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Performance of Dual-Energy Contrast-enhanced Digital Mammography for Screening Women at Increased Risk of Breast Cancer

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Background: Contrast agent–enhanced digital mammography (CEDM) has been shown to be more sensitive and specific than two-dimensional full-field digital mammography in the diagnostic setting. Few studies have reported on its performance in the screening setting.

Purpose: To evaluate the performance of CEDM for breast cancer screening.

Materials and Methods: This retrospective study included women who underwent dual-energy CEDM for breast cancer screening from December 2012 through April 2016. Medical records were reviewed for age, risk factors, short-interval follow-up and biopsies recommended, and cancers detected. Sensitivity, specificity, positive predictive value of abnormal findings at screening (PPV_1), positive predictive value of biopsy performed (PPV_3), and negative predictive value were determined.

Results: In the study period 904 baseline CEDMs were performed. Mean age was 51.8 years ± 9.4 (standard deviation). Of 904 patients, 700 (77.4%) had dense breasts, 247 (27.3%) had a family history of breast cancer in a first-degree relative age 50 years or younger, and 363 (40.2%) a personal history of breast cancer. The final Breast Imaging Reporting and Data System score was 1 or 2 in 832 of 904 (92.0%) patients, score of 3 in 25 of 904 (2.8%) patients, and score of 4 or 5 in 47 of 904 (5.2%) patients. By using CEDM, 15 cancers were diagnosed in 14 of 904 women (cancer detection rate, 15.5 of 1000). PPV_3 was 29.4% (15 of 51). At least 1-year follow up was available in 858 women. There were two interval cancers. Sensitivity was 50.0% (eight of 16; 95% confidence interval [CI]: 24.7%, 75.3%) on the low-energy images compared with 87.5% (14 of 16; 95% CI: 61.7%, 98.4%) for the entire study (low-energy and iodine images; $P = .03$). Specificity was 93.7% (789 of 842; 95% CI: 91.8%, 95.2%); PPV_1 was 20.9% (14 of 67; 95% CI: 11.9%, 32.6%), and negative predictive value was 99.7% (789 of 791; 95% CI: 99.09%, 99.97%).

Conclusion: Contrast-enhanced digital mammography is a promising technique for screening women with higher-than-average risk for breast cancer.

Mammography is the primary imaging modality used for breast cancer screening and is the only imaging test shown to reduce mortality from breast cancer (1–3). Although effective, one major limitation of mammography is its limited sensitivity, especially in women with dense breasts. The sensitivity of mammography in young women with dense breasts is reported to be as low as 38%–50% (4,5).

Breast MRI is known to be the most sensitive imaging modality to detect breast cancer. However, breast MRI is restricted to screening women at high risk and, more recently, women with a personal history of breast cancer and dense breasts or who are diagnosed before age 50 years primarily because of its high cost and limited availability (6–14). Contrast agent–enhanced digital mammography (DM)(CEDM) is a contrast agent–based imaging test performed by using a modified DM unit. Studies (15–18) have reported that CEDM had improved sensitivity and specificity compared with conventional mammography in the diagnostic setting. To our knowledge, only two studies have evaluated the use of screening CEDM. The first study (19) was a small study of 307 women that compared screening CEDM with breast MRI and found that both CEDM and MRI depicted cancers not seen at conventional mammography. A more recent study (20) evaluated the performance of screening CEDM in 611 women at intermediate risk. In that study, CEDM was more sensitive than standard DM, with the addition of contrast enhancement resulting in an incremental cancer detection rate of 13.1 of 1000. The overall cancer detection rate in that study was high, at 31 of 1000 (19 cancers in 611 women).

CEDM has been offered as a screening test at our Comprehensive Cancer Center since December 2012. Referring physicians may order CEDM as an alternative screening examination to conventional mammography. CEDM is most commonly performed to screen women at intermediate risk such as women with a

Abbreviations

BI-RADS = Breast Imaging Reporting and Data System, CEDM = contrast-enhanced DM, CI = confidence interval, DM = digital mammography, PPV = positive predictive value, PPV_1 = PPV of abnormal findings at screening, PPV_2 = PPV of biopsies recommended, PPV_3 = PPV of biopsy performed

Summary

For screening women at increased risk for breast cancer, the sensitivity of contrast-enhanced digital mammography was 87.5%, compared with 50.0% for digital mammography ($P = .03$), with a specificity of 93.7%.

