Screening, Imaging, and Image-Guided Biopsy Techniques for Breast Cancer

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INTRODUCTION
Diagnostic imaging and image-guided needle biopsies play a central role in the diagnosis, treatment planning, and staging of patients with breast cancer. Mammography remains the mainstay in breast cancer detection. Most patients with newly diagnosed breast cancer will have been imaged with mammography, ultrasonography, or both.

Breast cancer most often presents as a mass, calcifications, or both on imaging. Usually, masses indicate invasive breast carcinoma, whereas calcifications suggest ductal carcinoma in situ (DCIS). When breast cancer presents as a mass, initial evaluation generally includes characterization with mammogram and ultrasonogram plus an evaluation to identify satellite lesions and associated calcifications. As an example of the importance of breast imaging, when DCIS associated with a mass meets the criteria for extensive intraductal component, the likelihood of obtaining clear surgical margins is decreased and therefore the risk of local recurrence is increased.\(^1\)\(^2\) Carcinomas that

KEYWORDS
- Mammography
- Screening
- Breast ultrasonography
- Breast MRI

KEY POINTS
- Multidisciplinary care requires careful integration of imaging and pathologic information both prospectively and throughout the course of treatment of the patient with breast cancer.
- A thorough understanding of the appropriate strategies for breast cancer screening based on risk factors is essential to identify breast cancer in its earliest and most treatable stages.
- Although mammography remains the cornerstone imaging study for breast cancer diagnosis, other examinations, currently in use and still in development, may provide additional information that results in earlier detection, better staging and surgical planning, more precise assessment of response to treatment, earlier identification of recurrent carcinoma, and, hopefully, better patient outcomes.
present solely with calcifications should be imaged with mammographic magnification images to evaluate the extent of disease and, in some instances, with ultrasound to document the presence of underlying masses, which may indicate coexistent invasive carcinoma. Diagnostic imaging is also used to identify axillary adenopathy, involvement of the skin, pectoralis muscles and chest wall, and, when appropriate, distant metastases. Establishment of multifocal and multicentric carcinoma, which may not be apparent on initial imaging with mammography and ultrasonography, is also critical for optimal surgical management and ultimately successful treatment.

Preoperative magnetic resonance imaging (MRI) has been shown to detect unsuspected additional disease and change surgical management in patients diagnosed with breast cancer. MRI can also identify unsuspected, mammographically occult contralateral synchronous breast cancers in 3% to 5% of patients with newly diagnosed breast cancer. Nonetheless, the routine use of preoperative MRI remains controversial. There are little data about improvement in recurrence and mortality rates if preoperative MRI is used at the time of breast cancer diagnosis. In addition, false-positive findings on MRI may lead to unnecessary, additional workup and biopsies and, thus, delay treatment.

MAMMOGRAPHY

A mammogram is a radiographic examination of the breast, either displayed on a film or on a computer monitor. Screening mammograms are performed on women who are asymptomatic and include images of each breast in the CC (craniocaudal) and MLO (mediolateral oblique) projections (Fig. 1). Diagnostic mammograms are performed in women who have a clinical problem, such as a palpable mass or other symptom of breast disease, a history of breast cancer within the preceding 5 years, or have been recalled for additional imaging from an abnormal screening mammogram. Diagnostic mammograms may include special views such as focal compression of one area of the breast tissue or magnification images. Another variation on special mammographic views includes women with breast implants that should be evaluated with Eklund views. These views displace the implants and allow for an increase in the amount of imaged breast tissue compared with traditional mammographic views.

During a mammogram, the breast tissue is compressed between 2 plates, one a plastic compression paddle and the other an x-ray detecting plate. Compression is necessary to prevent the image from appearing unsharp due to motion, to physically spread out the glandular tissue, and to decrease the thickness of the breast tissue by reducing overlapping dense tissue. The average radiation dose from a 4-view mammogram is 0.4 mSv or roughly equal to 7 weeks of natural background radiation.

Full-field digital mammography (FFDM) replaces x-ray film with solid-state detectors that convert x-rays into electrical signals to produce images of the breasts. Digital mammography images can be viewed on a computer screen or on printed films. Computer-aided detection (CAD) assesses the data from a digital or digitized film-screen mammogram for signs of increased density or calcifications. CAD programs superimpose markings on mammographic images, drawing the radiologist’s attention to a potential abnormal. Early, retrospective studies demonstrated improved cancer detection when radiologists used CAD programs when interpreting mammograms. Subsequent research has shown more modest results and even decreased diagnostic accuracy and increased rate of biopsy without improvement in detection of invasive breast carcinoma.

