Breast-specific gamma imaging for the detection of mammographically occult breast cancer in women at increased risk

Rachel F. Brem, Rachel C. Ruda, Jialu L. Yang, Caitrín M. Coffey, Jocelyn A. Rapelyea

Authors:

Rachel F. Brem, MD*
Phone: 202-741-3003
Fax: 202-741-3029
rbrem@mfa.gwu.edu

Rachel C. Ruda, BA
Phone: 202-741-2244
Fax: 202-741-3011
rruda@mfa.gwu.edu

Jialu L. Yang, BS
Phone: 202-741-3012
Fax: 202-741-3011
lyang@mfa.gwu.edu

Caitrín M. Coffey, BS
Phone: 202-741-2244
Fax: 202-741-3011
cmc233@gwu.edu

Jocelyn A. Rapelyea, MD
Phone: 202-741-3033
Fax: 202-741-3019
jrapelyea@mfa.gwu.edu

* Corresponding Author, First Author
Word Count: 4,434

Address for all authors: The George Washington University Medical Faculty Associates
2300 M Street NW, 8th Floor, Washington, DC 20037

Funding: No funding was provided for this endeavor.

Disclosures: Rachel Brem, MD is on the Board of Managers of and has stock in Dilon Technologies. All other authors have nothing to disclose.

Note: This research was approved by the GWU Institutional Review Board.

Running Title: BSGI Detection of Breast Cancer
Breast-specific gamma imaging for the detection of mammographically occult breast cancer in women at increased risk

Breast-specific gamma imaging (BSGI) is a physiologic imaging modality that can detect sub-centimeter and mammographically occult breast cancer, with comparable sensitivity and specificity to MRI. The purpose of this study is to determine the incremental increase in breast cancer detection when BSGI is used as an adjunct to mammography in women at increased risk for breast cancer.

METHODS: All patients undergoing BSGI from April 2010 through January 2014 were retrospectively reviewed. Eligible patients were identified as women at increased risk for breast cancer and whose most recent mammogram was benign. Examinations exhibiting focally increased radiotracer uptake were considered positive. Incremental increase in cancer detection was calculated as the percentage of mammographically occult BSGI-detected breast cancer and the number of mammographically occult breast cancers detected per 1,000 women screened.

RESULTS: 849 patients were included in which 14 BSGI exams detected mammographically occult breast cancer. Patients ranged in age from 26 to 83, with a mean age of 57 years. 11/14 cancers were detected in women with dense breasts. The addition of BSGI to the annual breast screen of asymptomatic women at increased risk for breast cancer yields 16.5 cancers per 1,000 women screened. When combining high-risk lesions and cancers, BSGI detected 33.0 high-risk lesions and cancers per 1,000 women screened.

CONCLUSION: BSGI is a reliable adjunct modality to screening mammography that increases breast cancer detection by 1.7% (14/849) in women at increased risk for breast cancer,
comparable to results reported for breast MRI. BSGI is beneficial in breast cancer detection in women at increased risk, particularly those with dense breasts.

**Keywords:** breast-specific gamma imaging; breast cancer; scintimammography; molecular breast imaging
INTRODUCTION

Breast cancer is the second most common cancer in American women (1). X-ray mammography (XRM) remains the standard of breast cancer screening and is an effective imaging tool that reduces mortality from breast cancer (2). However, it is an imperfect tool with an overall reported sensitivity of 85%, which decreases to 68% in women with dense breasts (3-4). In prospective trials among women at high risk for breast cancer due to a familial or genetic predisposition, mammography demonstrated a 30-40% sensitivity (5). Due to the limitations of mammography, supplemental imaging modalities, including Magnetic Resonance Imaging (MRI), whole breast screening ultrasound, and Breast Specific Gamma Imaging (BSGI), are becoming increasingly important for women at increased risk with the goal of detecting early stage breast cancer.

