Radiology

Dedicated Dual-Head Gamma Imaging for Breast Cancer Screening in Women with Mammographically Dense Breasts[1]

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Purpose: To compare performance characteristics of dedicated dual-head gamma imaging and mammography in screening women with mammographically dense breasts.

Materials and Methods: Asymptomatic women (n = 1007) who had heterogeneously or extremely dense breasts on prior mammograms and additional risk factors provided informed consent to enroll in an institutional review board–approved HIPAA-compliant protocol. Participants underwent mammography and gamma imaging after a 740-mBq (20-mCi) technetium 99m sestamibi injection. Reference standard (more severe cancer diagnosis or 12-month follow-up findings) was available for 936 of 969 eligible participants. Diagnostic yield, sensitivity, specificity, and positive predictive values (PPVs) were determined for mammography, gamma imaging, and both combined.

Results: Of 936 participants, 11 had cancer (one with mammography only, seven with gamma imaging only, two with both combined, and one with neither). Diagnostic yield was 3.2 per 1000 (95% confidence interval [CI]: 1.1, 9.3) for mammography, 9.6 per 1000 (95% CI: 5.1, 18.2) for gamma imaging, and 10.7 per 1000 (95% CI: 5.8, 19.6) for both (P = .016 vs mammography alone). One participant had a second ipsilateral cancer detected with gamma imaging only. Prevalent screening gamma imaging demonstrated equivalent specificity relative to incident screening mammography (93% [861 of 925] vs 91% [840 of 925], P = .069). Of eight cancers detected with gamma imaging only, six (75%) were invasive (median size, 1.1 cm; range, 0.4–5.1 cm); all were node negative. The ratio of the number of patients with breast cancer per number of screening examinations with abnormal findings was 3% (three of 88) for mammography and 12% (nine of 73) for gamma imaging (P = .01). The number of breast cancers diagnosed per number of biopsies performed was 18% (three of 17) for mammography and 28% (10 of 36) for gamma imaging (P = .36).

Conclusion: Addition of gamma imaging to mammography significantly increased detection of node-negative breast cancer in dense breasts by 7.5 per 1000 women screened (95% CI: 3.6, 15.4). To be clinically important, gamma imaging will need to show equivalent performance at decreased radiation doses.

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Across nine randomized trials, screening mammography has been shown to reduce mortality from breast cancer by 15%–32% (1). Absolute mortality reduction correlates with the magnitude of reduction in cancers that have spread to axillary lymph nodes at the time of diagnosis (2). Methods that depict node-negative cancers not detected with mammography should further improve mortality reduction, though this capability has not yet been shown.

The sensitivity of mammography is reduced in dense breasts (ie, those described as heterogeneously dense or extremely dense) (3). Estimates of mammographic sensitivity in women with extremely dense breasts range from 30% to 63% (4–11). The diagnosis of cancer during the interval between screening examinations is increasingly likely in women with dense breast tissue (odds ratio, 17.8 for interval cancer among women with ≥75% breast density compared with women with <10% breast density; 95% confidence interval [CI]: 4.8, 65.9) (12). Interval cancers are associated with a worse prognosis relative to screening-detected cancers. It is likely that a proportion of interval cancers are mammographically occult but present at the time of the last screening, and early detection of these cancers by other methods may have a survival benefit.

The combination of whole-breast screening ultrasonography (US) and mammography in women with dense breasts and elevated risk of breast cancer yielded a sensitivity of 77.5% versus 50% for either modality alone (13). However, the addition of US substantially increased false-positive findings, and the positive predictive value (PPV) of biopsy recommendation after US was less than 10%. Breast magnetic resonance (MR) imaging is superior to US and mammography in terms of sensitivity, but the relatively low specificity, complexity of interpretation, contraindications (eg, claustrophobia and implanted devices), and high cost are substantial disadvantages (14,15). To our knowledge, there have been no comparative trials of mammography and MR imaging limited to women with dense breasts and there is currently insufficient evidence for supplemental screening with MR imaging for this indication alone (16). The limitations of these modalities underscore the need for a screening method with both high sensitivity and reasonable cost for women with mammographically dense breasts.

Mammographic detection of breast cancer depends on the visual distinction of normal breast structures from tumor, a distinction that may be obscured by surrounding dense parenchyma. In contrast, nuclear medicine techniques exploit functional differences between tumor and normal cells that result in different levels of radiotracer uptake and are independent of the surrounding parenchymal density (17). The development of gamma cameras uniquely configured for breast imaging has yielded improved detection of small tumors (18,19). While studies (20–28) evaluating gamma technology for breast imaging have primarily focused on diagnostic applications, investigators in two studies in small numbers of patients (29,30) have suggested a promising role in breast cancer screening.

We reported the sensitivity of a dedicated dual-head gamma camera system to be greater than 90% for the detection of small breast tumors (25). Researchers (20,21,27,31) who have studied a number of other dedicated nuclear medicine–based techniques, including positron emission mammography, breast specific gamma imaging, and various other dedicated technologies under investigation, also reported high sensitivities for detection of small breast tumors. In our work to date, we have referred to the use of dedicated cadmium zinc telluride (CZT)-based detectors in a dual-head configuration as molecular breast imaging to distinguish this functional imaging method from anatomically based techniques, such as mammography. It

Advances in Knowledge

- Addition of dedicated dual-head gamma imaging with ^{99m}Tc-sestamibi to screening mammography increased the absolute sensitivity for breast cancer detection from 27% with mammography alone to 91% with the combination of imaging tests (P = .016).
- The number of patients with breast cancer per number of screening examinations with abnormal findings (PPV_1) was 3% for mammography and 12% for gamma imaging (P = .01).
- Addition of gamma imaging to mammography significantly increased the detection of node-negative breast cancer in dense breasts by 7.5 per 1000 women screened (95% confidence interval: 3.6, 15.4).

Implications for Patient Care

- Findings in this proof-of-principle study demonstrate the effectiveness of dedicated dual-head gamma imaging as a supplemental screening tool in women with mammographically dense breasts.
- To be of clinical importance for screening, dedicated dual-head gamma imaging will need to show equivalent performance at decreased radiation doses.

