

Supplemental Breast Cancer Screening With Molecular Breast Imaging for Women With Dense Breast Tissue

Robin B. Shermis¹
 Keith D. Wilson¹
 Malcolm T. Doyle¹
 Tamara S. Martin¹
 Dawn Merryman¹
 Haris Kudrolli²
 R. James Brenner^{3,4,5}

Keywords: adjunct breast screening, dense breast screening, molecular breast imaging

DOI:10.2214/AJR.15.15924

Received November 24, 2015; accepted after revision March 17, 2016.

R. B. Shermis and R. J. Brenner serve on the scientific advisory board of Gamma Medica, Inc.

¹Department of Radiology, ProMedica Breast Care, 2121 Hughes Dr, 1st Fl, Toledo, OH 43606. Address correspondence to R. B. Shermis (rshermis@bex.net).

²Gamma Medica Inc., Salem, NH.

³Bay Imaging Consultants, Walnut Creek, CA.

⁴Alta Bates Summit Medical Center, Oakland, CA.

⁵Department of Radiology, University of California San Diego, San Diego, CA.

This article is available for credit.

AJR 2016; 207:450–457

0361–803X/16/2072–450

© American Roentgen Ray Society

OBJECTIVE. Molecular breast imaging was implemented in routine clinical practice at a large community-based breast imaging center. The aim of this study was to retrospectively assess the clinical performance of molecular breast imaging as a supplementary screening tool for women with dense breast tissue.

MATERIALS AND METHODS. Women with dense breasts and negative mammography results who subsequently underwent screening with 300 MBq (8 mCi) ^{99m}Tc-sestamibi molecular breast imaging were retrospectively analyzed. Outcome measures included cancer detection rate, recall rate, biopsy rate, and positive predictive values (PPVs).

RESULTS. Molecular breast imaging screening of 1696 women in this study resulted in the detection of 13 mammographically occult malignancies, of which 11 were invasive, one was node positive, and one had unknown node positivity. The lesion size ranged from 0.6 to 2.4 cm, with a mean of 1.1 cm. The incremental cancer detection rate was 7.7% (95% CI, 4.5–13.1%), the recall rate was 8.4% (95% CI, 7.2–9.8%), and the biopsy rate was 3.7% (95% CI, 2.9%–4.7%). The PPV for recall (PPV 1) was 9.1% (95% CI, 5.4–15.0%), and the PPV for biopsy (PPV 3) was 19.4% (95% CI, 11.4–30.9%).

CONCLUSION. When incorporated into a community-based clinical practice environment, molecular breast imaging yielded a high incremental cancer detection rate of 7.7% at an acceptable radiation dose. These results show the utility of molecular breast imaging as a supplementary screening tool to mammography for women with dense breasts.

The value of screening mammography in the detection and diagnosis of breast cancer has been validated by single-institution trials [1], service screening trials [2, 3], and randomized control studies [4–9]. Although these investigations used film-screen mammography equipment, which is considered inferior to current digital technology, follow-up data as long as 29 years have shown a beneficial effect of screening mammography on mortality rates [10]. The more recent American College of Radiologic Imaging Network Digital Mammographic Imaging Screening Trial [11] showed the relative equivalency of screen film and digital techniques, with trends that favored the use of higher-contrast digital imaging for denser breasts. Nonetheless, detecting mammographic signs of breast cancer in dense breasts presents a challenge to radiologists interpreting such studies, with sensitivities that are lower than those for breasts that contain predominantly fatty tissue [12–14].

Breast density has been shown to be an independent risk factor for developing breast cancer. Although this risk may be overstated in studies that compare the risk of women with the most dense breast tissue to those with the least dense breast tissue [15], when standardized to average breast tissue, women with heterogeneously dense breasts have a 1.2 times greater risk of developing breast cancer compared with a 2.0 times greater risk for women with severely dense breasts [16]. Thus, women with dense breasts—not adjusting for family history, genetic predisposition, or body mass index—generally have a higher risk of developing breast cancer, and their breast cancer is more difficult to detect on screening mammography [11].

Although MRI has been validated as an effective supplementary screening approach for mammography for very-high-risk women [17], it is expensive, has limited availability in small communities, and may not be fully reimbursed by insurance for women who have a calculated lifetime risk of less than

20–25%, as benchmarked by the American Cancer Society according to mathematical models [18]. Other screening modalities, notably whole-breast ultrasound, have been advocated for women with dense breasts [19, 20]. Recent published studies retrospectively reviewed the implementation of whole-breast screening ultrasound as a supplement to mammography for women with dense breast tissue in Connecticut, which was the first state to pass the breast density notification law [21–23]. These studies found an increase in cancer detection rate along with correspondingly large increases in the false-positive rate, number of biopsies conducted, and extensive interpretation time. These results raise serious questions about the utility and practicality of whole breast ultrasound for screening dense breast screening [24, 25].

For many years, there has been interest in using ^{99m}Tc -sestamibi as a radiotracer to detect breast cancer [26]. Although ^{99m}Tc -sestamibi was originally synthesized for use as a myocardial perfusion imaging agent, it has a stronger affinity to cancer cells compared with other myocardial perfusion agents [27]. Because ^{99m}Tc -sestamibi is a lipophilic cation, it is driven into the mitochondria by the electron gradient between plasma and mitochondrial membrane potentials [28]. Consequently, its strong preferential uptake in cancer cells has been found in *in vitro* studies [29]. *Ex vivo* measurements of ^{99m}Tc -sestamibi uptake in excised healthy tissue and tumor tissue from patients undergoing breast surgery confirmed significantly higher uptake in the samples containing carcinoma, with a mean contrast ratio of nearly 6:1 compared with that of the surrounding normal breast or fat tissue [30].