Key Points

- In a screening setting for breast cancer, contrast agent–enhanced digital mammography (CEDM) had a cancer detection rate of 15.5 of 1000.
- CEDM had greater sensitivity than did two-dimensional full-field digital mammography (87.5% vs 50.0%, respectively; $P = .03$).
- For CEDM, the positive predictive value of recommended biopsy and positive predictive value of performed biopsy were both 29.4%.

personal history of breast cancer or a history of a high-risk lesion. Some women at high risk (≥20% lifetime risk) are also screened at CEDM if their annual mammography and breast MRI are staggered at 6-month intervals, which has been suggested to be more effective than stacked screening (ie, both examinations performed on the same day) (21). In these instances, CEDM is performed in place of conventional DM so that a contrast-enhanced screening test is performed every 6 months because of the patient's high risk for breast cancer. The purpose of our study was to evaluate the performance of CEDM in the screening setting compared with standard noncontrast-enhanced two-dimensional full-field DM.

Materials and Methods

This retrospective Health Insurance Portability and Accountability Act–compliant review was approved by our institutional review board. The need for informed consent was waived. This research was funded in part through the National Institutes of Health/National Cancer Institute Cancer Center support grant (grant number P30 CA008748).

Study Patients

Retrospective review of the radiology department database identified 1069 consecutive screening CEDM examinations from December 2012 through April 2016. Only baseline CEDM examinations were included, leaving a study population of 904 screening CEDM examinations (Fig 1). At our institution, screening CEDM must be specifically ordered by the referring physician or performed as part of a research study. The inclusion criteria included all women who were referred for a CEDM. The exclusion criteria were women with a history of allergy to iodinated contrast agents. Informed consent for iodine injection is not required when CEDM is performed as part of clinical care. CEDM examinations were interpreted by one of 23 breast imaging radiologists as part of routine clinical care.

Of the 904 women included in our current study, 307 women were included in a previous study (19) that compared screening contrast-enhanced mammography and breast MRI that found three cancers (three cancers were found at MRI, two were found at CEDM). We included 212 women who were included in a study (22) that compared background parenchymal enhancement at MRI and CEDM. Our study is a larger cohort and compared performance metrics of the low-energy images alone to the complete CEDM (low-energy and iodine images) and does not evaluate background parenchymal enhancement. We also included 28 women who were included in a study (23) that compared and found equivalence between the low-energy images of CEDM and two-dimensional full-field DM.

CEDM Parameters

All CEDM examinations were performed with a dual-energy mammography system (Senographe Essential; GE Medical Systems, Milwaukee, Wis). Iohexol (Omnipaque 350; GE Healthcare) at a dose of 1.5 mL/kg was intravenously power injected at a rate of 3 mL/sec up to a maximum dose of 150 mL. After contrast agent injection, each woman was positioned, and imaging was initiated 2.5–3 minutes after injection. Mediolateral oblique and craniocaudal views were obtained in each breast. The order of the breasts (right vs left) imaged and the projection (craniocaudal vs mediolateral oblique) were performed at the discretion of the technologist because previous studies (24) showed that the acquisition order does not affect image quality. Each view was imaged almost simultaneously at two exposures, a low-energy exposure (26–30 kVp) and a high-energy exposure (45–49 kVp), straddling the k-edge of iodine. The low-energy image served as the equivalent of a two-dimensional full-field digital mammographic examination, which was previously demonstrated (23,25,26). Iodine images recombine the low- and high-energy images by using a proprietary algorithm to highlight areas of contrast enhancement. One final assessment was assigned combining the results of the low-energy and iodine images by using the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) categories from 1 to 5 (27). The radiation dose of CEDM is approximately 20% greater than two-dimensional full-field DM or the equivalent of one additional view (24).

Evaluation of Lesions Suspicious for Cancer

Radiology reports were reviewed for breast density and to record whether a finding was seen on the low-energy or iodine images, or both, which is part of standard reporting at our institution. If not specified, a radiologist (L.L., D.D., D.K., and M.S.J.) assessed this by reviewing the imaging while blinded to the outcome.

Findings on low-energy images (calcifications, masses, asymmetries, and areas of architectural distortion) were evaluated at the time of CEDM with additional mammographic views and/or US as per routine standard of care before they were given a final BI-RADS assessment. Breast MRI was obtained to evaluate areas of enhancement with no mammographic and no sonographic correlate because there is currently no U.S. Food and Drug Administration–approved CEDM biopsy device to sample

lesions only seen on the iodine images. In these cases, the final BI-RADS assessment following the breast MRI was used. Breast MRI was performed with the patient in the prone position with a 1.5-T or 3.0-T commercially available system (GE Healthcare) by using a dedicated breast surface coil. Imaging sequences included a localizing sequence, a fat-suppressed T2-weighted sequence, a nonfat-saturated T1-weighted sequence, and fat-saturated T1-weighted sequences before and three times after rapid bolus injection of a gadolinium chelate contrast agent. If there was an MRI correlate suspicious for cancer, biopsy was performed at MRI. If no correlate suspicious for cancer was observed at MRI, BI-RADS category 3 recommendation was given and a 6-month follow-up CEDM was recommended.