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Abbreviations:
BI-RADS = Breast Imaging Reporting and Data System
CI = confidence interval
CZT = cadmium zinc telluride
DCIS = ductal carcinoma in situ
IDC = invasive ductal carcinoma
ILC = invasive lobular carcinoma
PPV = positive predictive value
PPV_1 = ratio of the number of patients with breast cancer per number of screening examinations with abnormal findings
PPV_3 = number of breast cancers diagnosed per number of biopsies performed

Author contributions:
Guarantors of integrity of entire study, D.J.R., C.B.H., S.W.P., M.K.O.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, D.J.R., C.B.H., S.W.P., M.K.O.; clinical studies, all authors; statistical analysis, D.J.R., C.B.H.; and manuscript editing, all authors

Potential conflicts of interest are listed at the end of this article.

is also important to differentiate this semiconductor-based technology from the scintillating crystal detector of commercially available breast-specific gamma imaging units. CZT detector technology offers substantial advantages over the traditional scintillating detectors in terms of intrinsic spatial and energy resolution. The CZT-based dual-head dedicated gamma camera technology is now commercially available, and administration of the radiotracer is Food and Drug Administration approved.

The purpose of this study was to prospectively and independently compare performance characteristics of dedicated dual-head gamma imaging and mammography in screening women with mammographically dense breasts.

Materials and Methods

Study Population

Women with heterogeneously or extremely dense breasts, characterized as such on the basis of findings on the most recent prior mammogram, who were 25 years old and older and were undergoing routine screening mammography were enrolled in an institutional review board–approved, Health Insurance Portability and Accountability Act–compliant protocol. We also allowed women younger than 50 years who had not undergone prior mammography to enroll, as most of such women have dense breasts (32,33). To increase the likelihood of cancer in the study population and power the study to detect significant differences in diagnostic performance, we required subjects to have at least one of the risk factors listed in Table 1. Pregnant and lactating women were excluded. Women who had undergone breast surgery in the prior 12 months or needle biopsy in the prior 3 months were excluded, as were those taking tamoxifen citrate (Nolvadex; AstraZeneca, Wilmington, Del), raloxifene (Evista; Eli Lilly, Indianapolis, Ind), or an aromatase inhibitor.

Imaging Procedures and Interpretation

At least two-view gamma imaging was performed by using one of two dual-head systems (Fig 1) that were mounted on a modified mammographic gantry. Each system comprised two opposing 20 × 20-cm CZT-based detectors (Prototype CZT, GE Medical Systems, Haifa, Israel; LumaGem, Gamma Medica-Ideas, Northridge, Calif) that were previously described (25,34). Patients received a single intravenous injection of 740 MBq (20 mCi) of the radiopharmaceutical technetium Tc 99m (^{99m}Tc) sestamibi (Cardiolite; DuPont Merck, Wilmington, Del), and imaging commenced 5 minutes after injection. Each breast was imaged in both craniocaudal and mediolateral oblique positions for 10 minutes per view by using light compression to limit patient motion. Nuclear medicine technologists were trained in breast positioning.

Two-view mammography was performed by Mammography Quality Standards Act–certified technologists by using either screen-film (Lorad M-IV; Hologic, Bedford, Mass) or digital (Selenia; Hologic) mammography. Mayo Clinic was in the process of transitioning from screen-film mammography units to digital mammography units during the course of this study. At the start of the study in 2005, most participants underwent screen-film mammography. By April 2008, all participants underwent digital mammography. The determination of whether patients underwent screen-film or digital mammography was entirely independent of their participation in this study.

Women were enrolled prior to undergoing screen-film or digital

Figure 1

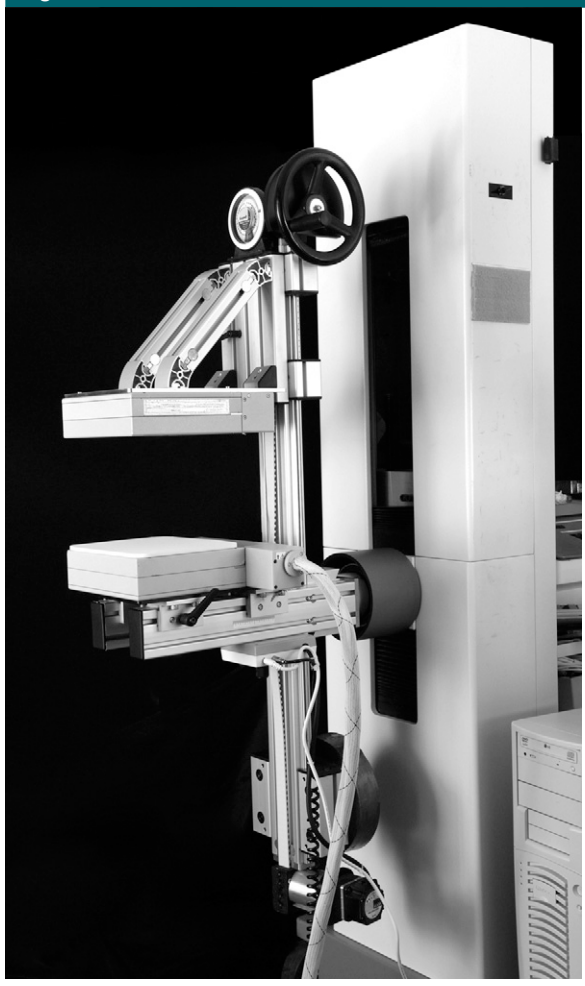


Figure 1: Dedicated dual-head gamma imaging system comprising two CZT-based gamma cameras mounted on a modified mammographic gantry. The breast is positioned between the two detector heads and lightly compressed.