Breast-specific gamma imaging with dedicated single-head scintillating gamma cameras using a prescribed dose of 1110 MBq (30 mCi) ^{99m}Tc -sestamibi improves the ability to detect breast lesions as compared with general purpose gamma cameras [31]. Molecular breast imaging, which uses cadmium zinc telluride detectors in a dual-head configuration, also showed high sensitivity and specificity to detect cancer at a lowered dose of 740 MBq (20 mCi) [32]. However, these prescribed doses of 740–1110 MBq correspond to an effective radiation dose to the person of 6.3–9.4 mSv, which is too high for routine clinical use [33]. Improvements in molecular breast imaging technology, in particular to the collimator design, reduced the prescribed dose to 300 MBq (8 mCi), corresponding to

an effective radiation dose of 2.4 mSv. Recent studies from the Mayo Clinic [34, 35] found favorable outcomes and cost effectiveness in using molecular breast imaging with this lower dose. Here, we describe using molecular breast imaging in a large community-based practice with similar equipment, patient management, and radiation dose as used in the Mayo Clinic reports, and compare this experience to other published supplementary screening modalities.

Materials and Methods

Screening Method

This HIPAA-compliant retrospective study involving human subjects was conducted after institutional review board approval was received through the Chesapeake institutional review board (study number Pro00007668). Informed consent was waived. Study participants (Table 1) consisted of asymptomatic women aged 25–90 years with heterogeneously or extremely dense breasts who presented for routine screening mammography at ProMedica Breast Care Center (Toledo, OH) between May 2011 and August 2014. In response to the dense breast notification legislation movement, which started in Connecticut in 2009, and in anticipation of Ohio state legislation that became effective in June 2015, this center had initiated a multitier approach toward screening women with dense breasts. Under this approach, women who underwent screening were imaged with digital mammography (Selenia, Hologic). Breast density assessment software (Volpara versions 1.2 and 1.59, VolparaSolutions) was used to complement

subjective evaluation by the radiologist to categorize the mammograms according to the BI-RADS classifications of breast density [36]: A, fatty tissue; B, scattered fibroglandular; C, heterogeneously dense; or D, extremely dense. Each participant's lifetime risk of developing breast cancer was assessed using the Modified Gail and Tiner-Cuzick models, embedded within commercial mammography management software (PenRad version 5, PenRad Technologies). The higher of the two model scores was used as the basis for recommending supplementary screening. Women with BI-RADS category 1 or 2 findings on mammography, who also had a BI-RADS density category C or D and whose lifetime risk was 20% or more, were recommended for adjunct screening with MRI (Aurora Breast MRI, Aurora Health Care), whereas women with risk less than 20% were recommended for molecular breast imaging (LumaGEM, Gamma Medica). The molecular breast imaging system consists of dual-head cadmium zinc telluride detectors with 1.6-mm pixel size detectors and tungsten registered collimators.

Women undergoing a molecular breast imaging evaluation received 300 MBq (8 mCi) of ^{99m}Tc -sestamibi via IV injection. Syringes (3 mL; Monoject, Covidien) were used to inject the radiotracer, resulting in 30 MBq (0.8 mCi) to 52 MBq (1.4 mCi) left behind in the syringe [37]. Therefore, the administered dose to the individual was generally between 248 MBq (6.6 mCi) and 270 MBq (7.2 mCi). Imaging commenced immediately after injection using only light breast compression in the mediolateral oblique and craniocaudal views, with exposures of 7–10 minutes per view.

TABLE 1: Study Participant Characteristics

Characteristics	Eligible Women (<i>n</i> = 2900)	Analysis Set (<i>n</i> = 1696)
Age at index molecular breast imaging (y)		
Median (interquartile range)	49 (43–57)	49 (43–57)
Range	25–90	25–87
Mean (SD)	50.8 (10.6)	50.2 (9.7)
Mammographic breast density		
Almost entirely fatty	22 (2)	0 (0)
Scattered areas of fibroglandular density	86 (8)	34 (6)
Heterogeneously dense	437 (43)	264 (42)
Extremely dense	468 (46)	319 (52)
Not reported or unknown	1887	1079
Risk category		
Risk ≥ 20%	86 (9)	45 (8)
Risk < 20%	884 (91)	553 (92)
Unknown	1930	1098

Note—Except for age, data are number (%) of patients, with percentages calculated as a fraction of the reported values, not as a fraction of the total population.

The molecular breast images were interpreted by one of four breast radiologists at the facility, who also had access to the participants' mammograms, other pertinent studies, and clinical information. The molecular breast image findings were assessed as BI-RADS categories 0 through 6, using the standard BI-RADS scoring system. Molecular breast imaging BI-RADS assessments of categories 0, 3, 4, or 5 are considered test positive, and categories of 1 or 2 are considered test negative. Women with a finding of BI-RADS category 6 (confirmed malignancy) were excluded from the analysis. Test-positive molecular breast imaging findings triggered additional diagnostic evaluation by methods such as ultrasound or additional mammographic views, whereas the test-negative findings were recommended for annual mammography follow-up. Biopsies were primarily conducted using sonographic guidance, but stereotactic- or MRI-guided biopsies were performed in women whose lesion was not visible with ultrasound.

Study Population and Reference Standard

Analysis of this study was restricted to women aged 25 through 90 years who had a mammographic study that was considered negative or benign within 100 days of the index molecular breast imaging. The positive reference standard was a histopathologic diagnosis of breast cancer. Because this study was a retrospective evaluation of a large clinical practice, follow-up information was missing on a number of women; thus, complete data on interval cancers were unavailable. Therefore, absolute sensitivity and specificity could not be calculated.

