by Jochelson et al., 1.3% of patients had predominantly mild reactions after contrast administration. One woman who had had a reaction to gadolinium the day before had a moderate reaction but did well [46]. Houben et al. reported five minor reactions when performing 839 CEM examinations (0.6%) for patients recalled from

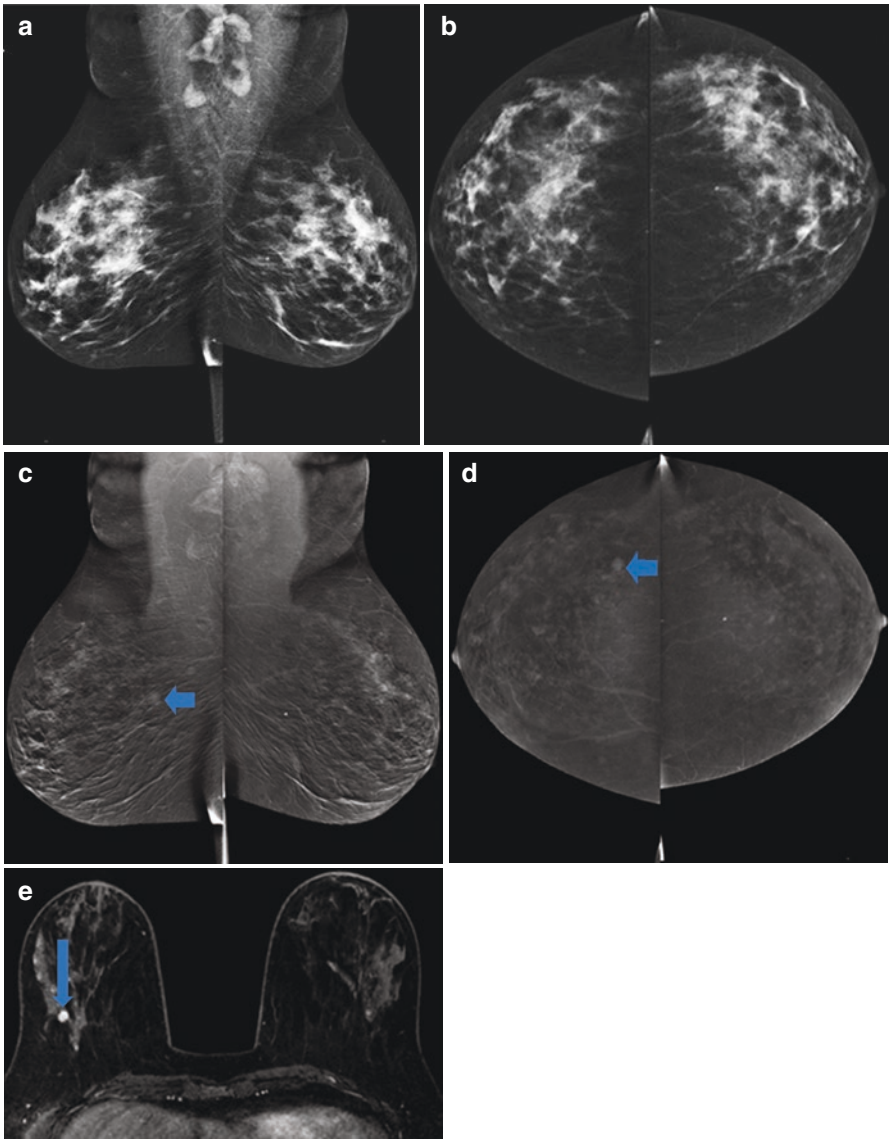

Fig. 7.6 A 55-year-old woman undergoing screening. History of lobular carcinoma in situ. False-negative ultrasound. (**a**, **b**). Bilateral mediolateral oblique and craniocaudal views demonstrate heterogeneously dense breast tissue with no abnormalities. (**c**, **d**). Subtraction images show mild background parenchymal enhancement and a small enhancing mass (arrows) in the upper outer quadrant of the right breast posteriorly. This could not be seen on ultrasound. (**e**) Axial post-contrast MRI demonstrates 1.5 cm enhancing mass (arrow) corresponding to CEM finding. MRI-guided biopsy yielded invasive ductal carcinoma

screening [53]. It is critical to carefully screen patients for any contrast allergy history. It is our practice to exclude any woman with any history of reaction to iodine from screening with CEM. Even though type A reactions officially do not require premedication or avoidance of contrast administration, it is our belief that due to the idiosyncratic nature of contrast reactions, it is not worth taking a chance when there are alternative methods of screening.

The potential for renal toxicity is another minor concern when doing CEM. Iodine is rarely toxic in the setting of normal renal function. Nevertheless, in older women or women with diabetes, multiple myeloma, or other risks for renal injury, renal function must be assessed before administering iodinated contrast. Again, if there are any abnormalities, contrast should not be used.

Radiation dose is increased when performing CEM. While use of as little radiation as possible is the goal, the limited additional dose is less than that of FFDM plus DBT and falls well within the Mammography Quality Standards Act guidelines.

7.4 Conclusions

Preliminary data for the use of CEM in the screening setting are promising. From both studies of its use in the diagnostic setting and early screening studies, it is quite clear that CEM is more sensitive and specific than mammography alone, probably more sensitive than mammography and ultrasound, and more specific than mammography plus ultrasound. CEM approaches the sensitivity of breast MRI and is likely more specific. However, the total number of patients studied in the screening setting thus far is small and performed as single-institution studies. What is needed now are prospective multicenter trials which will compare sensitivity, specificity, PPV, negative predictive value, and accuracy of CEM with that of standard screening studies such as FFDM, DBT, whole-breast screening ultrasound, combinations of FFDM or DBT with screening ultrasound, and breast MRI (complete or abbreviated). Additionally, since mammography is currently the only examination which has been demonstrated to reduce breast cancer mortality, as with all potential screening studies, it is critical to evaluate not only improvement in sensitivity but also if that improvement in sensitivity translates into decreased number of interval cancers and increases mortality reduction over that of mammography.

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