Table 1

Participant Characteristics

Characteristic	Eligible Women (*n* = 969)	Analysis Set (*n* = 936)*
Mean age at enrollment (y)†	55.5 (25–89)	55.7 (25–89)
Race or ethnicity		
White	860 (89)	828 (88)
Hispanic or Latina	1 (0)	1 (0)
Black or African American	1 (0.1)	1 (0)
Native Hawaiian or other Pacific Islander	0	0
Asian	6 (1)	6 (1)
American Indian or Alaskan native	1 (0)	1 (0)
Unknown or data missing	100 (10)	99 (11)
Menopausal status		
Premenopausal	324 (33)	309 (33)
Perimenopausal	65 (7)	61 (7)
Postmenopausal	529 (55)	517 (55)
Surgical menopause	51 (5)	50 (5)
Mammographic breast density‡		
Almost entirely fat	7 (1)	7 (1)
Scattered fibroglandular densities	129 (13)	127 (14)
Heterogeneously dense	702 (72)	679 (73)
Extremely dense	131 (14)	123 (13)
Risk factors§		
Known mutation in *BRCA1* or *BRCA2* gene	5 (1)	5 (1)
History of chest, mediastinal, or axillary irradiation‖	1 (0)	1 (0)
Personal history of breast cancer	73 (8)	67 (7)
History of prior biopsy showing atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ, or atypical papilloma	23 (2)	22 (2)
Gail or Claus model lifetime risk ≥20%	165 (17)	156 (17)
Gail model 5-y risk ≥2.5%	297 (31)	287 (31)
Gail model 5-y risk ≥1.6%	238 (25)	232 (25)
One first-degree relative with history of breast cancer	82 (8)	81 (9)
Two second-degree relatives with history of breast cancer	85 (9)	85 (9)
Screening mammography type		
Screen-film	264 (27)	259 (28)
Digital	705 (73)	677 (72)
Time mammogram obtained before study entry		
<425 d	694 (72)	676 (72)
425–730 d	198 (20)	189 (20)
>730 d	69 (7)	63 (7)
None obtained#	5 (1)	5 (1)
Unknown or data missing	3 (0)	3 (0)

Note.—Unless otherwise specified, data are numbers of patients. Numbers in parentheses are percentages, and percentages were rounded.

* The analysis set includes participants in whom both initial screening mammographic and gamma imaging studies were completed and cancer status was verified.

† Numbers in parentheses are ranges.

‡ Eligibility was determined by density assessed on a previous mammogram prior to study entry; mammographic density reported in this table refers to density assessed from the study mammogram.

§ Although participants may have qualified for multiple risk factor categories, they were assigned to only one risk factor category in this table. These risk factors are listed in order of priority. The last two risk factors with respect to first- and second-degree relatives with a history of breast cancer refer to subjects who qualified on the basis of family history but did not meet the Gail or Claus model risk threshold levels.

‖ Chest, mediastinal, or axillary irradiation was received prior to age 30 years and at least 8 years prior to study enrollment.

A total of five women younger than 50 years old with no prior mammogram were enrolled, and all had heterogeneously dense breasts on the mammogram obtained at the time of the study.

mammography to exclude selection bias. Dedicated dual-head gamma imaging was performed within 21 days of mammography, and gamma images were independently interpreted, with blinding to mammographic results. All biopsies were performed after screening mammography and gamma imaging were completed.

Figure 2

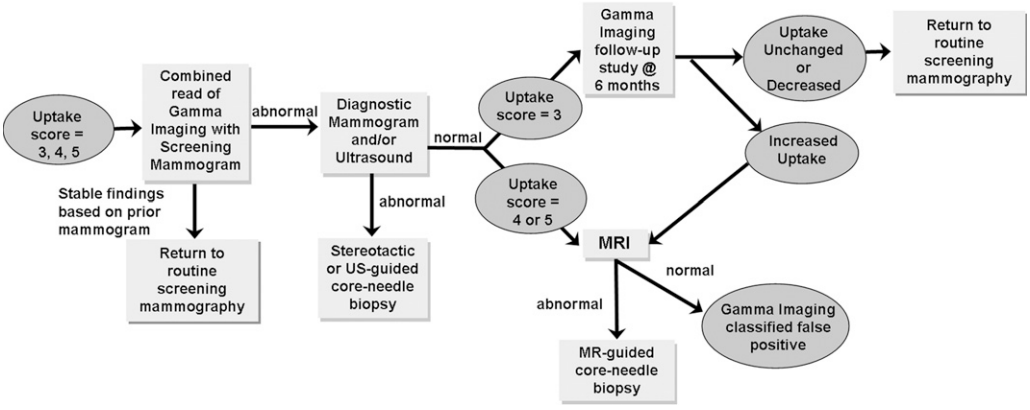


Figure 2: Diagnostic evaluation algorithm for gamma imaging uptake scores of 3–5.

All screening mammograms were performed and interpreted at Mayo Clinic (Rochester, Minn) by dedicated breast radiologists in the course of routine clinical practice. Radiologists who interpreted the screening mammograms were blinded to study participation and gamma imaging results, had standard access to relevant clinical information and prior mammograms, and used standard Breast Imaging Reporting and Data System (BI-RADS) terminology (3). BI-RADS assessments and linked recommendations for mammography were as follows: category 1, negative results, routine screening; category 2, benign, routine screening; category 3, probably benign, 6-month follow-up; category 4, suspicious, consider biopsy; category 5, highly suggestive of malignancy, take appropriate action; and category 0, incomplete, additional imaging recommended (diagnostic mammography, US and/or MR imaging). An assessment of category 0, 4, or 5 was considered to indicate a test with positive results. Percentage of density on the current mammogram was visually assessed as fatty replaced (<25%), scattered fibroglandular densities (25%–50%), heterogeneously dense (51%–75%), or extremely dense (>75%).