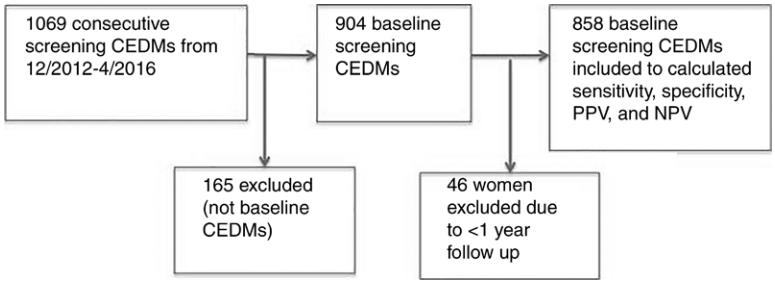


Figure 1: Patient inclusion and exclusion flowchart. CEDM = contrast-enhanced digital mammography, NPV = negative predictive value, PPV = positive predictive value.

Contrast Agent Reactions

Any woman who developed a reaction to contrast agent was evaluated by a nurse and radiologist. Reaction to contrast agents were recorded and graded as mild, moderate, or severe by following the guidelines outlined in the American College of Radiology Manual on Contrast Media (*www.acr.org/clinical-resources/contrast-manual*).

Statistical Analysis

Medical records were reviewed for age and risk factors (ie, family history of breast cancer, personal history of breast cancer, *BRCA* mutation status, and history of high-risk lesion or thoracic radiation). The number of biopsies recommended, cancer detection rate, and tumor characteristic were recorded. On a lesion basis, positive predictive value (PPV) of biopsy recommended (PPV_2) and PPV of biopsy performed (PPV_3) were calculated. Cancer detection rate was defined as the number of women diagnosed with cancer per 1000 screens. At least 1-year follow-up imaging was available in 858 women; data from these 858 women were used to calculate sensitivity, specificity, PPV, and negative predictive value on a patient level. BI-RADS categories 1 and 2 were considered to be negative for cancer and BI-RADS categories 3, 4, and 5 were considered to be positive for cancer. PPV_1 was defined as the number of examinations with cancer detected among patients with screening tests positive for cancer. Interval cancers were defined as breast cancer diagnosed within 365 days after a screening CEDM negative for cancer. All statistical calculations were made by using a standard statistical package (Stata 14; StataCorp, College Station, Tex). Statistical significance levels (*P* values) were calculated by the methods described in Pepe (28).

Results

Study Population

During the study period, 904 baseline CEDM examinations were performed. Median patient age was 52 years ± 9 (standard deviation; age range, 27–82 years). Table 1 summarizes the study population characteristics: 700 of 904 (77.4%) patients had dense breasts, 439 of 904 (48.6%) patients had a family history of breast cancer in a first-degree relative, and 363 of 904 (40.2%) patients had a personal history of breast cancer. Of the 904 patients, 681 patients (75.3%) had undergone previous contrast-enhanced breast MRI.

Table 1: Clinical Characteristics of Women Included in the Study

Characteristic	Result (*n* = 904)
Mean age at screening CEDM (y)	52 ± 9 (27–82)*
Breast density	
BI-RADS category A or B	204 (22.5)
BI-RADS category C or D	700 (77.4)
Risk factors	
Personal history of breast cancer	363 (40.2)
Age ≤50 years	243 (26.9)
Age >50 years	120 (13.3)
Family history	439 (48.6)
First degree relative age ≤50 years	247 (27.3)
First degree age >50 years	192 (21.2)
BRCA mutation	82 (9.1)
High-risk lesion	269 (29.8)
Mantle radiation	18 (2.0)

Note.—Unless otherwise indicated, data are number of women and data in parentheses are percentages. BI-RADS = Breast Imaging Reporting and Data System, CEDM = contrast-enhanced digital mammography.

* Data are ± standard deviation; data in parentheses are range.