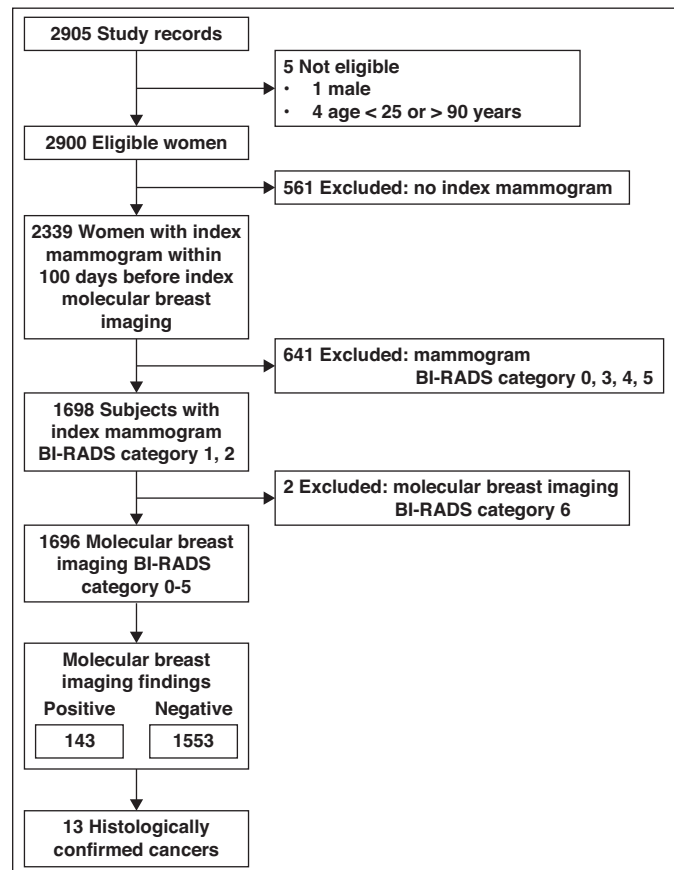
Statistical Analysis

For women with verified cancer status, analysis included the cancer detection rate, recall rate, biopsy rate, positive predictive value (PPV) for recall (PPV 1), and PPV for biopsies (PPV 3). PPV 1 was defined as the number of malignancies per abnormal screening examinations (BI-RADS categories 0, 3, 4, and 5). PPV 3 was defined as the number of malignancies per total biopsies performed within 60 days of the index molecular breast imaging. The 95% CI computations were two sided, with a statistical significance level of 0.05 calculated using the Wilson score method.

Results

The review of the clinical data for molecular breast imaging performed between May 24, 2011, and August 29, 2014, was conducted by polling the clinic's patient database on September 4, 2014. Figure 1 shows the detailed breakdown of the selection criteria. The data comprised 2905 individuals, but one was male and four women did not meet

Fig. 1—Flowchart showing selection criteria of mammogram screening records for retrospective analysis.



the age criteria; thus, 2900 individuals were eligible. Of these eligible women, 561 were excluded because they did not have an index mammogram in the system or their mammogram was conducted more than 100 days before the molecular breast imaging examination. Of the remaining 2339 women, 641 had an index mammogram with BI-RADS category 0, 3, 4, or 5 findings and therefore were excluded from this analysis. Two women had a molecular breast imaging examination with BI-RADS category 6 findings and were excluded from the analysis. Therefore, 1696 women had an index mammogram with BI-RADS category 1 or 2 findings followed by molecular breast imaging within 100 days and were included in our analysis.

Women ranged in age from 25 through 90 years, with a median age of 49 years (interquartile range, 43–57 years) (Table 1). Of the women with documented breast density, 94% (581/617) had breasts that were heterogeneously dense or extremely dense. The 6% of the women who had a lower density assessment had complex parenchymal pattern with multiple asymmetries and therefore were referred for secondary screening. Ninety-two

percent (553/598) of women in the study with documented data had mathematically determined lifetime risk of less than 20%. The 8% of women who had risk greater than 20% were contraindicated for MRI.

Of the 1696 women in the analysis set, 1553 (91.6%) had benign or negative molecular breast imaging findings. Figure 2 shows an example of a molecular breast imaging negative finding. Molecular breast imaging had a positive finding in 143 (8.4%) women, which triggered additional diagnostic evaluation by ultrasound or additional mammographic views. Of these 143 women with positive molecular breast imaging findings, 13 malignancies were histopathologically proven. Eleven (85%) of these malignancies were invasive. As shown in Table 2, two of these findings were ductal carcinoma in situ (DCIS), six were invasive ductal carcinoma, three were invasive lobular carcinomas, one was bilateral cancer of invasive lobular carcinoma and DCIS, and one was invasive mammary carcinoma with ductal and lobular features (Fig. 3). Seven malignancies were found in heterogeneously dense breasts and six in extremely dense breasts.