Review of gamma images was performed by either of two Mayo Clinic dedicated breast radiologists (S.W.P. and D.H.W., with experience in interpreting images in more than 100 studies) who were blinded to the screening mammographic interpretation and all other ancillary clinical information. Images were examined for the presence of abnormal tracer uptake and assigned a score by using an uptake score on a scale of 1–5, as follows: score 1, no abnormal uptake; score 2, benign, normal physiologic uptake; score 3, indeterminate uptake; score 4, uptake suspicious for malignancy; and score 5, uptake highly suspicious for malignancy. Uptake scores of 3, 4, or 5 were considered to indicate a test with positive results, and scores of 1 or 2 were considered to indicate a test with negative results. This five-point uptake scale differed from BI-RADS categories in that a mammogram with an assessment of BI-RADS category of 3 was considered to be negative because it does not lead to immediate diagnostic evaluation, whereas a gamma image with an uptake score of 3 (indeterminate uptake) was defined a priori as positive because it triggered a combination read of gamma images and mammograms, which in turn was used to guide additional diagnostic evaluation. A combination read was performed only for gamma imaging studies with uptake scores of 3–5. Figure 2 provides the algorithm that was used for diagnostic evaluation in patients with positive gamma images.

Determination of Reference Standard

Cancer status was verified as disease positive on the basis of any histopathologic diagnosis of invasive breast cancer or ductal carcinoma in situ (DCIS) within 365 days of initial study mammographic imaging. Similar to other breast imaging trials, a negative cancer status verification was targeted for 365 days as determined with negative or benign findings at imaging at least 330 days after initial study mammography, with benign histopathologic findings, or with medical record review or patient interview confirming no breast cancer diagnosis (10,13).

The final histopathologic findings in each lesion were determined from the most severe of surgical excision or core needle biopsy results. All malignancies and atypical lesions were excised. Lesions that were detected by using gamma imaging but not by using other modalities, and therefore those for which a patient did not undergo biopsy, were classified as false-positive results if further diagnostic imaging and/or clinical findings at 365-day follow-up revealed no cancer.

Statistical Analysis

Diagnostic yield (ie, the proportion of women with positive results of a screening test and positive results with the reference standard), sensitivity, specificity, recall rate, and positive predictive values (PPVs) were calculated in patients with verified cancer status. Recall rate was defined as the percentage of patients recalled for follow-up studies initiated because of abnormal findings with mammography or gamma

Figure 3

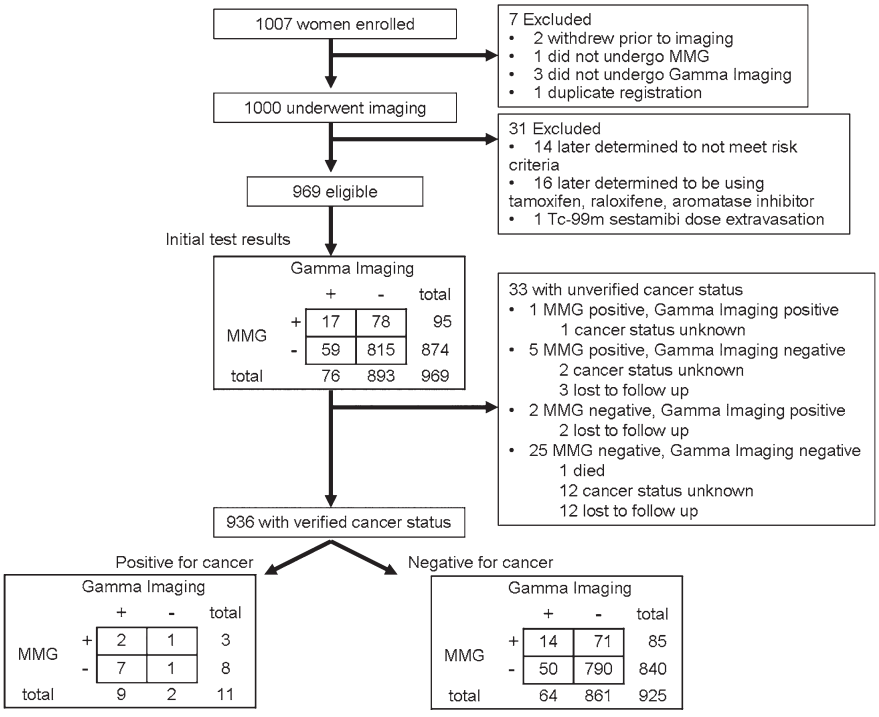


Figure 3: Protocol flowchart. *MMG* = mammography.

imaging. PPVs were calculated as the ratios of the number of patients with breast cancer per number of screening examinations with abnormal findings (PPV_1) and the number of breast cancers diagnosed per number of biopsies performed (PPV_3). The McNemar test for correlated proportions was used to assess significance for sensitivity, specificity, and recall rate. *P* values for the PPV were calculated by using methods described by Moskowitz and Pepe (35). All *P* values were reported as two sided. $P < .05$ was set as the threshold value for a significant difference, and CIs were reported at the 95% level. Exact 95% CIs were calculated by using the Wilson method without continuity correction (36).

Reader Variability

Images from a subset of 96 gamma imaging studies, comprising all studies with breast lesions (11 with breast cancer, three with atypia, 26 with benign lesions) and images from 56 randomly selected studies without breast lesions were used for reader variability analysis. Of the images from 96 studies, 49 were originally interpreted by one author (S.W.P.) and 47 were originally interpreted by another author (D.H.W.). Both radiologists were blinded for the interpretation of images from the entire subset of 96 studies after a period greater than 6 months following the original interpretation to allow calculation of interreader and intrareader variability. The Cohen unweighted κ statistic was calculated to assess the proportion of interreader and intrareader agreement expected beyond chance, where κ of 1 corresponds to perfect agreement and κ of 0 indicates agreement expected by chance alone (37). Landis and Koch (38) suggested that κ values of less than 0.20 indicate slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, almost perfect agreement. The variability analysis was performed by using five distinct uptake score categories of 1–5 that were previously described and by using three combined categories of 1 or 2; 3; and 4 or 5.