Final BI-RADS Assessment

The final BI-RADS assessments were as follows: BI-RADS category 1 or 2 in 832 of 904 (92.0%) patients, BI-RADS category 3 in 25 of 904 (2.8%), and BI-RADS category 4 or 5 in 47 of 904 (5.2%) patients. There were 49 targeted US examinations performed. Breast MRI was recommended in 44 of 904 (4.9%) patients to evaluate enhancement observed only on the iodine images. After MRI, nine patients were found to be negative for cancer and no 6-month follow up CEDM performed (one patient underwent prophylactic mastectomies; one patient was downgraded to BI-RADS category 2 after MRI; in four patients, the radiologist who interpreted the CEDM images recommended 1-year follow-up if findings at MRI were negative for cancer; and in three women, the 6-month follow up was recommended but not performed), a 6-month follow-

Table 2: Characteristics of Women with Detected Breast Cancer, Pathologic Type of Cancer, and Imaging Modality of Breast Cancers Detected

Patient No.	Age (y)	Risk Factor*	Breast Density	Cancer Type	Invasive Cancer Size (cm)	Tumor Grade	Receptor Status	Node Status	Modality
1	50	FH > 50, ADH	HD	DCIS	NA	2	ER+	NA	LE
2	64	FH > 50	HD	DCIS with microinvasion	<1†	3	ER+	Neg	LE
3	66	FH > 50, LCIS	HD	DCIS	NA	3	ER−	NA	LE, enh
4	50	PH ≤ 50	HD	DCIS	NA	1	ER−	NA	LE, enh
5	50	PH ≤ 50	ED	IDC	0.8	3	ER−/PR−/HER2+	Neg	LE, enh
6	50	FH > 50, *BRCA*+	SFG	IDC	0.8	2	ER+/PR+/HER2−	Neg	LE, enh
7	52	PH ≤ 50, LCIS	HD	IDC	1.6	1	ER+/PR+/HER2−	Neg	LE, enh
8	57	FH > 50	SFG	IDC	0.3	1	ER+/PR+/HER2−	Neg	LE, enh
9	51	PH > 50	HD	DCIS	NA	2	ER+	NA	Enh
10	67	ADH	HD	DCIS	NA	1	ER+	NA	Enh
				IDC	0.8	1	ER+/PR+/HER2−	Neg	Enh
11	65	PH > 50, FH > 50	HD	IDC	0.8	2	ER+/PR+/HER2−	Neg	Enh
12	43	PH ≤ 50, FH ≤ 50	ED	IAC	0.4	1	ER−/PR−/HER2−	Neg	Enh
13	50	FH > 50, LCIS	HD	ILC	0.8	1	ER+/PR+/HER2−	Neg	Enh
14	61	PH > 50	HD	ILC	0.6	2	ER+/PR−/HER2−	NA	Enh

Note.—Data are from 14 women. Tumor grade I is low, grade II is intermediate, and grade III is high. ADH = atypical ductal hyperplasia, DCIS = ductal carcinoma in situ, ED = extremely dense, enh = iodine images, ER = estrogen receptor, FH = family history, HD = heterogeneously dense, HER2 = human epidermal growth factor receptor 2, IAC = invasive adenosquamous carcinoma, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, LCIS = lobular carcinoma in situ, LE = low-energy/two-dimensional imaging, NA = not applicable, neg = negative, PH = personal history, PF = predominantly fatty, PR = progesterone receptor, SFG = scattered fibroglandular densities.

* 50 = age 50 years.

† Units are millimeter; there was a less than 1-mm invasion.

up CEDM was negative for cancer in 14 patients, and biopsy was recommended in 21 patients.

The BI-RADS category 3 recommendation rate was 2.8% (26 lesions in 25 of 904 women). Ten lesions in 904 women were seen on the low-energy images (with or without contrast enhancement) and 16 lesions were seen on the iodine images only. One-year imaging follow-up was available for 23 of the 25 women whose study was given a BI-RADS category 3 assessment; no cancers were detected at follow-up.

Biopsy was recommended for 51 lesions in 47 women (5.2%; 47 of 904). Twenty-three biopsies were recommended in 23 women (2.5%; 23 of 904) for lesions observed on the low-energy images (10 without contrast enhancement,13 with associated contrast enhancement). Twenty-eight biopsies were recommended in 24 women for lesions only seen on the iodine images. All lesions in which biopsy was recommended were sampled; therefore, PPV_2 and PPV_3 were equivalent.

Screen-detected Cancers

A total of 15 screen-detected cancers were diagnosed in 14 women (one woman had bilateral breast cancers) for a cancer detection rate of 15.5 of 1000. The PPV_2 and PPV_3 were 29.4% (15 of 51). For findings seen on the low energy images (with or without associated contrast enhancement), the cancer detection rate was 8.8 of 1000 (in eight of 904 women), and the PPV_2 and PPV_3 were 34.8% (eight of 23). Risk factors of women diagnosed with breast cancer, tumor characteristics, and imaging modality for the detected cancers are summarized in Table 2.

Two of 15 screen-detected cancers were detected only on the low-energy images. Both manifested as calcifications and were ductal carcinoma in situ, one with microinvasion.

Six cancers (two ductal carcinomas in situ and four invasive cancers) were seen on both the low-energy and iodine images (Fig 2). Three of the four invasive cancers manifested as enhancing masses or asymmetries. One of the four invasive cancers manifested as calcifications with enhancement.