Molecular Breast Imaging for Women With Dense Breast Tissue

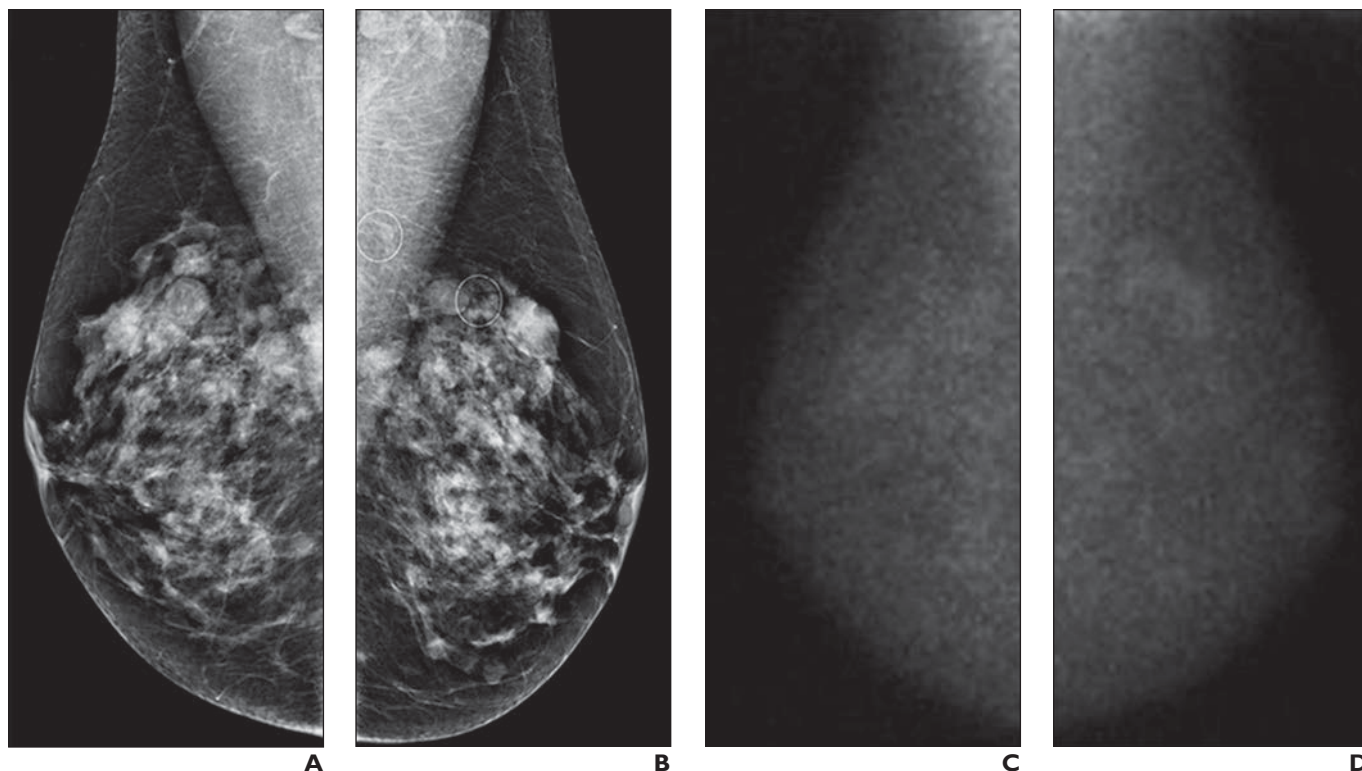


Fig. 2—63-year-old woman with mammographically dense breasts and negative molecular breast imaging findings.

A, Right mediolateral image from digital screening mammogram.

B, Left mediolateral image from digital screening mammogram. Ovals denote ROIs.

C, Right mediolateral molecular breast image.

D, Left mediolateral molecular breast image.

The lifetime risk, as measured by the higher of the Modified Gail and Tirer-Cuzick models, ranged between 6.1% and 17.2%. The average size of the longest diameter of the invasive component was 1.1 cm and ranged from 0.6 to 2.4 cm. Only one woman among the 12

with reported nodal information had positive nodal involvement. One woman had a 2.4-cm invasive lobular carcinoma in one breast and DCIS on the contralateral side.

Table 3 tabulates the performance metrics of molecular breast imaging along with their

two-sided 95% CIs. Because 13 malignant lesions were found by supplemental screening with molecular breast imaging, the incremental cancer detection rate was 7.7% (13/1696). Positive molecular breast imaging findings occurred in 143 of the 1696 women

TABLE 2: Summary of the 13 Cancers Identified in 13 Women

Pathology	Size (cm)	Nodes	Patient Age (y)	Breast Density	Breast	Risk (%)
IDC	0.9	Negative	58	Extremely	Left	14.90
IDC	0.9	Negative	87	Heterogeneous	Left	
DCIS		Negative	48	Extremely	Right	10.60
DCIS	1.0	Negative	60	Heterogeneous	Left	7.50
IDC	1.2	Positive	52	Extremely	Right	15.24
ILC/DCIS	2.4	Negative	63	Heterogeneous	Bilateral	6.10
ILC	1.2	Unknown	46	Extremely	Right	17.22
ILC	1.0	Negative	53	Extremely	Left	12.40
IDC	1.2	Negative	57	Heterogeneous	Right	11.70
ILC	1.0	Negative	67	Heterogeneous	Left	6.40
IMC	0.9	Negative	68	Heterogeneous	Right	10.80
IDC	1.5	Negative	66	Heterogeneous	Left	16.50
IDC	0.6	Negative	42	Extremely	Right	15.80

Note—IDC = invasive ductal carcinoma, DCIS = ductal carcinoma in situ, ILC = invasive lobular carcinoma, IMC = invasive mammary carcinoma.

(14 BI-RADS category 0, 73 BI-RADS category 3, 55 BI-RADS category 4, and one BI-RADS category 5), resulting in a recall rate of 8.4% (143/1696) and PPV 1 of 9.1% (13/143). Women with BI-RADS category 3 lesions were typically referred for a 6-month follow-up, unless they requested biopsy instead of surveillance. One of the true-positive cases was a BI-RADS category 3 lesion, which resulted in a 6-month follow-up with ultrasound and biopsy after our 60-day biopsy criteria. Therefore, it was discounted in the PPV 3 calculations, which was calculated as 19.4% (12/62).

Discussion

Of the 1696 participants in this study, 143 (8.4%) had a positive finding on molecular breast imaging. Positive findings led to short-term diagnostic follow-up by ultrasound- or stereotactic-guided biopsy (62 women) or MRI-guided biopsy (three women). The 13 cancers found in this study were confirmed by ultrasound-guided biopsy in nine women and by stereotactic-guided biopsy in four women.

Fourteen (< 1%) molecular breast imaging image sets in this dataset were assessed as BI-RADS category 0: incomplete analysis that required additional evaluation. Of the 11 women who underwent MRI examination, five had no evidence of suspicious contrast enhancement with MRI and six had positive MRI findings that led to further diagnostic workup. Seven of these 14 women under-

TABLE 3: Performance Characteristics of Molecular Breast Imaging at Participant Level

Characteristic	No./Total of Patients	Estimate (95% CI)
Cancer detection rate (%)	13/1696	7.7 (4.5–13.1)
Invasive cancer detection rate (%)	11/1696	6.5 (3.6–11.6)
Recall rate (%)	143/1696	8.4 (7.2–9.8)
Recall rate, BI-RADS category 4 or 5 (%)	56/1696	3.3 (2.6–4.3)
Biopsy rate (%)	62/1696	3.7 (2.9–4.7)
Positive predictive value 1 (%)	13/143	9.1 (5.4–15.0)
Positive predictive value 3 (%)	12/62	19.4 (11.4–30.9)

went biopsies, of which five were performed using ultrasound and returned negative results. One positive MRI finding led to an MRI-guided biopsy with benign pathologic findings. One woman underwent stereotactic biopsy, which was positive for malignancy. Thus, of the 14 indeterminate molecular breast imaging findings, one (7%) returned a malignant result.

