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The Efficacy of Breast Specific Gamma Imaging Over Mammography for Breast Cancer Screening in All Women.

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Abstract
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Method: An extensive search of available medical literature was conducted using variations of the keywords: Breast Cancer, Gamma Imaging and Mammography. Three observational articles were used for this systematic review.

Results: A large study of 936 participants with BI-RADS rated dense breast tissue where mammography and Breast Specific Gamma Imaging (BSGI) were compared for screening sensitivity and specificity. Two smaller studies evaluated BSGI’s ability to find occult foci after positive screening on mammography. Overall BSGI demonstrated superior sensitivity and specificity over mammography in all three studies.

Conclusion: Based on the results BSGI is recommend as adjunct imaging. The articles used were evaluated using GRADE and were found to be of moderate level of evidence, with the recommendations contingent upon further research.

Keywords: Breast Cancer, Dense Breast Tissue, Gamma Imaging.

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A course paper presented to the College of Health Professions in partial fulfillment of the requirements of the degree of Master of Science

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To my parents: Thank you for your unwavering support and belief. You always saw the best in me and encouraged pursuit of my dreams regardless of where they lead me.

To my uncle and cousins: I would never have considered this career, been prepared for or gotten into this program, let alone succeeded without your support and confidence in me. Thank you.

To Ryan: Thank you for answering phone calls in the middle of the night, talking me down from panic attacks, taking care of all our responsibilities by yourself, road trips, your empathy, support and for loving me.

To Emily, Heather, Reed and Duane: You know better than anyone else what it takes to get through this program and I never would have made it without your laughter, patience, ninja like genius and most of all your friendship. Thank you.
ABSTRACT

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Keywords: Breast Cancer, Dense Breast Tissue, Gamma Imaging.
INTRODUCTION

Background

In the United States 202,964 women were diagnosed with and 40,598 women died of cancer of the breast in 2007 (Centers for Disease Control and Prevention [CDC], 2010). It is the second most diagnosed cancer in women and one in eight women will develop invasive breast cancer over the course of her lifetime (Breastcancer.org, 2011). Early detection continues to have the greatest effect on survival rates and mammography has been, and continues to be, the gold standard of screening for breast cancer (American Cancer Society [ACS] 2009). In numerous randomized trials it is the single most effective imaging method for decreasing the mortality rate from breast cancer due to early detection (ACS, 2009).

Mammography is used to detect cancer by the relative difference in density represented by grey scale on film or digital imaging. This mechanism relies on cancerous tumors which appear as an opaque abnormality when compared to the surrounding tissue of the breast. The breast contains epithelial, glandular ducts and fibrous connective tissue which appears opaque while fatty adipose tissue appears dark on mammograms. The ability for a radiologist to accurately read the mammogram greatly depends on the amount of dense to fatty tissue in the breast.

Radiologists have developed general categories to describe breast composition and will place the image in the following classes: fatty replaced if < 25% of the breast is dense, scattered densities for 25 – 50%, heterogeneously dense >51-75% and extremely dense > 75% (American College of Radiology [ACR], 2008) (Appendix C. Boyd, 2009). These classifications are also a part of the Breast Imaging – Reporting and Data System (BI-RADS) which ensures the standardization for interpreting and recommending a specific course of
further action (ACR, 2008). Category one and two are considered negative, category three is probably benign but recommends short interval follow up, category four and five are considered highly suspicious and require further imaging and biopsy, finally category zero is unreadable, indeterminate and requires further imaging. The latter two classes’ heterogeneously and extremely dense breast tissue, usually fall into category zero because both dense breast tissue and tumors appear white on the mammogram. A mammogram’s ability to detect cancer in dense breasts is significantly decreased due to this masking effect (Pinsky and Helvie, 2010). The significance of mammograms decreased sensitivity in dense breast tissue is most acutely demonstrated in the US Preventive Services Task Force guidelines from 2009. The review describes a range of mammogram sensitivity between 77-95% and specificity between 94-97% with the lowest percentages in younger women with dense breast tissue (USPSTF, 2009). After reviewing the data on mammograms the task force increased the age of recommended annual screenings from 40 to 50 (USPSTF, 2009). They concluded it was a matter of absolute risk reduction, ultimately deciding the magnitude of benefit was insufficient to outweigh the harms in women under 50. In response to this assessment there was an outcry from cancer and radiology associations denouncing the recommendations.