Results

Of 1007 women enrolled between September 2005 and February 2009, 969 completed imaging and met eligibility criteria (Fig 3); of 969 eligible participants, 33 (3%) were excluded because of lack of the reference standard. The final analysis set comprised 936 participants with verified cancer status: Cancer status was verified by using negative or benign findings on a subsequent annual mammogram in 898 (96%), positive pathologic findings in 11 (1%), negative pathologic findings in prophylactic mastectomy specimens in five (0%), negative pathologic findings at core biopsy in three (0%), patient interview in 15 (2%), and negative clinical examination findings in four (0%). Of the 898 patients with cancer status verified by using findings on a subsequent annual mammogram, 23 (3%) returned earlier than the 365-day target, six (1%) returned between 330 and 344 days, and 17 (2%) returned between 345 and 364 days after gamma imaging.

Of 936 women, 802 (86%) had heterogeneously dense or extremely dense breasts on a study mammogram; because study entry was based on the density on the prior rather than on the current mammogram, women whose current mammogram was not considered to show dense breasts were included.

Table 2 summarizes the main outcome measures of diagnostic yield, sensitivity, specificity, recall rate, and PPV for mammography and dedicated dual-head gamma imaging.

Of 936 participants, 11 had cancer: In one patient, cancer was detected only with mammography; in seven patients, cancer was detected only with gamma imaging; in two patients, cancer was detected with both modalities; and in one patient, cancer was not detected with either modality (Tables 3, 4). Diagnostic yield was 3.2 per 1000 (95% CI: 1.1, 9.4) for mammography and 9.6 per 1000 (95% CI: 5.1, 18.2) for gamma imaging ($P = .07$, mammography vs gamma imaging). Diagnostic yield was

Table 2

Diagnostic Performance Characteristics of Screening Mammography and Gamma Imaging at the Participant Level in 936 Women

Characteristic	Mammography		Gamma Imaging		Combination of Both		*P* Value	
	No. of Patients	95% CIs	No. of Patients	95% CIs	No. of Patients	95% CIs	Mammography vs Gamma Imaging	Mammography vs Both
Diagnostic yield*	3/936 (3.2)	1.1, 9.4	9/936 (9.6)	5.1, 18.2	10/936 (10.7)	5.8, 19.6	.07	.016†
Sensitivity								
All cancers	3/11 (27)	9.7, 56.6	9/11 (82)	52.3, 94.9	10/11 (91)	62.3, 98.4	.07	.016†
Invasive cancers	2/7 (29)	8.2, 64.1	7/7 (100)	64.6, 1.0	7/7 (100)	64.6, 1.0	.063	.063
DCIS	1/4 (25)	4.6, 69.9	2/4 (50)	15.0, 85.0	3/4 (75)	30.0, 95.4	>.99	.5
Specificity	840/925 (91)	88.8, 92.5	861/925 (93)	91.3, 94.5	788/925 (85)	82.8, 87.3	.069	<.001†
Recall rate	88/936 (9)	7.7, 11.4	71/936 (8)	6.1, 9.5	143/936 (15)	13.1, 17.7	.218	<.001†
PPV_1	3/88 (3)	1.2, 9.6	9/73 (12)	6.6, 21.8	11/145 (8)	4.3, 13.1	.01†	.158
PPV_3‡	3/17 (18)	6.2, 41	10/36 (28)	15.9, 44	11/45 (24)	14.2, 38.7	.36	.516

Note.—Unless otherwise specified, numbers in parentheses are percentages, and percentages were rounded.

* Proportions in parentheses are per 1000 women screened.

† Significant difference ($P \leq .05$).

‡ PPV_3 was calculated by using the number of biopsies performed as the denominator.

10.7 per 1000 (95% CI: 5.8, 19.6) for mammography and gamma imaging combined ($P = .016$), with a supplemental yield of 7.5 per 1000 women screened (95% CI: 3.6, 15.4). One participant had a second ipsilateral cancer that was detected with gamma imaging only.

Ten of 12 cancers were detected with gamma imaging, and three were detected with mammography. Eight cancers were detected with gamma imaging only and not with mammography, as follows: DCIS, two; invasive ductal carcinoma (IDC), three; invasive lobular carcinoma (ILC), two; and tubulolobular carcinoma, one. Axillary lymph nodes were negative for metastatic carcinoma in five of seven patients with invasive cancer and in all patients with invasive cancers detected with gamma imaging and not with mammography. Examples of these cancers are in Figures E1–E3 (online).

The median size of the largest invasive cancer per participant was 11 mm (range, 4–51 mm; mean, 20 mm). The median size of the six invasive cancers detected by using gamma imaging only was 11 mm (range, 4–51 mm; mean, 16 mm). The largest invasive cancer detected by using gamma imaging but not by using mammography was a 51-mm ILC. The cancer that was detected by using mammography only and not by using gamma imaging manifested as microcalcifications involving a tumor size less than 5 mm, with a histopathologic finding of DCIS. Two cancers were detected by using both modalities: one 13-mm IDC and one 34-mm IDC. One tumor was undetected by using both mammography and gamma imaging: The patient with this tumor had DCIS involving the entire breast, which was interpreted as BI-RADS category 3 (probably benign) with screening digital mammography, US, and MR imaging performed at the time of the gamma imaging study but was later detected at 6-month follow-up diagnostic mammography.

At the participant level, sensitivity of mammography was 27% (three of 11), and sensitivity of dedicated dual-head gamma imaging was 82% (nine of 11), with $P = .07$. The sensitivity of

Table 3

Summary of Cancers Detected at 365 Days Following Study Entry as a Function of Participant Characteristics