MRI was primarily used when molecular breast imaging showed findings for which there were no conventional imaging correlates. Of the 1696 participants studied, MRI was used in 17 instances (1%) to help resolve a positive molecular breast imaging finding not visible on mammogram or targeted ultrasound. Eleven of these involved BI-RADS category 0 findings on molecular breast imaging, as already discussed. Three MRI studies were performed to follow up on

molecular breast imaging BI-RADS category 4 results, which led to one diagnosis of fat necrosis and two MRI-guided biopsies that showed no malignancy. In three women with BI-RADS category 3 findings on molecular breast imaging, MRI was used as the short-term follow-up modality, of which one led to an ultrasound-guided biopsy. The limited use of MRI to complement molecular breast imaging provides a less-expensive approach toward cancer screening and diagnosis and has been addressed previously [35]. False-positives with proven pathology in our cohort included 25% (11/44) fibroadenoma, 7% (3/44) papilloma, 5% (2/44) atypical ductal hyperplasia, 2% (1/44) phyllodes tumor, 2% (1/44) hamartoma, 2% (1/44) pseudoangiomatous stromal hyperplasia, 2% (1/44) fat necrosis, and 55% (24/44) fibrocystic change, such as apocrine metaplasia or fibrosis.

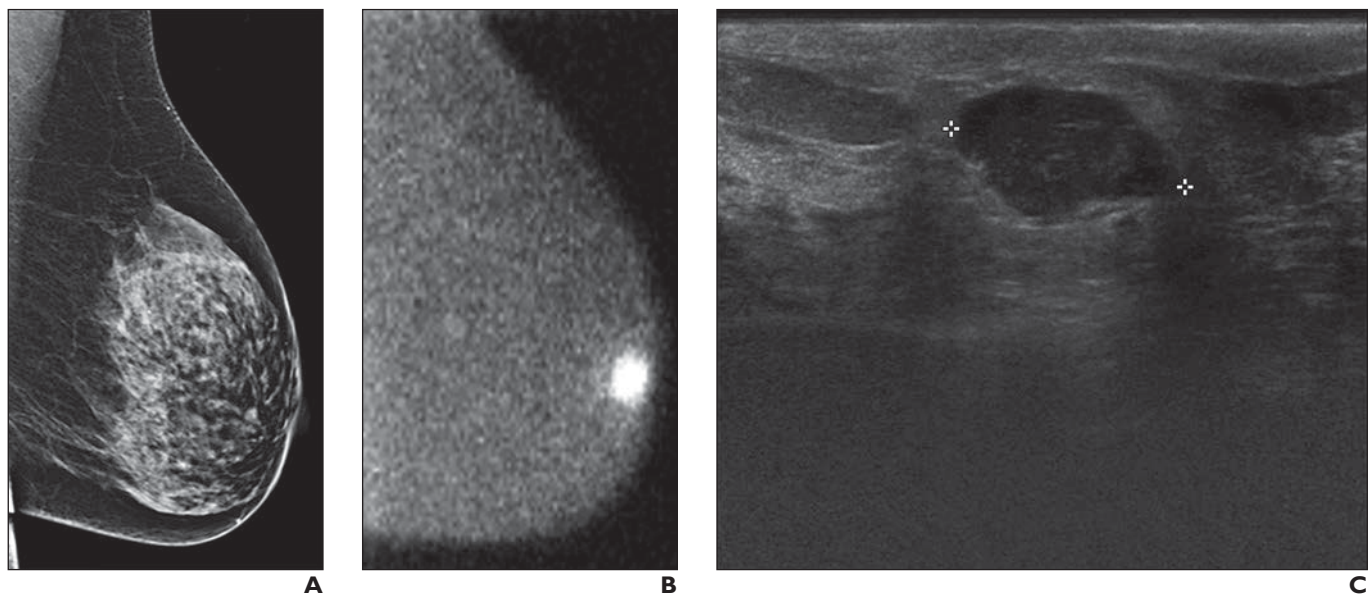


Fig. 3—68-year-old woman with mammographically occult invasive mammary carcinoma detected by molecular breast imaging.

A, Left mediolateral image from digital screening mammogram was interpreted as negative.

B, Adjunct mediolateral molecular breast image shows intense uptake.

C, Sonographic image shows lesion (*between calipers*) detected by molecular breast imaging.

Molecular Breast Imaging for Women With Dense Breast Tissue

Previously, when whole-breast ultrasound was used for supplementary screening in high-risk cohorts as part of the American College of Radiologic Imaging Network 6666 trial, an incremental cancer detection rate of 3.7‰ was reported [20]. In supplementary screening for dense breasts for general populations using ultrasound, an incremental cancer detection rate of 1.8–3.3‰ was reported [21–23]. However, the PPV for biopsy (PPV 3) of this approach ranges from 11% in the high-risk cohort to 5–6% in non-high-risk women with dense breasts. This trade-off between resource-intensive biopsy, which improves sensitivity but entails higher out-of-pocket expense for the individual, has been criticized in the

clinical community [24, 25]. Thus, our finding of an incremental cancer detection rate of 7.7‰ and PPV 3 of 19.4% shows that molecular breast imaging significantly improves the results of screening breast ultrasound.