There is an added complication to this recommendation considering the relationship between breast density and risk of breast cancer. As early as 1976 Wolfe proposed an association between mammographic pattern of breast parenchyma and risk of breast cancer. Since then, over 50 studies have shown that breast density is a strong risk factor for breast cancer (Doheny, 2010). Dense breast tissue has been linked to a four to six fold increased risk of developing breast cancer (Barlow et al., 2006). Breast density is more common in
younger women and density decreases with age, never-the-less there are women who will maintain dense breast tissue even into old age. Approximately 40 percent of all women have dense breast tissue with the largest population being under the age of 50 (Dmyterko, 2010).

Molecular imaging has historically been used for imaging pulmonary V/Q scans, thyroid imaging and whole body scans such as bone density and PET scanning. The original attempt at using gamma imaging for breast cancer detection was less than impressive. The recent advances in high resolution, small field of view cameras have overcome the two major limitations that previously prevented gamma imaging from being a viable option for imaging the breast (Zhou, 2009). The main differentiation between mammography and gamma imaging is the mechanism of detection. Mammography relies on anatomical differences to highlight abnormal appearing tissue based on density. Gamma imaging is based on the physiological difference between cancer and normal healthy tissue (Appendix C, Feldman, 2009). A radiotracer, usually 99Tc-sestamibi is injected just before imaging begins. This radiotracer is picked up by mitochondria, which are abundant in the very metabolically active cancer cells. This difference in process is precisely why gamma imaging is not affected by the density of the surrounding tissue, making it an ideal method to supplant mammography in women with dense breast tissue.

Purpose of the Study

Despite all the advances in modern medicine the cause of cancer remains elusive. For individuals that continue to be afflicted with this disease the best advantage is early detection. The purpose of this review is to systematically evaluate the literature to determine the efficacy of breast gamma imaging for detecting breast cancer in women. It seems appropriate to push the industry to evaluate any new technology in the effort to gain even the slightest advantage
against a disease that effects so many. The significance of finding a new tool to improve the ability to screen for cancer in women would be extremely advantageous, if not pivotal in improving survival rates. The articles used in this study were subjected to Grading of Recommendations Assessment, Development and Evaluation (GRADE) which will be used to evaluate the strength of the evidence (Guyatt et al., 2006).

METHOD
An extensive literature search was conducted using Medline, Pubmed, CINAHL, Ovid and Google Scholar. The following keywords were searched in each database individually and in combination: breast cancer, breast neoplasm, dense breast, gamma camera, breast specific gamma imaging, BSGI, molecular breast imaging, MBI, and scientimammography. The results were then limited to human subjects, English language and studies published since 2008. Duplicate articles, narrative reviews, editorials and letters to the editor were excluded. The remaining titles and abstracts were evaluated for content. Studies comparing gamma imaging, regardless of nomenclature, with mammography were included. Articles that did not mention dense breast tissue in the abstract or that focused on lymph node detection and intra-operative use of gamma imaging were excluded. The references of the remaining two studies were also searched, with the same limitations imposed, for possible articles or further background information. One additional study was identified and these three studies were included in the systematic review.

RESULTS
In this observational study 969 asymptomatic women with extremely dense or heterogeneously dense breast tissue on their most recent mammogram, underwent both mammography and breast specific gamma imaging (BSGI). The study population was between the ages of 25 and 89 with a mean age of 55.5 years. To increase the power of the study the authors included participants with at least one risk factor for developing breast cancer. BSGI was obtained on a dedicated dual head gamma imaging system comprising two CZT-based detectors (prototype CZT, GE medical systems, Haifa, Israel; Luma Gem, Gamma Medica-Ideas, Northridge, California); in combination with 740 MBq IV injection of Tc 99m sestamibi radiotracer five minutes prior to imaging. Two view imaging in the craniocaudal and mediolateral positions was done in both BSGI and mammography. The radiologists interpreting the screening mammograms were blinded to study participation and gamma imaging results. BI-RADS scale was used for interpretation of mammography and categories zero, four and five were considered positive. BSGI results were read by dedicated breast radiologists blinded to mammography interpretation. A five point uptake score was used to quantify results with one and two being no or normal uptake and considered to be a negative screen. Three points were deemed indeterminate while four points were considered suspicious for malignancy and five points were deemed highly suspicious for malignancy. Scores of three, four and five were considered positive. Cancer status was determined by histology. Inter-reader variability was assessed using the Cohen unweighted K statistic, which found substantial agreement with interreader agreement of $K = .62$ and intrareader agreement of $K = .66$.