Characteristic	All Cancers*	Detected with Mammography Only	Detected with Gamma Imaging Only	Detected with Both	Undetected with Both†
Total no. of cancers	12	1	8	2	1
Menopausal status					
Premenopausal	3	0	2	0	1
Perimenopausal	2	0	1	1	0
Postmenopausal	5	1	4	0	0
Surgical menopause	2	0	1	1	0
Breast density					
Almost entirely fat	0	0	0	0	0
Scattered fibroglandular densities	1	0	1	0	0
Heterogeneously dense	7	1	5	1	0
Extremely dense	4	0	2	1	1
Risk factors					
Known mutation in *BRCA1* or *BRCA2* gene	1	0	1	0	0
History of chest, mediastinal, or axillary irradiation	0	0	0	0	0
Personal history of breast cancer	1	1	0	0	0
Atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ, or atypical papilloma	0	0	0	0	0
Gail or Claus model lifetime risk ≥20%	1	0	0	0	1
Gail model 5-year risk ≥2.5%	3	0	3	0	0
Gail model 5-year risk ≥1.6%	5	0	4	1	0
One first-degree relative with history of breast cancer	0	0	0	0	0
Two second-degree relatives with history of breast cancer	1	0	0	1	0
Screening mammography type					
Screen-film	4	1	2	1	0
Digital	8	0	6	1	1
Time mammogram obtained before study entry					
<425 days	8	1	5	1	1
425–730 days	2	0	2	0	0
>730 days	2	0	1	1	0
None obtained	0	0	0	0	0
Unknown or data missing	0	0	0	0	0

* A total of 12 cancers were detected in 11 patients. In one patient with two tumors, one was detected with gamma imaging only and one was detected with both mammography and gamma imaging.

† Cancer was detected at 6-month follow-up diagnostic mammography performed 184 days following study entry.

mammography and gamma imaging combined was 91% (10 of 11), with $P = .016$ for the combination versus mammography alone. If we had defined a finding on the screening digital mammogram of BI-RADS category 3 as indicative of a positive result, the combined sensitivity of mammography and gamma imaging would be 100% (11 of 11), compared with the sensitivity of mammography alone, which was 36% (four of 11), with $P = .016$. Gamma imaging was more sensitive to invasive cancer than was mammography (seven of seven versus two of seven), with $P = .063$ (Fig 4).

Four of 936 (0%) patients were diagnosed with atypical lesions. Two participants had atypical ductal hyperplasia detected with mammography only, and one participant had atypical ductal hyperplasia detected with gamma imaging only. One atypical papilloma was found with gamma imaging only. There were no upgrades to malignancy at excision.

Thirty-seven benign lesions in 35 patients were detected: five with mammography only, 22 with gamma imaging only, six with both modalities, and four with either subsequent US or MR imaging. Three of the benign lesions did not warrant biopsy because of previous confirmation at biopsy. The 28 false-positive lesions detected with gamma imaging comprised 10 fibroadenomas, five papillomas, two cases of stromal fibrosis, one case of pseudoangiomatous hyperplasia, one case of focal inflammation, and nine areas of benign breast tissue.

Of patients with verified cancer status, 143 were recalled for additional diagnostic studies because of abnormal findings: Of 936 patients, 72 (8%) were recalled because of abnormal findings with mammography only, 55 (6%) were recalled because of abnormal findings with gamma imaging only, and 16 (2%) were recalled because of abnormal findings with both modalities. The total recall rates for mammography and gamma

Table 4

Summary of 12 Cancers Identified in 11 Study Participants at 365 Days Following Study Entry

Patient No.	Histopathologic Finding*	Tumor Size (cm)	Age (y)	TNM Staging	Breast Density	Gamma Imaging†		Mammography		
						Tracer Uptake Score	Result	BI-RADS Score	Result‡	Type
1§										
Lesion a	IDC, grade II	2.0	49	T1cN1M0	Extremely dense	5	Positive	0	Positive	Screen-film
Lesion b	IDC, grade II	1.3	49	T1cN1M0	Extremely dense	5	Positive	1	Negative	Screen-film
2	DCIS, low grade	0.8	50	TisN0M0	Heterogeneously dense	3	Positive	2	Negative	Screen-film
3	ILC, grade I	1.1	75	T1cN0M0	Extremely dense	3	Positive	1	Negative	Digital
4	DCIS, intermediate grade‖	All quadrants	49	TisN0M0	Extremely dense	2	Negative	3	Negative	Digital
5	IDC, grade I	0.7	69	T1bN0M0	Heterogeneously dense	5	Positive	1	Negative	Digital
6	IDC, grade III	3.4	55	T2N1M0	Heterogeneously dense	5	Positive	0	Positive	Digital
7	DCIS, high grade	Microcalcifications, <0.5-cm area	61	TisN0M0	Heterogeneously dense	1	Negative	4	Positive	Screen-film
8	IDC, grade I, extensive DCIS, intermediate grade	0.4 for IDC, 1.9 for DCIS	74	T1aN0M0	Scattered fibroglandular densities	5	Positive	1	Negative	Digital
9	Tubulolobular carcinoma, grade I	1.0	69	T1bN0M0	Heterogeneously dense	5	Positive	1	Negative	Digital
10	DCIS, high grade	1.2	50	TisN0M0	Heterogeneously dense	5	Positive	1	Negative	Digital
11	ILC, grade I	5.1	45	T3N0M0	Heterogeneously dense	4	Positive	1	Negative	Digital

* Histopathologic findings were classified according to reference 39.

† Gamma imaging results were considered negative for tracer uptake scores of 1 and 2 and positive for tracer uptake scores of 3–5.

‡ Screening mammogram was negative for BI-RADS scores of 1–3 and positive for BI-RADS scores of 0, 4, and 5.

§ In patient 1, lesions a and b were both detected in the same breast.

‖ Cancer was detected on the basis of findings on the 6-month follow-up diagnostic mammogram obtained 184 days following study entry.