The Mammography Quality Standards Act (MQSA) was passed in 1992. MQSA was intended to ensure that mammography performed in the United States for detection of
Early breast cancer is safe and of reliable quality. Under MQSA, all facilities performing mammography in the United States must be certified by the US Food and Drug Administration (FDA) or an FDA-approved Certifying State. MQSA requirements address the quality of mammographic equipment, personnel who perform and interpret mammography, and reporting. MQSA also stipulates that all facilities that perform mammograms must have a quality assurance program and procedures for following

Fig. 1. (A–D) Right CC and MLO mammograms, fatty. (A, B) Right CC and MLO mammograms, dense (C, D).
abnormal findings and obtaining and tracking pathologic results from biopsy procedures. Annual inspection by appropriately trained FDA or state inspectors is mandatory, and facilities are required to display their FDA certificates. The result of MQSA has been improved mammographic technique, lower radiation dose, and better training of personnel.\textsuperscript{16}

The Breast Imaging Reporting and Database System (BI-RADS) is the standardized method for reporting of mammographic findings.\textsuperscript{17} The BI-RADS lexicon is used to describe and classify findings on breast imaging studies. Originally developed for mammographic findings, the BI-RADS lexicon has been expanded to encompass findings on ultrasonography and MRI. Mammography reports also include an estimation of the relative fatty and fibroglandular composition of the breast tissue (Table 1).

On mammograms, carcinomas present as masses, asymmetries, and calcifications. By definition, a mass is a space-occupying lesion seen in 2 different planes. This is distinguished from a density, which is seen only in a single plane. The shape of masses is described as round, oval, lobular, or irregular, while the margins are identified as circumscribed (with well-defined margins), indistinct, and spiculated (with lines radiating from the margins) (Fig. 2). An asymmetry cannot be accurately described as any of the shapes previously described. An asymmetry is identifiable in 2 planes but lacks the borders and conspicuity of a mass and may simply represent an island of normal glandular tissue. Additional mammographic imaging of an asymmetry may identify a mass or architectural distortion. Architectural distortion, which can occur with or without a central mass, is used to describe spiculations radiating from a point and focal retraction at the edge of parenchyma. Architectural distortion can be seen in association with a mass or as an isolated finding.

Calcifications associated with benign disease are generally larger than those seen with malignancy and typically are coarse (round, lucent centered, or “layering” on 90° medial lateral or lateral medial images). Amorphous, indistinct, pleomorphic (or heterogeneous), fine, linear, or branching calcifications are more typical of carcinomas (Fig. 3).

DCIS typically presents with calcifications on mammography. In the past 30 years, there has been a large increase in the frequency of DCIS diagnosed in the United States because of the widespread adoption of screening mammography.

Finally, the BI-RADS lexicon requires a final assessment of one of 7 categories (0–6) and recommended follow-up plan (Table 2). Using the lexicon and assessment system, a quality audit is generated identifying the number of false-negative (ie, missed cancers) and false-positive findings, positive and negative predictive values, sensitivity, and specificity for each practice as a whole and for individual radiologists. The report of a breast imaging study must be sent to the referring health care provider,

<table>
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<th>Table 1</th>
<th>Breast imaging reporting and database system method for reporting of mammographic finding</th>
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<tr>
<td><strong>BI-RADS Description</strong></td>
<td><strong>Glandular Tissue (%)</strong></td>
</tr>
<tr>
<td>The breast is almost entirely fat</td>
<td>&lt;25</td>
</tr>
<tr>
<td>Scattered fibroglandular tissue</td>
<td>25–50</td>
</tr>
<tr>
<td>Heterogeneously dense breast tissue</td>
<td>51–75</td>
</tr>
<tr>
<td>Extremely dense</td>
<td>&gt;75</td>
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and a written report in lay language must be sent to the patient within 30 days of the mammographic study. If the assessment is “suspicious” or “highly suggestive of malignancy,” the report should be communicated to the health care provider and patient as soon as possible (ideally within 3–5 days).

**Full-Field Digital Mammography**

In 2000, the FDA approved the use of FFDM in the United States. In 2005, the Digital Mammographic Imaging Screening Trial studied 49,528 women who presented for screening mammography in the United States and Canada.\(^{18}\) The overall diagnostic accuracy was found to be similar for digital and film mammography. The accuracy of digital mammography exceeded that of film mammography in women younger than 50 years, women with heterogeneously or extremely dense breasts, and premenopausal and perimenopausal women.

Since 2000, FFDM has largely replaced film-screen mammography. Based on the MQSA National Statistics as of June 1, 2012, from the US FDA, 7313 of 8626 (84.8%) mammography facilities and 10,639 of 12,367 (86%) mammography units in the United States are FFDM units.\(^{19}\) Nonetheless, the transition to digital mammography has not eliminated the issues with mammography as a screening tool. Overall, the sensitivity and specificity of mammography are 79% and 90%, respectively, and both are lower in younger women and women with dense breast tissue.
Fig. 3. (A) Tangential mammogram image demonstrating skin calcifications. (B) Multiple skin calcifications. (C) Layering milk of calcium on 90° lateral mammogram image. (D) Coarse, popcorn-type calcifications in a fibroadenoma. (E) Coarse linear and branching secretory type calcifications. (F) Vascular calcifications. (G) Linear branching calcifications in DCIS. (H) Linear branching calcifications in DCIS.
ULTRASOUND IMAGING