The outcomes considered in this study were diagnostic yield, sensitivity, specificity and positive predictve value (PPV). BSGI showed an increase in diagnostic yield 9.6 per 1000
with a 95% CI range of 5.1 – 18.2 vs. 3.2 per 1000 with a 95% CI range of 1.1 – 9.4 for mammography. BSGI alone generated a total of 28 biopsies yielding 8 cancers, 2 atypical lesions and 18 benign findings. Mammography alone had 9 biopsies with 1 cancer, 2 atypical lesions and 6 benign results. BSGI was also more sensitive at 82% versus 27% as well as specific 93% versus 91%. The sensitivity was only statistically significant when BSGI was combined with mammography calculated at 91% with a p value of .016. The same cannot be said for the combined specificity which was lower than in mammography alone 85% versus 91% with a p value < .001. Finally with a p = .01 the PPV of BSGI was significantly higher than mammography 12% versus 3%. The authors concluded BSGI should be used in conjunction with mammography for women with dense breast tissue (Appendix C, Rhodes, 2011).

Spanu et al. 2008

The next study reviewed was an observational case series of 145 women aged 33 – 82 years, median age of 62, with suspected breast lesions on clinical exam and/or conventional diagnostic imaging, either mammogram or ultrasound, who were screened for additional lesions with BSGI. All images were obtained in cranio-caudal and medio-lateral positions. BSGI was acquired by 740 MBq IV injection of Tc-99m tetrofosmin radiotracer ten minutes prior to imaging on a high resolution small field of view dedicated breast camera (DBC) with CZT semiconductor heads (LumaGEM 3200S/12k, Gamma Medica-Ideas Inc). Mammograms were read by one radiologist and classified as suspicious for malignancy, inconclusive, indeterminate in the presence of high breast density or negative. BSGI was evaluated by two experienced nuclear medicine physicians who were blinded to all other
findings. Images were considered positive in areas of increased focal radiotracer uptake. Histology was used as a final determination of cancer status.

BSGI sensitivity of 97.6% and specificity of 86.4%. Globally BSGI was more accurate than mammography in 42/145 cases (29%) detecting cancer in 9 patients with mammogram indeterminate for dense breasts. The authors concluded BSGI should be used as adjunct imaging for women with positive mammogram screening to detect occult foci.

Spanu et al., 2009

The last study reviewed was an observational case controlled cohort study of 264 women between the ages of 26 to 81 years (median age 56) with suspicious breast lesion who were scheduled for a biopsy. Lesions and breast density were described using BI-RADS terminology and categories four and five were considered positive. BSGI was performed on a LumaGEM 3200S/12k high-resolution small field of view compact dedicated breast camera, ten minutes after IV injection of 740MBq 99m Tc setrofosmin. Results were categorized into three levels of radiotracer uptake; faint, high and absent. Interobserver variability was extremely low and resolved by consensus in three cases.

Forty four patients were positive for breast cancer out of the 232 participants in the study. Forty participants had ipsilateral multifocal/multicentric primary breast cancer and four had bilateral breast cancer. The breast cancer cases were further broken down into three groups for analysis. Group one: 24 of 40 (60%) had multiple invasive foci in one breast, group two: 16 of 40 (40%) with extensive carcinoma in situ in one breast and group three: 4 patients with bilateral breast cancer. The overall sensitivity rate for BSGI was 93.7% and 89.6% for mammography. The overall specificity rate was 88.2% for BSGI and 52.9% for
mammography. Mammography was false negative in 3 of 16 patients with ipsilateral multifocal and multicentric primary breast cancer in situ, with intermediate breast density in one and high density in two patients. The authors concluded BSGI should be used as adjunct imaging in women with positive mammogram to detect occult foci.

Appendix B = Gamma imaging vs. Mx
1) overall sensitivity and specificity
2) 95% CI of DI yield in Rhodes study

Appendix C = Pictures of Gamma vs. Mx

DISCUSSION

Throughout all three studies BSGI was superior to mammography in both sensitivity and specificity, though sensitivity was only statistically significant in the Rhodes (2011) study when combined with mammography (Appendix B, Table 2). While the Rhodes study was the only one in which women with increased breast density were the studied population, BSGI continued to demonstrate superior breast cancer identification in the other two studies. Though not considered direct outcomes, both Spanu studies did identify cases in which BSGI out performed mammography in women with dense breast tissue. Spanu (2009) demonstrated BSGI’s ability to find mammographic occult foci, indicating favorable use as adjunct imaging to mammography in women with a primary breast cancer diagnosis. All three studies recommended BSGI be considered as adjunct imaging to mammography.

Rhodes et al. (2011) was a large observational study producing significant contributions in this area, never-the-less it does have some limitations. They first identified their population
was not randomized and results may not be generalized to women without increased cancer risk criteria or to other imaging centers. The inclusion criteria of breast density at last mammogram ended up including women who did not have dense breast tissue on the current mammogram, in total 14% of the population. They also pointed out flaws in the study process where a quarter of the mammograms were done on film, the rest were done digitally. Lastly an issue of reported false negative outcomes is questionable as any lesion that was detected but not biopsied was considered a false positive. Without histology this characterization of false positive is only assumed and not proven, it is unfortunate more information was not included to clarify the reasons behind this assumption.