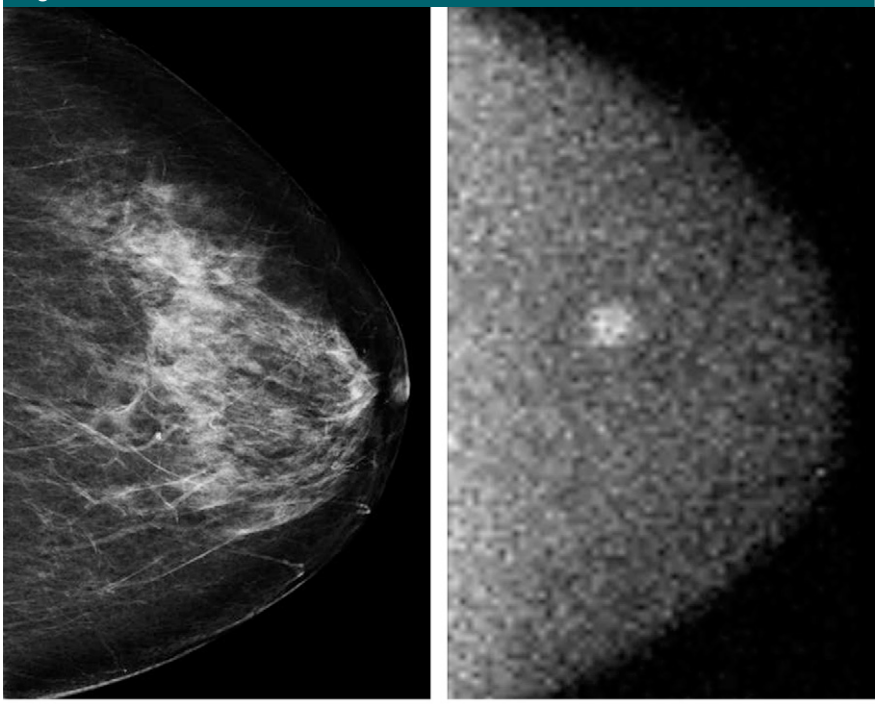
imaging were 9% (88 of 936) and 8% (71 of 936), respectively ($P = .218$). PPV_1 for mammography and gamma imaging was 3% (three of 88) and 12% (nine of 73), respectively ($P = .01$).

Of 88 patients recalled because of abnormal screening mammographic findings, recommendations included diagnostic or extra mammographic views in 83, directed US in 50, MR imaging in five, and biopsy in 17. Gamma imaging was positive in 73 patients, which triggered a combination read with screening mammography. Of these 73, in two, interpretation was resolved through review of the current screening mammogram, and in 71, patients were recalled for additional diagnostic evaluation, which included diagnostic or extra mammographic views in 66, directed US in 69, MR imaging in 13, biopsy in 36, and 6-month follow-up gamma imaging in 25.

Biopsies were performed in 50 lesions in 45 patients, yielding 12 cancers, four atypical lesions, and 34 benign results. Nine biopsies in 1% (nine of 936) of patients were prompted by mammography only, resulting in one cancer, two atypical lesions, and six benign lesions. Twenty-eight biopsies in 3% (28 of 936) of patients were prompted by findings with gamma imaging only, resulting in detection of eight cancers, two atypical lesions, and 18 benign lesions. Eight biopsies in 1% (eight of 936) of patients were prompted by both mammographic and gamma imaging findings, resulting in detection of two cancers and six benign lesions. Five biopsies in 1% (five of 936) of patients were prompted by other imaging or clinical findings, resulting in detection of one cancer and four benign lesions.

Three of 17 (18%) biopsies prompted by mammographic findings yielded a cancer diagnosis, and 10 of 36 (28%) biopsies prompted by gamma imaging findings yielded a cancer diagnosis ($P = .36$). The 17 mammographic finding–prompted biopsies were performed with either a stereotactic ($n = 9$) or US-guided ($n = 8$) core biopsy technique. The 36 gamma imaging finding–prompted biopsies were performed by using a stereotactic ($n = 1$), US-guided ($n = 31$),

Figure 4



a. b.

Figure 4: Images in 69-year-old woman with a 1.0 × 0.8 × 0.8-cm tubulolobular carcinoma in the left breast. **(a)** Negative digital screening mammogram. **(b)** Gamma image demonstrated focal tracer uptake in the tumor.

or MR imaging–guided (n = 3) core biopsy technique, and in one patient, an excisional biopsy was performed.

Of participants without cancer, 840 of 925 (specificity, 91%) had true-negative findings with mammography, and 861 of 925 (specificity, 93%) had true-negative findings with gamma imaging (P = .069). The specificity of mammography and gamma imaging combined was significantly less than that for mammography alone: With the combination of both tests, 788 participants had true-negative findings ($P < .001$).

When uptake categories of 1–5 were used, moderate agreement was observed between ($\kappa = 0.52$) and within ($\kappa = 0.56$) readers. Use of the three combined categories resulted in substantial agreement, with interreader agreement of $\kappa = 0.62$ and intrareader agreement of $\kappa = 0.66$.

Discussion

We compared mammography and dedicated dual-head gamma imaging as screening methods for breast cancer in women with dense breasts. Mammography and gamma imaging combined was significantly more sensitive than was mammography alone in the detection of cancer (91% vs 27%, P = .016). The specificity of gamma imaging and mammography was similar (93% and 91%, respectively), although the specificity of gamma imaging and mammography combined was significantly lower than that of mammography alone ($P < .001$). Screening mammograms were read in the context of available clinical background and comparison with current and prior breast imaging studies, whereas this was a prevalent screening for gamma imaging, in which images were read without the benefit of any other imaging or clinical information. As has been seen with mammography and MR imaging, the specificity of gamma imaging would likely increase with annual incidence screening when results of prior studies would be available for review (40).

The PPV of a screening examination with abnormal findings (PPV_1) was significantly higher for gamma imaging compared with mammography (12% vs 3%, P = .01). Although the recall rates for mammography and gamma imaging did not differ significantly, there was a trend toward a lower recall rate for gamma imaging. Although findings at gamma imaging prompted more biopsies than did those at mammography, the PPV of gamma imaging finding–prompted biopsies (PPV_3) was higher than was the PPV of mammographic finding–prompted biopsies, although this difference did not reach significance.

Dedicated dual-head gamma imaging compares very favorably with other modalities in the screening of women with dense breasts. In a subgroup analysis of the Digital Mammography Imaging Screening Trial, digital mammography demonstrated improved sensitivity to screen-film mammography only in the subgroup of women younger than 50 years old who had dense breasts and who were of pre- or perimenopausal status; however, even in this subgroup, the sensitivity was below 60% (10,41).