Breast MRI is a physiologic imaging modality recommended as a supplemental screening tool to mammography for high-risk women (≥20-25% lifetime risk) (6). MRI has demonstrated an incremental detection rate of 9.5 cancers per 1000 high-risk women screened (7), and variable sensitivity and specificity ranging from 71-92% and 54-86%, respectively (8-10). However, MRI is costly, time-consuming for radiologists to interpret, poorly tolerated by some patients due to claustrophobia, and inaccessible to patients who are obese, have implanted devices, or have renal insufficiency. Whole breast ultrasound has also been studied as a supplemental screening tool, improving sensitivity from 50% to 77.5% when used with mammography (11). It has been shown to yield an additional 1.9-3.25 detected cancers per 1000 women screened compared to screening mammography alone (12-14). However, the use of whole breast ultrasound is correlated with a higher callback and false-positive biopsy rate (15).
Like MRI, BSGI is a physiologic imaging tool used to detect breast cancer. BSGI has demonstrated a sensitivity of 92-96% and a specificity of 71-80% (8, 16-17), and has been shown to reliably detect mammographically occult breast cancers (18). BSGI uses a radiotracer, technetium 99m ($^{99m}$Tc) sestamibi, to identify physiological differences between malignant and normal breast tissue. $^{99m}$Tc sestamibi gamma imaging, when utilized with mammography for breast cancer screening in women at increased risk and with dense breasts, significantly improves the sensitivity and positive predictive value (PPV), as well as increases the number of breast cancers detected by 7.5-8.8 per 1,000 women (19-20). Furthermore, BSGI has been shown to detect additional foci of mammographically occult breast cancer in 9% of women with newly diagnosed breast cancer (21). A comprehensive meta-analysis of relevant studies from 1984-2012 concluded that BSGI detected mammographically occult cancer in 4% of patients with benign mammograms, and additional cancers in 6% of those with abnormal mammograms or new biopsy-proven breast cancer (17). A preliminary review of a population of high-risk women with benign mammographic imaging (n=94) found that this modality was able to detect small (<1 cm), mammographically occult lesions in women at increased risk for breast cancer (22).

To date, no large-scale studies have been published examining the clinical utility of BSGI in women at increased risk for breast cancer. The purpose of this study is to determine the incremental increase in breast cancer detection when using BSGI in addition to mammography for women at increased risk of developing breast cancer.

**MATERIALS AND METHODS**

*Study Population*

This study was approved by the Institutional Review Board and is Health Insurance Portability and Accountability Act compliant. All results and data were obtained retrospectively.
from patients’ medical records with waived patient consent. All women who had a BSGI examination from April 2010 through January 2014 were retrospectively reviewed. Patients were included who were determined to be at increased risk for breast cancer and whose most recent screening or diagnostic mammogram was negative or probably benign (BI-RADS 1, 2, or 3). Women were identified as being at increased risk if they had one or more of the following risk factors: a personal history of breast cancer, a known mutation in the BRCA1 or BRCA2 gene, a family history of breast cancer in at least one first-degree or two second-degree relatives, a history of axillary or mediastinal irradiation, or a personal history of an atypical high-risk lesion, including atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), lobular carcinoma in situ (LCIS), papilloma, flat epithelial atypia (FEA), or radial scar.

Patients were excluded who were symptomatic, had newly diagnosed breast cancer, had breast surgery or biopsy up to one month prior to the BSGI, as the effects of post-biopsy or post-surgical changes have not yet been established, or whose most recent mammogram was abnormal. Patients whose most recent mammogram was abnormal or incomplete, but whose follow-up with ultrasound, MRI, or biopsy was negative or benign were included as there was documentation that the mammographic abnormality was not due to cancer, provided that the biopsy was three or more months prior to the BSGI. For patients who routinely received MRI for high-risk screening, their most recent mammogram or MRI must have been negative or probably benign to qualify for inclusion. Patients undergoing treatment for breast cancer at the time of their BSGI were not included, although patients on chemopreventative such as tamoxifen, were included.

Breast Density
Breast density was determined by the patient’s most recent mammography report prior to BSGI. Breast density reported as fatty replaced or scattered fibroglandular tissue (BI-RADS a or b) were classified as non-dense, and density reported as heterogeneously dense or extremely dense (BI-RADS c or d) were classified as dense (23).

BSGI

All BSGI examinations were performed with a single head, high resolution breast specific gamma camera (6800; Dilon Technologies, Newport News, VA). Patients were imaged in a seated position. Patients were injected in the dorsal venous complex of the hand or antecubital vein with radiotracer and imaging began immediately after injection of the radiotracer. Initially a mean of 21.1 mCi or 781 MBq (high-dose; range 16.0-32.1mCi or 592-1188 MBq) technetium 99m sestamibi (Miraluma; Radiology Services of Northern Virginia, Herndon, VA) was used (n=653). However, in November 2012 the protocol was modified to use a mean of 8.0 mCi or 296 MBq (low-dose; range 7.0-13.5 mCi or 259-500 MBq) of radiotracer (n=196). Images were obtained in the craniocaudal (CC) and mediolateral oblique (MLO) views for a minimum of 100,000 counts per image, with imaging beginning immediately after injection of the radiotracer isotope. Average acquisition time for each image ranged from 6 to 10 minutes for a total imaging time of approximately 40 minutes per study.