Hruska et al. [35] from the Mayo Clinic reported that the use of molecular breast imaging to supplement mammography lowered the cost per cancer detected compared with mammography alone. Our findings for the incremental cancer detection rate (7.7‰), recall rate (8.4%), biopsy rate (3.7%), PPV 1 (9.1%), and PPV 3 (19.4%) broadly match the Mayo Clinic study results, which were incremental cancer detection rate over mammography of 8.8%, molecular breast imaging recall rate of

7.5%, biopsy rate of 3.2%, PPV 1 of 14.3%, and PPV 3 of 33.3% [34]. One caveat in this comparison is that the Mayo Clinic study was a controlled prospective study, whereas the current report is a retrospective analysis of our clinical experience.

Our study responds to the need for supplementary screening modality for women with dense breasts whose mammograms are difficult to interpret, and who may be at elevated risk for breast cancer, but who do not have a sufficient risk profile to qualify for reimbursed breast MRI. However, any discussion of a method requiring the systemic injection of radiotracers needs to address the issue of radiation exposure and weigh the potential

TABLE 4: Total Effective Radiation Dose for Different Tissues From Mammography and Molecular Breast Imaging

Modality, Tissue	ICRP 80 Tissue Dose (mGy)	ICRP 103 Weighting Factor	Effective Dose (mSv)	Contribution (%)
Mammography				
Breasts	4.6	0.1200	0.56	100
Total for 5.3 cm thickness compressed breast			0.56	
Molecular breast imaging				
Adrenal glands	1.91	0.0092	0.0177	1
Bladder	2.81	0.0400	0.1123	5
Bone surfaces	2.09	0.0100	0.0209	1
Brain	1.33	0.0100	0.0133	1
Breasts	0.97	0.1200	0.1164	5
Colon	6.13	0.1200	0.7353	32
Gallbladder	9.96	0.0092	0.0919	4
Heart wall	1.61	0.0092	0.0148	1
Kidneys	9.19	0.0092	0.0848	4
Liver	2.81	0.0400	0.1123	5
Lungs	1.17	0.1200	0.1409	6
Muscles	0.74	0.0092	0.0068	0
Esophagus	1.05	0.0400	0.0419	2
Ovaries	2.32	0.0800	0.1859	8
Pancreas	1.97	0.0092	0.0181	1
Red marrow	1.40	0.1200	0.1685	7
Remaining organs	1.00	0.0092	0.0092	0
Salivary glands	3.57	0.0100	0.0357	2
Skin	0.79	0.0100	0.0079	0
Small intestine	3.83	0.0092	0.0353	2
Spleen	1.66	0.0092	0.0153	1
Stomach	1.66	0.1200	0.1991	9
Thymus	1.05	0.0092	0.0097	0
Thyroid	2.02	0.0400	0.0807	4
Uterus and cervix	1.99	0.0092	0.0184	1
Total for 255 MBq (6.9 mCi) administered dose			2.2933	

Note—Doses were calculated using the International Commission on Radiological Protection (ICRP) report 80 [38] effective tissue doses and the ICRP report 103 [40] tissue-weighting factors for mammography and molecular breast imaging.

risks versus the benefits of early detection of cancer. It is well known that conventional mammography also exposes individuals to a very small radiation dose, but this risk is generally accepted as negligible compared with the benefit of early detection [33].

Comparison of radiation dose from a mammogram to that of a molecular breast imaging procedure is a source of ongoing confusion in the breast imaging community. The metric to compare radiation risks across different radiation imaging modalities is effective dose, which is measured in units of millisieverts. For mammography, the radiation dose is administered only to the breasts, with minimal scattered radiation surrounding the breast, and is typically reported in units of milligrays. To calculate the effective dose, this administered radiation dose in milligrays is multiplied by the International Committee on Radiation Protection (ICRP) Standard 103 (ICRP 103) [38] tissue-weighting factor of 0.012 for the breasts. The typical effective dose to the body is 0.56 mSv for average size breasts in digital mammography [33]. The typical effective dose to the body from tomosynthesis varies by manufacturer and imaging protocol but ranges from 0.5 to 1.2 mSv [39].

To calculate the effective dose to the body from ^{99m}Tc -sestamibi, we calculated the contributions of total effective dose from different tissues using the ICRP Standard 80 effective tissue doses. In this study, the prescribed dose of ^{99m}Tc -sestamibi was 300 MBq (8 mCi), but taking into account the residual dose in the syringe, the mean administered dose was 255 MBq (6.9 mCi). Using the ICRP 80 effective tissue doses and the ICRP 103 tissue-weighting factors [40], we calculated the total effective dose to the body as approximately 2.3 mSv (Table 4). The largest contributor to the effective dose was the colon at 32%, whereas the breast contributed only 5% to the total effective dose. Internal organs that contributed to the total effective dose were stomach (9%), ovaries (8%), red marrow (7%), lungs (6%), bladder (5%), liver (5%), gallbladder (4%), kidneys (4%), and thyroid (4%).

Although the effective dose to the body from molecular breast imaging (2.3 mSv) is four times the dose from digital mammography (0.56 mSv), it is still lower than the annual radiation exposure from natural sources in the United States, which is about 3 mSv, predominantly from radon gas escaping from granite rock underground [41]. This calculation also revealed that the effective dose for molecular breast imaging is only twice that of 2D or 3D mammography. Taking into consideration the policy statement from the American Association of Physicists in Medicine,

which advises that radiation risk is too low to be detected for imaging procedures where the effective dose is less than 50 mSv or 100 mSv for a single procedure or multiple procedures over a short time, respectively [42], we conclude that the risks associated with molecular breast imaging at these low administered radiation doses are acceptable in light of the benefit of early detection of breast cancer.

Weighing the need to minimize radiation exposure against the benefit of early breast cancer detection, we currently recommend annual screening with mammography and biannual supplementary screening with molecular breast imaging. Further studies, comparing interval cancer rates and breast cancer sizes between women who elect molecular breast imaging and those who do not, are needed to evaluate the appropriateness of this periodicity. The cost of the molecular breast imaging instrument is similar to that of a mammography instrument and has similar room requirements. The Current Procedural Terminology code under which this procedure is billed is 78801 ("Radiopharmaceutical localization of tumor, multiple areas") and is covered by Medicare [43]. In Ohio, most private insurance companies cover the procedure, provided that we have applied for prior authorization. Despite the low cost, low radiation dose, and other favorable factors compared with other tests, we estimate about 10% of women recommended for molecular breast imaging in this study underwent the procedure. This number is expected to rise as awareness of molecular breast imaging and breast density legislation increases, but further studies to investigate reasons for nonparticipation are warranted.