Seven cancers (two ductal carcinomas in situ and five invasive cancers) in six women were detected because of contrast enhancement on the iodine images (Fig 3). Two of the five invasive cancers were invasive lobular cancers.

Performance Metrics of Screening CEDM

In the 1-year period following the screening CEDM, eight women were diagnosed with metastatic breast cancer not within the breast, four women underwent bilateral prophylactic mastectomies, two women were diagnosed with nonbreast cancers, and one woman died of complications of a heart trans-

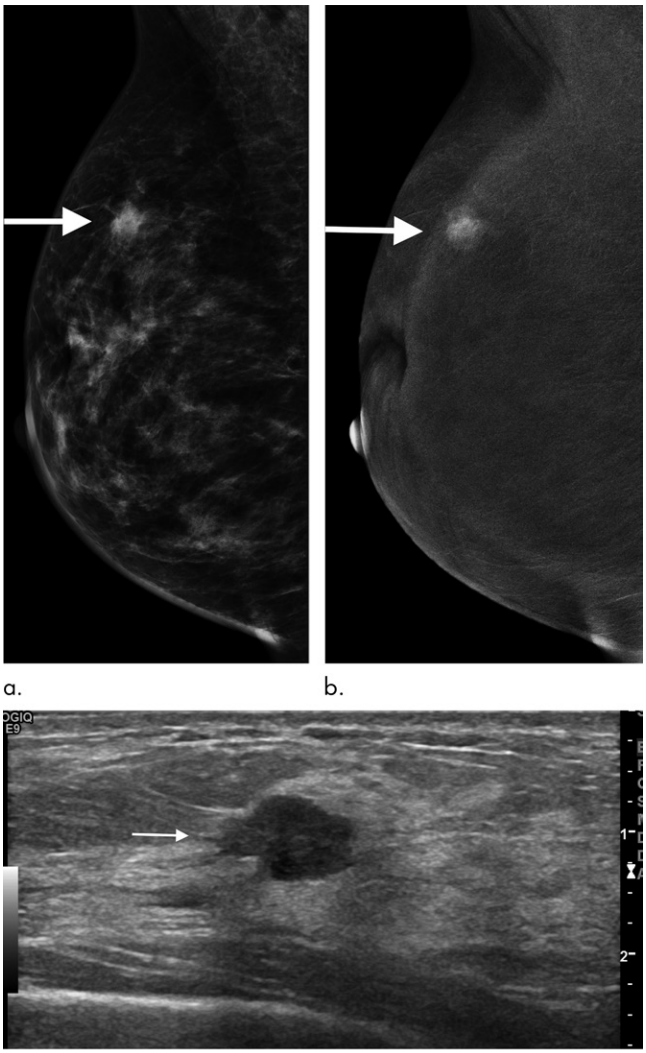


Figure 2: Images in 52-year-old woman with a 1.6-cm, node-negative, grade-1 estrogen receptor–positive/progesterone receptor–positive/human epidermal growth factor receptor 2–negative invasive ductal cancer evident on both the low-energy and iodine images. **(a)** An asymmetry (arrow) is in the superior right breast on the right mediolateral oblique view. **(b)** This focal asymmetry is enhanced (arrow) after contrast agent administration on the mediolateral oblique iodine image. **(c)** Targeted US helped to identify a sonographic correlate of an irregular 1.1-cm mass (arrow) at the 11:00 axis. Subsequent biopsy yielded invasive ductal carcinoma.

plant. Thirty-one women were lost to follow up. One-year follow up breast imaging was therefore available in 858 women.

Two women developed interval cancers within the breast. One woman had a bilateral MRI and screening CEDM as part of a research study. The CEDM was negative for cancer, but the MRI showed a right breast mass suspicious for malignancy. The woman deferred biopsy and elected for follow-up. At follow-up MRI, biopsy was again recommended for that right breast mass that was found to represent ductal carcinoma in situ and for a new left breast mass that was an 8-mm invasive ductal carcinoma. In the second woman, ductal carcinoma in situ was depicted at a screening US performed 10 months after the CEDM that was negative for cancer.

