Molecular Imaging Approaches for Supplemental Screening in Women at Increased Breast Cancer Risk

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Mammography is an effective screening method that reduces breast cancer mortality (*1*). However, mammography is not a perfect test and its sensitivity is diminished in women with dense breast tissue (*2*). For women at increased breast cancer risk, the use of imaging modalities in addition to mammography, termed supplemental screening, can improve the overall cancer detection rate. Current guidelines recommend MRI for supplemental screening in women with greater than 20% lifetime risk of breast cancer (*3*). For women who cannot tolerate MRI, have mammographically dense breast tissue, or have an intermediate lifetime risk of breast cancer, screening ultrasound can be considered (*3*). However, these techniques have some drawbacks, which have fueled interest in alternative functional imaging–based methods for supplemental screening in high-risk women. In this issue of *The Journal of Nuclear Medicine*, Brem et al. investigate the diagnostic performance of a molecular imaging approach for supplemental breast cancer screening (*4*).

See page 678

Breast-specific γ-imaging (BSGI) is a Food and Drug Administration–approved radionuclide-based technique that can be used to detect breast cancer (*5,6*). A high-spatial-resolution, small-field-of-view γ-camera detects and localizes γ-ray energy emitted by the radiopharmaceutical ^{99m}Tc-methoxyisobutylisonitrile (sestamibi), which preferentially accumulates in malignant breast cells with increased vascular supply and concentration of mitochondria compared with surrounding normal breast tissue. Images are acquired immediately after intravenous injection of the radiopharmaceutical, with the patient seated in standard mammographic views (craniocaudal and mediolateral oblique views) with the breast in mild compression for a total of approximately 40 min. Interpretation of breast-specific γ-images follows a standardized lexicon and results in assessment categories and recommendations that parallel those of other imaging modalities outlined by the American College of Radiology Breast Imaging-Reporting and Data System (BI-RADS) (*7–9*).

Although several studies have evaluated the performance of BSGI for diagnosing breast cancer in a heterogeneous mix of clinical indications (*10*), data regarding the application of BSGI for supplemental screening for women at increased breast cancer risk are sparse. The study by Brem et al. is a single-institution, retrospective review of asymptomatic, increased-risk women undergoing BSGI from 2010 to 2014 whose most recent screening mammogram showed no suspicious abnormalities (*4*). The study population consisted of 849 women ranging in age from 26 to 83 y with a personal history of treated breast cancer, a family history of breast cancer, a personal history of an atypical or high-risk breast biopsy result, or a known genetic predisposition to breast cancer development. BSGI detected 14 mammographically occult cancers in 849 women, resulting in a supplemental cancer detection rate of 16.5 per 1,000 women screened. Furthermore, mammographic breast density did not affect BSGI's diagnostic performance; BSGI identified 11 cancers in 547 women with dense breast tissue and 3 cancers in 302 women with nondense breast tissue, which was not statistically different.

Brem et al. showed that the magnitude of increase in cancer detection rate when BSGI is added to screening mammography for high-risk women is comparable to that reported for screening breast MRI (*4*). A substudy of the American College of Radiology Imaging Network (ACRIN) 6666 trial demonstrated a supplemental cancer yield of 18.0 per 1,000 women screened with both MRI and mammography compared with mammography alone after 3 rounds of annual mammography and ultrasound screening (*11*). For comparison, supplemental cancer yield for screening breast ultrasound ranges from 1.9 to 4.4 per 1,000 women screened (*12–14*) and from 1.2 to 2.8 for digital breast tomosynthesis (*15–18*). Thus, functional breast imaging approaches, including MRI and BSGI, as adjunct screening modalities outperform the anatomic-based tools of ultrasound and tomosynthesis.

Another important parameter to consider besides the cancer detection rate when evaluating a new screening technique is the positive predictive value (PPV). Positive predictive value one (PPV_1) is the number of malignancies (true-positives) divided by the number of positive screening examinations and was 6.7% (14/212) for BSGI in the study by Brem et al. (*4*). PPV_3 (biopsy performed) was 14.4% (14/97) and corresponds to the number of malignancies divided by the number of biopsies performed. Fibrocystic change, benign breast tissue, cyst contents, and fibroadenoma accounted for the false-positive BSGI examinations, which decreases PPV. For comparison, the PPV_1 and PPV_3 for the ACRIN 6666 substudy were

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8.4% and 25.4%, respectively, for breast MRI, and the BI-RADS atlas recommends a practice audit benchmark range for PPV_3 between 20% and 50% (*7,11*). Thus, PPVs for supplemental screening using BSGI are slightly lower than the reported values for MRI despite similar cancer detection rates.

A clinically useful breast cancer screening tool should be able to identify biologically significant cancers at a size smaller than would be detected by palpation and before spread to axillary lymph nodes. In the study by Brem et al., greater than half of the cancers detected by screening BSGI were small (≤1 cm) invasive carcinomas or ductal carcinoma in situ (*4*). Furthermore, most (5/6; 83.3%) of the invasive carcinomas identified were histologic grade 2 and 3 with 2 triple-negative cancers and 1 cancer positive for human epidermal growth factor receptor 2 gene amplification. These results suggest that functional imaging through screening BSGI can identify clinically important cancers that are most likely to affect patient survival.

Despite a strong diagnostic performance of BSGI, concerns regarding lifetime radiation exposure will likely impede its widespread adoption as a serial supplemental screening method (*3*). Doses of ^{99m}Tc-sestamibi reported by Brem et al. initially ranged from 592 to 1,188 MBq (16.0 to 32.1 mCi), which is the Food and Drug Administration label–recommended dose, during the first 2 y of the study and then were reduced to approximately 259–500 MBq (7–13.5 mCi) during the last 2 y (*4*). The reduction in administered activity did not adversely affect image quality and did not have a statistically significant effect on the cancer detection rate. The resulting whole-body effective dose equivalent of the standard-dose examinations ranges from 5.9 to 9.4 mSv, which decreases to approximately 2.4 mSv for the low-dose examinations (*19,20*). For comparison, the effective dose equivalent of digital mammography is approximately 0.44 mSv and 1.2 mSv for digital mammography combined with tomosynthesis (*19*). Technologic improvements in instrumentation design combined with optimized patient preparation to increase radiopharmaceutical uptake have been pursued to reduce the radiation exposure to levels feasible to consider for breast cancer screening programs (*20–23*). Continued research into dose reduction methods or consideration of less frequent screening intervals will facilitate broader acceptance of radionuclide-based supplemental screening approaches in clinical practice.

Interest in applying functional imaging techniques for supplemental breast cancer screening continues to grow. This is in part due to the increasing recognition of the importance of individual formal risk assessments and establishment of dedicated specialty clinics, which advise high-risk women regarding screening strategies and risk-reducing interventions. Furthermore, there are an expanding number of states with legislation on breast density driven by patient advocacy group concern regarding the limited sensitivity of mammography in women with dense breasts. The work reported by Brem et al. in this issue, as well as other recently published studies, are important to ensure that clinical use of supplemental screening approaches continue to be evidence-based (*4,20*). Determination of the best supplemental screening tool will likely require direct comparison of the cancer detection rate, recall rate, and number of false-positive examinations in large, prospective multiinstitutional trials and include additional considerations such as radiation dose, cost, and accessibility.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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