The initial CC and MLO images were reviewed and additional views were obtained as deemed necessary by the interpreting radiologist. No additional radiotracer injection was used for additional imaging.

Interpretation of BSGI

All BSGI examinations were reviewed by three board-certified radiologists with a range of 6-20 years of experience in BSGI interpretation. Images were read with access to patient
history and adjunct imaging studies. Examinations were not reinterpreted for the purposes of this study. BSGI examinations with no focally-increased radiotracer uptake, scattered heterogeneous uptake, or stable uptake compared to previous benign BSGI were classified as normal, while those with an area of focally-increased radiotracer uptake were classified as abnormal. Images were assigned a score of 0-5, paralleling the BI-RADs assessment categories at the time of interpretation (23). Scores of 1, 2, or 3 were classified as a negative BSGI exam, and scores of 0, 4, or 5, were classified as positive for purposes of analysis (24). See Figure 1.

Data Collection and Analysis

Risk factors for breast cancer, age, race, menopausal status, breast density as noted in the patient’s most recent mammogram report, BSGI results including specific location of any areas of abnormal radiotracer uptake, and final pathology either from the minimally invasive biopsy or surgical excision were recorded for each patient. The data were analyzed to determine the number of asymptomatic women with mammographically occult BSGI-detected breast cancer. Incremental increase in breast cancer detection was calculated using Microsoft Excel as the number of women who had breast cancer detected on BSGI of all women studied. PPV₁ was calculated as the number of malignancies per all abnormal BSGI exams, and PPV₃ was calculated as the number of malignancies per all biopsies performed. Statistical significance of the difference in cancer detection rate between both high-dose and low-dose and dense and nondense subgroups of the population was performed using Chi-squared tests calculated by SPSS Statistics. All p-values were reported as two sided. P < 0.05 was set as the threshold value for a significant difference. The data were further analyzed with Microsoft Excel for positive predictive values. For the reference standard either pathologic results of biopsy or follow-up imaging within one year that did not demonstrate evidence of malignancy were used.
RESULTS

A total of 1,723 women had BSGI exams between April 2010 and January 2014. Of these, 849 patients (49.3%) were at increased risk with benign prior mammograms and were included in this study. Patients ranged in age from 26 to 83, with a mean age of 57 years.

Risk Factors

Among the 849 patients at increased risk who had BSGI exams, 230 (27.0%) had a family history of breast cancer and 430 (50.6%) had a personal history of breast cancer. Fifty-four (6.3%) had a personal history of an atypical, high-risk lesion. Two of 849 patients had a known mutation in BRCA 1 or 2 (0.2%); one was BRCA1+, and one was BRCA2+. There were 133 of 849 patients (15.6%) with two or more of these risk factors and four of 849 (0.5%) patients with three of these risk factors.

Of the 849 patients at increased risk, 212 (25.0%) had positive BSGI exams, demonstrating focally-increased radiotracer uptake. Of the patients with BSGI-positive results, 67 (31.6%) had a family history of breast cancer and 89 (42.0%) had a personal history of breast cancer, and 20 (9.4%) had a personal history of an atypical, high-risk lesion. Neither of the patients with BRCA gene mutations had abnormal BSGI exams. Thirty-six of 212 patients (17.0%) had two or more of these risk factors, and no patients with BSGI-positive exams had three risk factors.

Fourteen BSGI-positive patients were found to have mammographically occult, BSGI detected breast cancer. One of 14 (7.14%) had a family history of breast cancer, seven of 14 (50.0%) had a personal history of breast cancer, and two of 14 (14.3%) had a history of atypia. Four of 14 patients (28.6%) had two or more of these risk factors. See Table 1.

Additional Imaging
Of the 849 patients at increased risk who had BSGI examinations, 637 (75.0%) were negative, stable, or likely benign (scores of 1, 2, or 3), with no focally-increased uptake, scattered heterogeneous uptake, or stable uptake.