In the 858 women with at least 1-year follow-up, sensitivity, specificity, PPV_1, and negative predictive value were calculated for the CEDM examination and if interpretation had been on the basis of the low-energy images alone (Table 3). Sensitivity was 87.5% (95% confidence interval [CI]: 61.7%, 98.4%); specificity, 93.7% (95% CI: 91.8%, 95.2%); PPV_1, 20.9% (95% CI: 11.9%, 32.6%); and negative predictive value, 99.7% (99.09%, 99.97%). The addition of contrast enhancement helped to identify six of the eight cancers not identified by using low-energy images alone (six of eight; 75.0%; 95% CI: 34.9%, 96.8%), which increased the number of women with cancers detected by 75%. However, although sensitivity increased from 50.0% to 87.5% ($P = .03$), specificity declined from 97.1% to 93.7% ($P < .001$) with 29 additional false-positive findings (ie, biopsies negative for malignancy or BI-RADS category 3 recommendations) in the 818 women with low-energy images negative for malignancy (29 of 818; 3.5%; 95% CI: 2.4%, 5.1%) or 789 of 818 women who were correctly identified as negative for malignancy (96.5%; 95% CI: 94.9%, 97.6%) (Fig 4).

Contrast Agent Reactions

There were reactions to contrast agent in 15 of 904 (1.7%) patients. One woman had a moderate reaction to contrast agent (dyspnea that resolved with diphenhydramine). The remaining 14 reactions to contrast agent were mild, of which only one required administration of diphenhydramine. The other 13 contrast reactions resolved completely without intervention. The most common reactions were nausea (in five women) and hives (in four women).

Discussion

The limitations of screening mammography, especially in women at increased risk for breast cancer and/or with dense breasts at mammography, have led to the search for improved screening techniques. Contrast-enhanced digital mammography (DM) (CEDM) has been shown to have higher sensitivity, specificity, and accuracy compared with DM in the diagnostic setting (15,17). However, few studies have evaluated the potential of CEDM as a screening test. To our knowledge, ours is the largest study reporting on the performance of CEDM for breast cancer screening. The addition of contrast enhancement improved sensitivity from 50.0% (eight of 16) to 87.5% (14 of 16); the addition of contrast enhancement helped to detect six of the eight (75%; 95% confidence interval [CI]: 34.9%, 96.8%) cancers missed at standard mammography. Six of 14 patients had cancers that were detected only because of contrast enhancement, and the specificity was 93.7% (789 of 842; 95% CI: 91.8%, 95.2%).

For any screening test, increased cancer detection must be balanced with false-positive findings. The addition of contrast agent increased the number of women with a biopsy recommendation from 23 to 47. However, the PPV_3 of CEDM in this study was 29.4% (15 of 51), which is comparable to established benchmarks for both mammography (20%–45%) and breast MRI (20%–50%) (29). Therefore, the increased