Our study has several limitations. This is a single-institution study, albeit community based, and the wider application of this technology may help to validate or modify our reported results. Selection bias may be present by those who accepted a molecular breast imaging study, and the availability of molecular breast imaging may have influenced the radiologist's decision to recommend it. As reported by other investigators [35], we depended on MRI to permit image-guided biopsies when the lesion could not be correlated to a sonographic finding because nuclear imaging-guided tissue sampling techniques for molecular breast imaging are not commercially available. The lack of 1-year follow-up information on a number of image sets (966 of 1696) precluded our ability to determine the total number of interval cancers and determine the absolute sensitivity and specificity of molecular breast imaging. Of these 966 image sets, 926 (96%) had negative mammogram and molecular breast imaging findings. Because the study

site is not only a screening site but is also a referral center for multiple screening sites within the integrated health care system, the incentive to return to this center for follow-up molecular breast imaging was likely lacking after a negative study, either by the referring center, the woman, or both. One-year follow-up information was available on 627 women who had negative molecular breast imaging assessments. Two malignancies, one of which was a DCIS, were discovered by mammography at their next annual screening, on days 356 and 357 after molecular breast imaging, and may be considered as interval cancers. Therefore, in this subset of data the negative predictive value for recall approximates 99.7% (625/627).

Tomosynthesis has shown reduced recall rates and improved cancer detection rates and may in the future replace 2D mammography [44]. Since our study period ended, the study site upgraded to 3D mammography (Genius 3D Mammography, Hologic) with the 2D images synthesized from the 3D projections (C-view) as the primary screening modality. The screening workflow remains the same as that described here in the Materials and Methods section, even after implementation of 3D mammography as the primary screening modality.

In summary, this study in a community-based mammography screening center shows that the use of molecular breast imaging detects additional cancers in women with dense breasts at an acceptable radiation exposure dose. Molecular breast imaging is well tolerated and provides an alternative to MRI for claustrophobic or obese persons. Molecular breast imaging is relatively easy to perform and interpret and is associated with low biopsy rates, thus overcoming some of the major limitations of screening ultrasound. As such, molecular breast imaging is a suitable supplementary screening modality for women with dense breast tissue.

Acknowledgments

We thank Stephen Wanjiku and Rochelle Keen for their help with the data analysis and Roberta E. Redfern for editorial assistance.

References

1. Shapiro S, Strax P, Venet L. Periodic breast cancer screening in reducing mortality from breast cancer. *JAMA* 1971; 215:1777-1785
2. Tabar L, Yen MF, Vitak B, Chen HH, Smith RA, Duffy SW. Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening. *Lancet* 2003; 361:1405-1410
3. Jonsson H, Nyström L, Törnberg S, Lenner P. Service screening with mammography of women