The Spanau et al. (2008) study’s population included subjects who already had a suspicious lesion on mammography, ultrasound or clinical exam and were not randomized. The size of the study was small with only 145 subjects and the reporting of the data left much to be desired. None of the raw data from mammography was reported, only statistical comparisons to BSGI were included. They failed to calculate the effects of breast density on the outcome. Lastly they did not analyze the limitations of their own study.

Spanau et al. (2009) study also began with subjects who already had a suspicious lesion on mammography. The study size was small using 232 non-randomized subjects, though breast density was reported it was not specifically considered as a variable and no calculations as to its effect were published.

As there was limited research specific to the detection of primary breast cancer between mammography and BSGI, additional larger, prospective and multi institutional studies are needed to compare. It also seems likely that the population with the most to benefit from BSGI as a screening tool is women with dense breast tissue, so further study in this population
specifically, seems appropriate. Studies that focus on analyzing the cost effectiveness and radiation exposure comparison are also needed. As gamma imaging for the breast continues to advance, clinicians should consider recommending BSGI as adjunct imaging in women with mammographic dense breast tissue. On imaging with BI-RADS rating 3, 4 and 5 clinician’s should also consider BSGI to find occult foci. If BSGI continues to demonstrate superior effectiveness over mammography it will be interesting to see if it will supplant mammography as a screening tool or remain as adjunct imaging. As the field expands and BSGI gains in acceptance there are other applications which could also be explored such as BSGI guided biopsy or perhaps its use inter-operatively during lumpectomies.

Grading outcomes between interventions in the three studies included in this systematic review was considered moderate (Appendix A, Table 1). The category of moderate quality evidence is described as “further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate” (Guyatt et al., 2006). These observational studies together were upgraded based upon the large magnitude of effect. The recommendations made from this systematic review are made conditionally as there has been no study evaluating the difference in radiation exposure compared to mammography.

Appendix A: GRADE table
REFERENCES


## APPENDIX

### APPENDIX A

**Table 1: GRADE Table**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Quantity and type of evidence</th>
<th>Finding(s)</th>
<th>Starting grade</th>
<th>Decrease GRADE</th>
<th>Increase GRADE</th>
<th>Grade of Evidence for Outcome</th>
<th>Overall GRADE of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Specific Gamma Imaging versus Mammography</td>
<td>Sensitivity</td>
<td>3 observational studies</td>
<td>BSGI superior</td>
<td>Low</td>
<td>NA</td>
<td>+ 0 0 0</td>
<td>Moderate</td>
<td>MODERATE</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>3 observational studies</td>
<td>BSGI superior</td>
<td>Low</td>
<td>NA</td>
<td>+ 0 0 0</td>
<td>Moderate</td>
<td></td>
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</tbody>
</table>
APPENDIX B

TABLE 1: Sensitivity and Specificity of BSGI vs. Mammography

*As no data for mammography was reported in this study the median percentage from the commonly accepted range of sensitivity and specificity for mammography as reported by USPSTF was used for comparison.

TABLE 2: 95% Confidence Interval for Diagnostic Yield per 1000 Rhodes 2011
APPENDIX C
Photographic examples of BSGI vs. Mammography

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.

Rhodes 2011
Figure 2. This 57-year-old woman presented with a new palpable breast mass in the right upper outer quadrant. CC (A), XCC (B), and MLO (C) mammographic images reveal dense fibroglandular tissue with a lobulated mass in the right upper outer quadrant and associated enlarged adjacent right axillary lymph nodes. CC (D), XCC (E), and MLO (F) BSGI views demonstrate intensely increased radiotracer uptake in the area corresponding to the lobulated mass at 10 o’clock as well as four smaller foci of increased uptake, at 12 and 6 o’clock in the anterior breast posterior to the nipple, and at 9 and 11 o’clock in the right upper quadrant. Second-look ultrasound was performed. At the corresponding 11 o’clock position, dilated ducts with internal debris were seen, but no discrete mass or nodule was identified. Other foci were identified on second-look ultrasound and biopsied. Also biopsied were the right axillary lymph nodes. Histopathology for these lesions is as follows: 10 o’clock lobulated mass—invasive ductal carcinoma, well to moderately differentiated; 9 o’clock—fibroadenoma; lymph nodes—compatible with metastatic breast malignancy.

Feldman, 2009
Fig. 1. Six categories of mammographic density: A) density = 0%; B) density = >0% to <10%; C) density = 10% to <25%; D) density = 25% to <50%; E) density = 50% to <75%; F) density = >75%.

Boyd, 2009