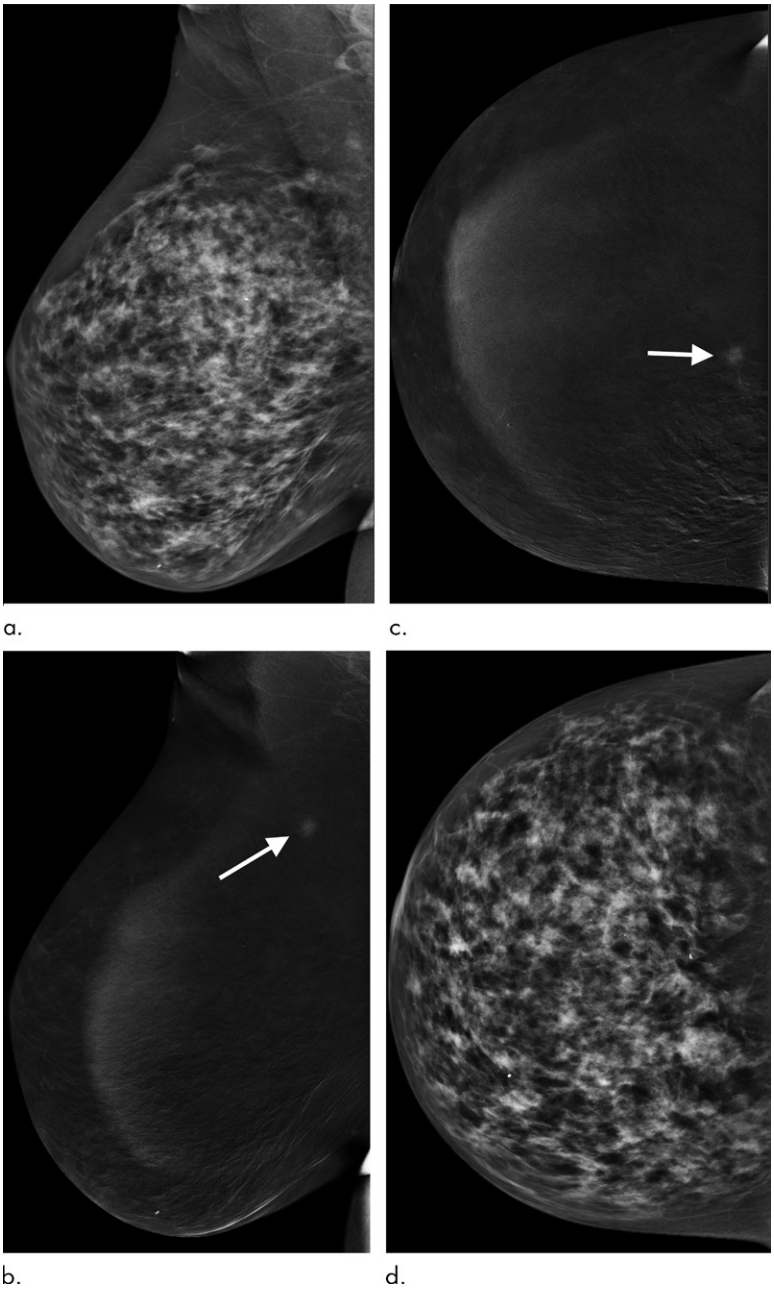


Figure 3: Images in a 65-year-old woman with a 0.8-cm, node-negative, grade 2, estrogen receptor–positive/progesterone receptor–positive/human epidermal growth factor receptor 2–negative invasive ductal cancer only evident at contrast-enhanced digital mammography (CEDM) because of contrast enhancement. No abnormality was depicted on the **(a)** right mediolateral oblique and **(d)** craniocaudal views from low-energy images of the screening CEDM. A 5-mm enhanced mass (arrows in **b** and **c**) is visible only after contrast administration on the **(b)** mediolateral oblique and **(c)** craniocaudal iodine images. Subsequent biopsy yielded invasive ductal carcinoma.

number of biopsies recommended is warranted given the increased number of cancers detected.

The BI-RADS category 3 recommendation rate of CEDM in our study was low at 2.8% and comparable to the rate of BI-RADS category 3 found at DM (30). Specificity of CEDM was 93.7%, comparable to that of DM (88.9%–95%), digital breast tomosynthesis (91.3%), MRI (90%–97%) and screening US (91.8%) (5–7,31). In our study, 4.9% of women underwent breast MRI for further evaluation of a finding observed only on the iodine images. Women and referring physicians should be aware of the potential need for additional imaging and possible benign biopsies when considering whether to perform screening CEDM.

Another recent study (20) that evaluated screening CEDM in 611 women at intermediate risk also reported increased cancer detection with contrast enhancement. The cancer detection rate (34 of 1000 vs 15.5 of 1000, respectively), incremental cancer detection rate (13.1 of 1000 vs 6.6 of 1000, respectively), and rates of BI-RADS categories 3, 4, and 5 in that study were substantially higher than in our study. These differences may reflect differences in screening practices in Israel, where that study was performed, compared with the United States.

Patient reactions to the intravenous iodinated contrast agent were rare. All were mild except for in one woman with a moderate reaction (dyspnea) that resolved with diphenhydramine. Women with a history of reaction to iodinated contrast at our institution are not recommended to undergo breast cancer screening with CEDM, even if premedicated for their allergy.