Two hundred and twelve of the 849 BSGI exams were positive (scores of 0 or 4). Among those with positive examinations, 110 of 212 (51.9%) positive exams were found to be benign through additional imaging: directed ultrasound was negative in 83 patients, directed second-look mammography was negative in 10 patients demonstrating either stable fibroadenoma, stable intramammary lymph nodes or stable benign calcifications, breast MRI was negative in 16 patients, and repeat BSGI at a different time in the patient’s menstrual cycle was negative in one patient. Additionally, one woman with a personal history of breast cancer in the contralateral breast underwent prophylactic mastectomy, which demonstrated benign fibrocystic findings. All patients with negative additional imaging were confirmed benign by mammographic, sonographic, or MRI imaging follow-up (one year following abnormal BSGI).

Additional imaging was abnormal in 99 of 212 (46.7%) of the patients with BSGI-positive exams and was unavailable for two patients with positive BSGI exams (1.4%). Ninety-seven of the 212 BSGI-positive patients (45.7%) underwent biopsies: ultrasound-guided biopsy in 43, fine-needle aspiration in 19, stereotactic biopsy in seven subsequent to directed second-look mammography, BSGI-guided biopsy in 10\(^i\), MRI-guided biopsy in 16, and surgical excisional biopsy in two patients. Two BSGI-positive patients with abnormal additional imaging did not undergo biopsy at our facility and their pathological reports were not available.

Benign Biopsy Results

\(^i\) BSGI-guided biopsy has been offered in our imaging facility since May 2011.
Biopsy due to BSGI findings was benign in 66/97 patients (68.0%). Benign findings included fibrocystic changes (n=45), benign breast tissue (n=8), fibroadenoma (n=6), and cyst contents (n=7). Three of the patients who underwent biopsy with fine needle aspiration resulted in samples that were insufficient for diagnosis; two of these patients received follow-up imaging revealing benign findings, ruling out the need for repeat biopsy, and one patient underwent a follow-up BSGI-guided biopsy yielding benign pathology.

Benign high-risk lesions were found in 14/97 (14.4%) of biopsied lesions: atypical ductal hyperplasia (ADH) (n=3), atypical lobular hyperplasia (ALH) (n=2), lobular carcinoma in situ (LCIS) (n=3), radial scar (n=1), flat epithelial atypia (FEA) (n=1), and papillary lesion (n=4). All high-risk lesions were subsequently surgically excised. This study finds that BSGI detects 16.5 high-risk lesions for every 1,000 patients at increased risk screened for breast cancer.

Malignant Biopsy Results

Of 849 patients at increased risk, BSGI detected fourteen (1.7%) mammographically occult breast cancers, with a PPV1 of 6.7% (14/212) and a PPV3 of 14.4% (14/97). Eleven of the 14 cancers (11.3%) were diagnosed at initial biopsy; three high-risk lesions (one radial scar, two ADH) upgraded at surgical excision to DCIS (see Table 2). The other cancers detected were five IDC, one ILC, and eight DCIS (see Figure 2). Invasive breast cancers ranged in size from 0.3 - 4.0 cm (see Table 3). Biopsy was performed under ultrasound guidance in eight of the 14 BSGI-detected cancers, MRI guidance (2/14), BSGI guidance (2/14), and surgical excision (2/14). This study finds that BSGI detects 16.5 mammographically occult cancers for every 1,000 patients at increased risk screened for breast cancer.

When combining high-risk lesions and cancers, BSGI detects an additional 33.0 cancers and high-risk lesions for every 1,000 patients screened at increased risk for breast cancer.
**High-Dose vs. Low-Dose BSGI Injections**

Comparing the results of patients who received low-dose versus high-dose BSGI injections, low-dose exams yielded 2 cancers of 196 exams, with a PPV$_1$ and PPV$_3$ of 3.9% (2/51) and 10.5% (2/19) respectively, while high-dose exams yielded 12 cancers of 653 exams, with a PPV$_1$ and PPV$_3$ of 7.4% (12/161) and 15.4% (12/78) respectively. BSGI detected 18.4 and 10.2 mammographically occult cancers for every 1,000 patients screened among patients receiving high and low doses of injections, respectively. Analysis of the difference in cancer detection rate between low-dose and high-dose BSGI exams yielded Chi-squared value of 0.62, which was not statistically significant (95% CI=0.12-2.48, $p=0.44$).