- aged 50–69 years in Sweden: effects on mortality from breast cancer. *J Med Screen* 2001; 8:152–160
4. Shapiro S, Venet W, Strax P, Venet L, Roeser R. Selection, follow-up, and analysis in the Health Insurance Plan Study: a randomized trial with breast cancer screening. *Natl Cancer Inst Monogr* 1985; 67:65–74
 5. Andersson I, Aspegren K, Janzon L, et al. Mammographic screening and mortality from breast cancer: the Malmö mammographic screening trial. *BMJ* 1988; 297:943–948
 6. Frisell J, Lidbrink E, Hellström L, Rutqvist LE. Followup after 11 years: update of mortality results in the Stockholm mammographic screening trial. *Breast Cancer Res Treat* 1997; 45:263–270
 7. Bjurström N, Bjørneld L, Duffy SW, et al. The Gothenburg breast screening trial: first results on mortality, incidence, and mode of detection for women ages 39–49 years at randomization. *Cancer* 1997; 80:2091–2099
 8. Alexander FE, Anderson TJ, Brown HK, et al. 14 years of follow-up from the Edinburgh randomised trial of breast-cancer screening. *Lancet* 1999; 353:1903–1908
 9. Miller AB, To T, Baines CJ, Wall C. The Canadian National Breast Screening Study: update on breast cancer mortality. *J Natl Cancer Inst Monogr* 1997; 22:37–41
 10. Tabár L, Vitak B, Chen TH, et al. Swedish two-county trial: impact of mammographic screening on breast cancer mortality during 3 decades. *Radiology* 2011; 260:658–663
 11. Pisano ED, Gatsonis C, Hendrick E, et al.; Digital Mammographic Imaging Screening Trial (DMIST) Investigators Group. Diagnostic performance of digital versus film mammography for breast-cancer screening. *N Engl J Med* 2005; 353:1773–1783
 12. Whitehead J, Carlisle T, Kopecky KJ, et al. Wolfe mammographic parenchymal patterns: a study of the masking hypothesis of Egan and Mosteller. *Cancer* 1985; 56:1280–1286
 13. van Gils CH, Otten JD, Verbeek AL, Hendriks JH. Mammographic breast density and risk of breast cancer: masking bias or causality? *Eur J Epidemiol* 1998; 14:315–320
 14. Sala E, Warren R, McCann J, Duffy S, Day N, Luben R. Mammographic parenchymal patterns and mode of detection: implications for the breast screening program. *J Med Screen* 1998; 5:207–212
 15. Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. *N Engl J Med* 2007; 356:227–236
 16. Sickles EA. The use of breast imaging to screen women at high risk for cancer. *Radiol Clin North Am* 2010; 48:859–878
 17. Lehman CD, Isaacs C, Schnall MD, et al. Cancer yield of mammography, MR, and US in high-risk women: prospective multi-institution breast cancer screening study. *Radiology* 2007; 244:381–388
 18. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin* 2007; 57:75–89
 19. Brem RF, Tabár L, Duffy SW, et al. Assessing improvement in detection of breast cancer with three-dimensional automated breast US in women with dense breast tissue: the SonoInsight study. *Radiology* 2015; 274:663–673
 20. Berg WA, Zhang Z, Lehrer D, et al.; ACRIN 6666 Investigators. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. *JAMA* 2012; 307:1394–1404
 21. Hooley RJ, Greenberg KL, Stackhouse RM, Geisel JL, Butler RS, Philpotts LE. Screening US in patients with mammographically dense breasts: initial experience with Connecticut Public Act 09-41. *Radiology* 2012; 265:59–69
 22. Weigert J, Steenbergen S. The Connecticut experiment: the role of ultrasound in the screening of women with dense breasts. *Breast J* 2012; 18:517–522
 23. Parris T, Wakefield D, Frimmer H. Real world performance of screening breast ultrasound following enactment of Connecticut Bill 458. *Breast J* 2013; 19:64–70
 24. Sprague BL, Stout NK, Schechter C, et al. Benefits, harms, and cost-effectiveness of supplemental ultrasonography screening for women with dense breasts. *Ann Intern Med* 2015; 162:157–166
 25. Gartlehner G, Thaler KJ, Chapman A, et al. Adjunct ultrasonography for breast cancer screening in women at average risk: a systematic review. *Int J Evid-Based Healthc* 2013; 11:87–93
 26. Khalkhali I, Cutrone JA, Mena IG, et al. Scintimammography: the complementary role of Tc-99m sestamibi prone breast imaging for the diagnosis of breast carcinoma. *Radiology* 1995; 196:421–426
 27. Maublant JC, Zhang Z, Rapp M, Ollier M, Michelot J, Veyre A. In vitro uptake of technetium-99m-tetboroxime in carcinoma cell lines and normal cells: comparison with technetium-99m-sestamibi and thallium-201. *J Nucl Med* 1993; 34:1949–1952
 28. Cordobes MD, Starzec A, Delmon-Moingeon L, et al. Technetium-99m-sestamibi uptake by human benign and malignant breast tumor cells: correlation with *mdr* gene expression. *J Nucl Med* 1996; 37:286–289
 29. Delmon-Moingeon LI, Piwnicka-Worms D, Van den Abbeele AD, Holman BL, Davison A, Jones AG, et al. Uptake of the cation hexakis(2-methoxyisobutylisocyanide)-technetium-99m by human carcinoma cell lines in vitro. *Cancer Res* 1990; 50:2198–2202
 30. Maublant J, de Latour M, Mestas D, et al. Technetium-99m-sestamibi uptake in breast tumor and associated lymph nodes. *J Nucl Med* 1996; 37:922–925
 31. Brem RF, Floerke AC, Rapelyea JA, Teal C, Kelly T, Mathur V. Breast-specific gamma imaging as an adjunct imaging modality for the diagnosis of breast cancer. *Radiology* 2008; 247:651–657
 32. Rhodes DJ, Hruska CB, Phillips SW, Whaley DH, O'Connor MK. Dedicated dual-head gamma imaging for breast cancer screening in women with mammographically dense breasts. *Radiology* 2011; 258:106–118
 33. Hendrick RE. Radiation doses and cancer risks from breast imaging studies. *Radiology* 2010; 257:246–253
 34. Rhodes DJ, Hruska CB, Connors AL, et al. Journal club: molecular breast imaging at reduced radiation dose for supplemental screening in mammographically dense breasts. *AJR* 2015; 204:241–251
 35. Hruska CB, Connors AL, Jones KN, et al. Diagnostic workup and costs of a single supplemental molecular breast imaging screen of mammographically dense breasts. *AJR* 2015; 204:1345–1353
 36. D'Orsi CJ, Bassett LW, Berg WA, et al. BI-RADS: mammography, 4th ed. In: D'Orsi CJ, Mendelson EB, Ikeda DM, et al. *Breast Imaging Reporting and Data System: ACR BI-RADS—breast imaging atlas*. Reston, VA: American College of Radiology, 2003
 37. Swanson TN, Troung DT, Paulsen A, Hruska CB, O'Connor MK. Adsorption of ^{99m}Tc-sestamibi onto plastic syringes: evaluation of factors affecting the degree of adsorption and their impact on clinical studies. *J Nucl Med Technol* 2013; 41:247–252
 38. International Commission on Radiological Protection. Radiation dose to patients from radiopharmaceuticals (addendum to ICRP publication 53); ICRP publication 80. *Ann ICRP* 1998; 28(3)
 39. Svahn TM, Houssami N, Sechopoulos I, Mattsson S. Review of radiation dose estimates in digital breast tomosynthesis relative to those in two-view full-field digital mammography. *Breast* 2015; 24:93–99
 40. International Commission on Radiological Protection. The 2007 recommendations of the International Commission on Radiological Protection: ICRP publication 103. *Ann ICRP* 2007; 37:1–332
 41. Moeller DW, Sun LS. Comparison of natural background dose rates for residents of the Amargosa Valley, NV, to those in Leadville, CO, and the states of Colorado and Nevada. *Health Phys* 2006; 91:338–353
 42. American Association of Physics in Medicine (AAPM). AAPM position statement on radiation risks from medical imaging procedures: policy number PP 25-A. AAPM website. www.aapm.org/org/policies/details.asp?id=318&type=PP. Published December 13, 2011. Accessed April 5, 2016
 43. American Medical Association. *CPT 2015: professional edition*. Chicago, IL: AMA, 2015
 44. Friedewald SM, Rafferty EA, Rose SL, et al. Breast cancer screening using tomosynthesis in combination with digital mammography. *JAMA* 2014; 311:2499–2507

FOR YOUR INFORMATION

This article is available for CME and Self-Assessment (SA-CME) credit that satisfies Part II requirements for maintenance of certification (MOC). To access the examination for this article, follow the prompts associated with the online version of the article.