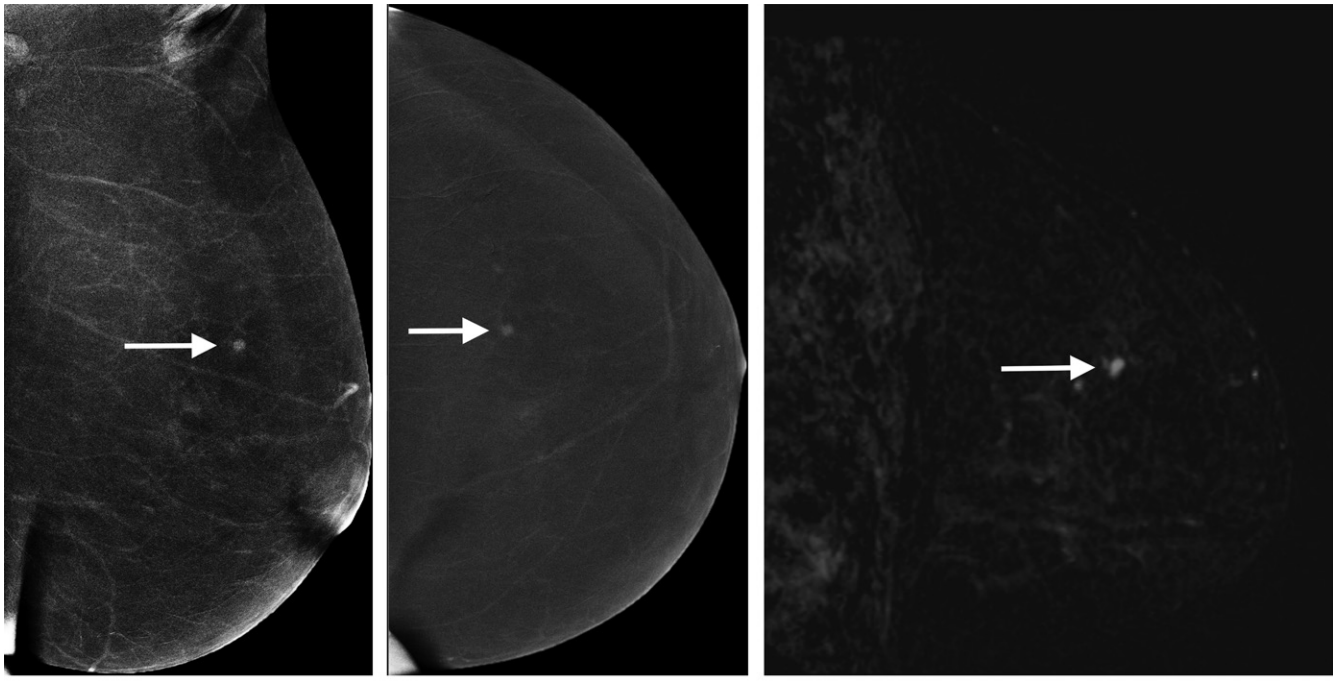
At our institution, CEDM has been offered since December 2012 as an alternative screening method primarily for women at intermediate risk for breast cancer. Screening guidelines for intermediate risk women are evolving and not yet well established. For example, the American Cancer Society states that there is insufficient evidence to recommend for or against screening breast MRI in women with a 15%–20% lifetime risk of breast cancer, including women with lobular carcinoma in situ or a personal history of breast cancer (32). Some more recent studies have suggested that women with a history of lobular carcinoma in situ benefit from supplemental screening with breast MRI, whereas others found no benefit (33–35). The American College of Radiology now recommends annual screening breast MRI in women with a personal history of breast cancer who have dense breasts or those diagnosed before age 50 years (14). CEDM has the potential to serve as an alternative vascular-based screening test in women who do not have access to breast MRI or who are not able to undergo MRI.

Screening CEDM may also be beneficial in women at high risk for breast cancer. Because of their increased risk of interval cancers, some women with *BRCA* mutations stagger their screening mammography and MRI at 6-month intervals, which may be more effective than stacked screening (21). CEDM may be an alternative to

Table 3: Comparison of Performance Metrics of Contrast-enhanced Digital Mammography and Low-Energy Images Alone in 858 Women with at Least 1 year of Follow-up

Parameter	Low-Energy Images (%)	CEDM Images (%)	*P* Value
Sensitivity	50.0 (8/16) [24.7, 75.3]	87.5 (14/16) [61.7, 98.4]	.03
Specificity	97.1 (818/842) [95.8, 98.2]	93.7 (789/842) [91.8, 95.2]	<.001
PPV_1	25.0 (8/32) [11.5, 43.4]	20.9 (14/67) [11.9, 32.6]	.39
NPV	99.0 (818/826) [98.1, 99.6]	99.7 (789/791) [99.09, 99.97]	.02

Note.—Contrast-enhanced digital mammography images are low-energy and iodine images. Data in parentheses are numerator/denominator; data in brackets are 95% confidence intervals. CEDM = contrast-enhanced digital mammography, NPV = negative predictive value, PPV_1 = Positive predictive value.



a. b. c.

Figure 4: Images in a 64-year-old woman with results that were false-positive for cancer at contrast-enhanced digital mammography. An enhancing 0.5-cm mass (arrows) is seen in the left upper outer quadrant on the **(a)** mediolateral oblique and **(b)** craniocaudal iodine views. No abnormality was observed on the low-energy images or at targeted US. **(c)** Subtraction image from MRI demonstrates a correlate (arrow). MRI-guided biopsy yielded fibroadenomatoid changes and other benign pathologic results.

conventional mammography so that these women undergo a vascular-based screening test every 6 months.

Limitations of our study include that this was a single-institution, retrospective study. Our study population included women who had previously undergone screening breast MRI examinations, which were used for comparison of areas of contrast enhancement at CEDM. Our study population was composed largely of women with dense breasts and increased breast cancer risk. The performance of CEDM in women with nondense breasts and/or average breast cancer risk may be different. Finally, our study included the first 904 baseline screening CEDM examinations performed at our institution. Performance metrics may improve with more experience.

For screening women at increased risk for breast cancer, the sensitivity of contrast-enhanced digital mammography (DM) (CEDM) was 87.5%, compared with 50.0% for DM (*P* = .03), with a specificity of 93.7%. Our results suggest that CEDM has the potential to be an alternative screening technique to two-dimensional full-field DM in women at increased risk of breast cancer.

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