**Breast Tissue Density**

Of the 849 patients at increased risk, 302 patients (35.6%) had non-dense breast tissue; 64 patients had fatty replaced breast tissue (BI-RADS a) and 238 had scattered fibroglandular breast tissue (BI-RADS b). Three of 14 breast cancers were detected in women with non-dense breast tissue (21.4%). Among women with non-dense breasts, BSGI detected a mammographically occult breast cancer in three of 302 patients (1.0%), or 9.9 cancers per 1,000 women screened. Five hundred and forty-seven patients (64.4%) had dense breast tissue; 445 patients with heterogeneously dense breast tissue (BI-RADS c) and 102 patients with extremely dense tissue (BI-RADS d). Eleven of 14 breast cancers detected by BSGI in the study occurred in women with dense breast tissue (78.6%). Among women with dense breasts, BSGI detected a mammographically occult breast cancer in 11 of 547 patients (2.0%), or 20.1 cancers per 1,000 women screened (see Table 4). Analysis of the difference in cancer detection rate in women with dense and non-dense breast tissue yielded a Chi-squared value of 1.24 (95% CI=0.14-1.77, $p=0.28$), which was not statistically significant. This is similar to data previously published that
BSGI demonstrates no difference in detecting cancers in women with dense and non-dense breasts (25).

**DISCUSSION**

In this retrospective review of 849 patients at increased risk for breast cancer with benign mammograms, 212 (25.0%) had positive BSGI exams. This recall rate falls within the range of previously reported BSGI recall rates in women with benign mammograms (22, 26). BSGI detected an additional 14 mammographically occult breast cancers (1.7%), or 16.5 cancers per 1,000 women screened. This is comparable to prior reports for MRI detection of occult cancer in high-risk populations of 9.5 cancers per 1000 women screened (7). Among women with personal histories of atypia including LCIS and ADH, incremental detection rates using MRI range from 1.6% - 4.5% (27-29).

Our findings suggest that the addition of BSGI can improve the ability to detect breast cancer in women at increased risk compared to mammography alone. Eleven of 14 (78.6%) mammographically occult cancers were detected in patients with heterogeneous or extremely dense breast tissue (BI-RADS c or d). This supports existing data which has demonstrated that unlike mammography, the detection of breast cancer with BSGI is not impacted by breast density (25).

Among the 14 mammographically occult, BSGI-detected cancers found in this study, eight were DCIS (57.1%), and six were invasive carcinomas (42.9%) ranging in size from 0.3cm to 4.0cm (Table 3). Due to the high sensitivity of BSGI in detecting both invasive and noninvasive cancers, BSGI is a valuable supplemental imaging tool to mammography in detecting breast cancer in women at increased risk.

*BI-RADS 3 Interval Imaging*
Patients were included in this study whose most recent mammogram was negative or probably benign (BI-RADS 1, 2, or 3). Thirty patients with BSGI+ exams received BI-RADS 3 diagnoses on their mammogram reports. Patients with BI-RADS 3 scores were indicated for six-month interval screening for reasons including post-surgical changes, asymmetry, and calcifications. Of these 30 patients, three were subsequently diagnosed with atypia, and three were diagnosed with cancer. As patients with BI-RADS 3 mammogram scores are recommended for various interval screening options (mammogram, ultrasound, MRI, BSGI) depending on their histories and diagnoses, these data suggest that BSGI is a viable interval screening option for women at increased risk for the earlier detection of breast cancer.

**BSGI vs. MRI**

Surveillance of patients at a higher risk for the development of breast cancer can also be achieved via screening MRI as an adjunct modality to mammography. However, MRI is more expensive, requires more interpretation time, is poorly tolerated by some patients due to severe claustrophobia, and is inaccessible to patients with renal insufficiency, implanted devices, or large body habitus. Nevertheless, MRI has advantages, including the absence of radiation and greater availability.

Studies have demonstrated that BSGI and MRI have similar sensitivity and specificity in breast cancer detection. MRI has been shown to have a sensitivity of 71%-99% and a specificity of 54%-95% (8-10). BSGI detects breast cancer with a sensitivity of 92-96% and a specificity of 71-80% (7, 16-17). In a study comparing DCIS detection using BSGI, MRI, and mammography, sensitivity for detecting DCIS was found to be slightly higher with BSGI (91%) than with MRI (88%) or mammography (82%) (30-31).
Studies have shown a similar incremental increase in breast cancer detection among high-risk women with MRI and BSGI: 9.5 cancers per 1,000 women screened with MRI and 7.5-8.8 cancers per 1,000 women with BSGI (7, 19, 20). Our study demonstrates that BSGI detects occult breast cancer in women at increased risk at a rate of 16.5 cancers detected per 1,000 women screened, higher than the rate reported for both MRI and screening ultrasound in women at increased risk for breast cancer (32). However, this difference may be due to a smaller sample size in our study. Additional larger studies are needed to further assess the incremental cancer detection rate with BSGI in women at increased risk.