Our study population was similar to that in the American College of Radiology Imaging Network National Breast Ultrasound Trial (13). Although we did not compare gamma imaging directly with US in our study, the sensitivity, PPV, and supplemental diagnostic yield reported in our study are higher than those reported for US.

The sensitivity of screening mammography is lower in our study compared with the sensitivity in the American College of Radiology Imaging Network National Breast Ultrasound Trial or to the Digital Mammography Imaging Screening Trial despite the fact that 73% of subjects in our study underwent digital mammography. However, the sensitivity of mammography in our study is comparable to the sensitivity of mammography in the prospective high-risk MR imaging screening trials (16). In five of the six studies, the sensitivity of mammography was 40% or lower, whereas the sensitivity of screening MR imaging ranged from 77% to 94% (16,42). Note that table 2 in the Saslow et al study (16) erroneously reports a

sensitivity of 100% for MR imaging in the Sardanelli study (42), which was listed as in press at the time the Saslow et al study was published, whereas the actual sensitivity from the published Sardanelli et al study is 94%. We hypothesize that the low sensitivity of mammography in our study and the MR imaging studies relates to the detection of small cancers by using gamma imaging and MR imaging that would have remained undetected by using digital mammography, whole-breast screening US, or clinical examination even at 1-year follow-up. Thus, these small cancers might not have been captured in sensitivity analyses of studies that relied on US and/or digital mammography as the reference standard for detection.

A current disadvantage of the technology evaluated in this study is the lack of direct biopsy capability. Of the 28 patients with lesions identified with gamma imaging that were occult at screening mammography, most were localized at diagnostic mammography and/or US, but three required MR imaging for localization. Biopsy capabilities have been developed for breast-specific gamma imaging and are under development for the dedicated dual-head gamma camera used in this study.

In the American Cancer Society guidelines for breast screening with MR imaging as an adjunct to mammography, it was concluded that data were insufficient to recommend screening MR imaging in women with extremely dense breasts, although results of studies pertaining to the evaluation of MR imaging in women with breast cancer and mammographically dense breasts suggest that density does not affect sensitivity (16,43–46). The results in our study and in other studies indicate that the sensitivity of gamma imaging is not reduced in women with dense breasts (17,25,30). Dense parenchyma is the factor most closely associated with failure to detect breast cancer by using mammography (4). Given that approximately one-half of women younger than the age of 50 years and one-third of women 50 years and older have mammographically dense breasts, the number of women at risk for mammographically occult cancer is substantial (32,33).

Administration of ^{99m}Tc-sestamibi is Food and Drug Administration approved for diagnostic breast imaging. The dose of 740 MBq (20 mCi) used in this study is approximately one-third that used in routine nuclear medicine cardiac studies but is high relative to that delivered by a mammogram. In a screening setting, annual administration of 740 MBq (20 mCi) ^{99m}Tc-sestamibi would pose a substantially higher cumulative radiation risk than would mammography. The effective (whole-body) dose from 740 MBq (20 mCi) ^{99m}Tc-sestamibi is approximately 6.5 mSv. By comparison, the radiation dose to the breast from a screening mammogram translates to an effective dose of 0.7–1.0 mSv. An advantage of dual-head CZT-based gamma imaging is the capability to improve technical aspects of the system to reduce administered radiation dose. Since the completion of the study, we optimized the gamma detector collimators, improved use of the CZT energy spectra, and introduced noise reduction algorithms that have allowed a reduction in the administered dose to approximately 148 MBq (4 mCi), yielding an effective dose of less than 1.3 mSv, which is comparable to that with screening mammography (47,48). While further study is needed to validate low-dose dedicated dual-head gamma imaging in a large screening study, this study demonstrates proof of principle of the effectiveness of gamma imaging in the screening setting.

Our study had several limitations. First, subjects were not randomized as to order of imaging studies. However, consents were obtained from all participants prior to imaging, and all images were interpreted by radiologists who were blinded to the results of the other imaging study, so it is unlikely that any bias was introduced. Second, the results may not be generalizable to women without the increased risk inclusion criterion or to other breast imaging centers. Third, because our institution was in the process of transitioning from screen-film to digital mammography during the course of this trial, approximately one-quarter of the participants had undergone screen-film mammography. Of eight patients with cancers that were not detected with mammography, seven underwent digital mammography. Fourth, because inclusion in the study was based on the breast density on the past prior mammogram, 14% (134 of 936) of subjects in the analysis set had nondense breasts at the time the study mammogram was obtained. If inclusion of these subjects introduced any bias, it would likely be in favor of mammography, as the sensitivity of mammography is higher in nondense versus dense breasts (4–11). Finally, our follow-up was limited in 3% of cases to less than 1 year for imaging and relied on patient interview for verification in 2% of cases. This could have decreased our false-negative rate.

Gamma imaging has the capability to depict small, node-negative breast cancers that are not detected with mammography; however, we have not demonstrated that this capability translates into a mortality reduction, an end point that would require years and considerable resources to investigate. We have relied on the surrogate end point of tumor size. The median size of supplemental tumors detected by using gamma imaging only was 11 mm. Investigators in numerous studies have demonstrated that tumor size correlates with mortality, with size less than 20 mm conferring a survival advantage (49–51). The association between lethality and tumor size is strongest in women with lymph node–negative cancer (52). In this series, all cancers detected by using gamma imaging only were node-negative.

Although mammography added little increased diagnostic yield to gamma imaging in this study, we consider gamma imaging as an adjunct rather than as an alternative to screening mammography, given that mammography remains the only screening modality for which an associated reduction in breast cancer mortality has been demonstrated. In addition, we do not yet have sufficient data to determine the sensitivity of gamma imaging for DCIS detection in a screening setting. Further studies are needed to see whether gamma imaging

could replace screening mammography in certain populations or whether the two modalities could be alternated synergistically.

The addition of dedicated dual-head gamma imaging to screening mammography yielded significantly improved sensitivity while maintaining equivalent specificity in women with mammographically dense breasts. With the implementation of radiation dose reduction techniques, gamma imaging may offer an effective supplemental imaging technique to the subgroups of women in whom the sensitivity of mammography is limited.

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