Risk from Radiation

The primary disadvantage of BSGI is the radiation exposure. However, when used as an adjunct in increased risk populations, this is a reasonable imaging option. One study showed that a dose of 300 MBq or 8.1 mCi was sufficient in the detection of breast cancer using BSGI, and further studies are being conducted to reduce the dose of radiotracer needed without compromising image quality (20, 33). In this study population, a dose of 20-30 mCi 99mTC sestamibi was originally used, which was reduced to 7-10 mCi 99mTC sestamibi partway through the study. The differences in PPV and incremental cancer detection between high and low doses were not statistically significant. In women who cannot or will not undergo MRI, the availability of BSGI gives women the option of physiologic imaging.

Treatment and Outcome of Atypical, High-Risk Lesions

Of the patients in this study with positive BSGI exams, 35/212 (16.5%) had personal histories of atypical, high-risk lesions. Of the patients diagnosed with cancer, four of 14 (28.6%) had a history of atypia. In this study, the upgrade rate from atypical lesions to cancer due to a finding on BSGI was 21.4% (3/14). This is comparable to existing data demonstrating upgrade
rates of 20-23% for MRI-detected atypia (34-35). These findings suggest that surgical excision should be recommended for all atypical, high-risk lesions found on BSGI. Additional studies are needed to determine the optimal management of BSGI-detected high-risk lesions.

Limitations

Limitations of this study include an absence of long-term follow-up to determine false-negative BSGI studies or subsequent malignant findings in the two instances in which the patient declined a biopsy. Additionally, this is a retrospective study, and the time intervals between mammograms and BSGI exams are varied. Furthermore, the change in radiotracer dose during the study period may have impacted findings. However, the difference in incremental increase in cancer detection between the high- and low-dose groups was not statistically significant.

CONCLUSION

This study demonstrates that BSGI detects mammographically occult breast cancer in 1.7% of women at increased risk of breast cancer with negative mammograms, or 16.5 additional cancers per 1,000 women screened in this population. It further finds that the use of BSGI detects a combined 33.0 high-risk lesions and cancers per 1,000 women screened. The detection of mammographically occult breast cancer was greater in women with dense breasts, but BSGI also detected additional cancers in women with non-dense breast tissue. Furthermore, this study suggests that high-risk women with BI-RADS 3 mammograms may benefit from BSGI in the earlier detection of breast cancer.

This study supports the use of breast-specific gamma imaging as a supplemental modality to mammography in women at increased risk for breast cancer, particularly for those with dense breast tissue or in whom MRI cannot be performed.
References


FIGURE 1. Positive versus Negative BSGI Imaging.
(a) Positive BSGI in right CC and MLO views exhibiting an area of focally-increased radiotracer uptake
(b) Negative BSGI in right CC and MLO views exhibiting no areas of focally-increased radiotracer uptake
FIGURE 2. BSGI exam outcomes.
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Increased-risk Population (n=849)</th>
<th>BSGI+ Population (n=212)</th>
<th>Malignant Population (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family History</td>
<td>230 (27.1%)</td>
<td>67 (31.6%)</td>
<td>7 (50.0%)</td>
</tr>
<tr>
<td>Personal History</td>
<td>430 (50.7%)</td>
<td>89 (41.9%)</td>
<td>1 (7.1%)</td>
</tr>
<tr>
<td>Atypia</td>
<td>54 (6.4%)</td>
<td>20 (9.4%)</td>
<td>2 (14.3%)</td>
</tr>
<tr>
<td>BRCA1/2</td>
<td>2 (0.2%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Family+Personal History</td>
<td>83 (9.8%)</td>
<td>19 (9.0%)</td>
<td>1 (7.1%)</td>
</tr>
<tr>
<td>Family History+Atypia</td>
<td>28 (3.3%)</td>
<td>13 (6.1%)</td>
<td>2 (14.3%)</td>
</tr>
<tr>
<td>Personal History+Atypia</td>
<td>10 (1.2%)</td>
<td>2 (0.9%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Family History+BRCA1/2</td>
<td>6 (0.7%)</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Personal History+BRCA1/2</td>
<td>2 (0.2%)</td>
<td>1 (0.5%)</td>
<td>1 (7.1%)</td>
</tr>
<tr>
<td>3+ Risk Factors</td>
<td>4 (0.5%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>
**TABLE 2. Biopsy Results (n=97*)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign Pathology (n=66)</strong></td>
<td></td>
</tr>
<tr>
<td>Benign breast tissue</td>
<td>8</td>
</tr>
<tr>
<td>Cyst contents</td>
<td>7</td>
</tr>
<tr>
<td>Fibrocystic changes</td>
<td>45</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>6</td>
</tr>
<tr>
<td><strong>Benign High-Risk Pathology (n=14)</strong></td>
<td></td>
</tr>
<tr>
<td>ADH</td>
<td>3</td>
</tr>
<tr>
<td>LN</td>
<td>5</td>
</tr>
<tr>
<td>FEA</td>
<td>1</td>
</tr>
<tr>
<td>Papilloma</td>
<td>4</td>
</tr>
<tr>
<td>Radial Scar</td>
<td>1</td>
</tr>
<tr>
<td><strong>Malignant Pathology (n=14)</strong></td>
<td></td>
</tr>
<tr>
<td>DCIS</td>
<td>8</td>
</tr>
<tr>
<td>IDC</td>
<td>5</td>
</tr>
<tr>
<td>ILC</td>
<td>1</td>
</tr>
</tbody>
</table>

* 3 patients had samples insufficient for diagnosis.
<table>
<thead>
<tr>
<th>Type</th>
<th>Grade</th>
<th>Size</th>
<th>Hormones</th>
<th>Density</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDC</td>
<td>2</td>
<td>2.0cm</td>
<td>ER/PR/Her2-</td>
<td>4</td>
<td>PH radial scar</td>
</tr>
<tr>
<td>IDC</td>
<td>2</td>
<td>2.5cm</td>
<td>ER/PR+, Her2-</td>
<td>3</td>
<td>PH cancer</td>
</tr>
<tr>
<td>IDC</td>
<td>1</td>
<td>Unavailable*</td>
<td>Unavailable*</td>
<td>3</td>
<td>FH cancer, PH ADH, PH LCIS</td>
</tr>
<tr>
<td>IDC</td>
<td>3</td>
<td>0.7cm</td>
<td>ER/PR-, Her2+</td>
<td>3</td>
<td>PH cancer</td>
</tr>
<tr>
<td>IDC</td>
<td>3</td>
<td>0.3cm</td>
<td>ER/PR/Her2-</td>
<td>3</td>
<td>PH cancer, BRCA2+</td>
</tr>
<tr>
<td>ILC</td>
<td>3</td>
<td>4.0cm</td>
<td>ER/PR+, Her2-</td>
<td>3</td>
<td>FH cancer</td>
</tr>
</tbody>
</table>

*Ultrasound-guided core needle breast biopsy was performed. Subsequent surgical excision was performed at an outside facility. Final pathological report from surgery is not available.
**TABLE 4. Breast Density in Patients Diagnosed with Cancer**

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Number of patients with mammographically occult, BSGI-detected breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-dense breast tissue</td>
<td>302</td>
</tr>
<tr>
<td>Dense breast tissue</td>
<td>547</td>
</tr>
</tbody>
</table>
Breast-specific gamma imaging for the detection of mammographically occult breast cancer in women at increased risk

Rachel F. Brem, Rachel C. Ruda, Jialu L. Yang, Caitrin M. Coffey and Jocelyn A. Rapelyea

J Nucl Med.
Published online: January 28, 2016.
Doi: 10.2967/jnumed.115.168385

This article and updated information are available at:
http://jnm.snmjournals.org/content/early/2016/01/27/jnumed.115.168385

Information about reproducing figures, tables, or other portions of this article can be found online at:
http://jnm.snmjournals.org/site/misc/permission.xhtml

Information about subscriptions to JNM can be found at:
http://jnm.snmjournals.org/site/subscriptions/online.xhtml

JNM ahead of print articles have been peer reviewed and accepted for publication in JNM. They have not been copyedited, nor have they appeared in a print or online issue of the journal. Once the accepted manuscripts appear in the JNM ahead of print area, they will be prepared for print and online publication, which includes copyediting, typesetting, proofreading, and author review. This process may lead to differences between the accepted version of the manuscript and the final, published version.