Ultrasound imaging uses high-frequency sound waves to generate images without the use of ionizing radiation. The current indications for breast ultrasonography include palpable findings (including as the initial imaging test of palpable findings in patients who are younger than 30 years, pregnant, or lactating), abnormalities or suspected abnormalities on mammography or MRI, problems with breast implants, suspected underlying mass in the setting of microcalcifications or architectural distortion on mammography, supplemental screening in women at high risk for breast cancer who are not candidates for or do not have easy access to MRI, and suspected axillary lymphadenopathy. Real-time imaging is also possible with ultrasonography, making it ideal for interventional procedures. Breast ultrasound imaging should be performed with a high-resolution real-time linear array transducer with a center frequency of at least 10 MHz, using the highest frequency with which adequate penetration of the tissue is feasible.

<table>
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<tr>
<th>Category</th>
<th>Assessment</th>
<th>Follow-up</th>
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<tbody>
<tr>
<td>0</td>
<td>Need additional imaging evaluation</td>
<td>Additional imaging needed before a category can be assigned</td>
</tr>
<tr>
<td>1</td>
<td>Negative</td>
<td>Continue annual screening mammograms (women older than 40 y)</td>
</tr>
<tr>
<td>2</td>
<td>Benign finding</td>
<td>Continue annual screening mammograms (women older than 40 y)</td>
</tr>
<tr>
<td>3</td>
<td>Probably benign</td>
<td>Initial short term follow-up (usually six month mammogram (&lt;2% chance of malignancy)</td>
</tr>
<tr>
<td>4</td>
<td>Suspicious abnormality</td>
<td>Biopsy should be considered (2%–95% chance of malignancy)</td>
</tr>
<tr>
<td>5</td>
<td>Highly suggestive of malignancy</td>
<td>Requires biopsy (&gt;95% chance of malignancy)</td>
</tr>
<tr>
<td>6</td>
<td>Known cancer</td>
<td>Biopsy-proven malignancy</td>
</tr>
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BI-RADS descriptors for ultrasound lesions include morphologic descriptors that are similar to those used in mammography. Masses are described by shape (oval, round, or irregular) and margins (circumscribed, indistinct, angular, or spiculated) (Fig. 4A–D). The ultrasound imaging lexicon also includes features unique to sonography, including orientation relative to the skin line (parallel or not parallel), lesion boundary (sharp or with an echogenic halo), posterior acoustic features (enhancement or shadowing), and vascularity. The echogenicity (shade of gray) of masses on ultrasound imaging is compared with normal fat lobules and described as hypoechoic, isoechoic, hyperechoic, or mixed echogenicity.

Elastography, the measurement of the elastic properties of tissues, is another method to evaluate breast lesions that can be performed with adaptation of sonographic equipment. Interest in using elastography arose from the observation that malignant tissues are firmer than benign tissues and, thus, less compressible. Elastography uses data before and after the application of compression (either manually applied “static” elastography or “shear wave” elastography where waves are emitted perpendicular to the ultrasound transducer).

MAGNETIC RESONANCE IMAGING OF THE BREAST

Breast MRI has evolved to become an integral part of breast cancer diagnosis and management. Current indications for breast MRI include screening of the contralateral breast in patients with newly diagnosed breast carcinoma, evaluation of patients in whom mammographic evaluation is limited by augmentation (including silicone and

![Fig. 4.](image)
saline implants and silicone injections), determining the extent of disease at the time of initial diagnosis of breast cancer (including identification of invasion of the pectoralis major, serratus anterior, and intercostal muscles), evaluation of inconclusive findings on clinical examination, mammography, and/or ultrasonography, and asymptomatic screening of patients at very high risk of breast carcinoma (in conjunction with routine mammography). Other uses of breast MRI include evaluation of response to neoadjuvant chemotherapy with imaging before, during, and/or after treatment, and identification of residual disease in patients with positive margins after lumpectomy. MRI may be useful in patients who present with metastatic disease or axillary adenopathy suspicious for breast origin with no primary identified on mammography.

According to the American College of Radiology Practice Guideline for the Performance of Contrast-Enhanced Magnetic Resonance Imaging (MRI) of the Breast, facilities that perform diagnostic breast MRI should either have the capability to perform MRI-guided biopsies for lesions seen only on MRI or have arrangements with another facility that can perform these services. This arrangement is necessary to ensure that findings seen on MRI can be biopsied.

Breast MRI is generally performed with a dedicated breast coil on a magnet of 1.5 T field strength or greater, using slice thickness of 3 mm or less, and in plane resolution of 1 mm or less. To detect small abnormalities, high spatial and temporal resolution is necessary, as well as optimization of contrast between normal tissue and carcinoma. T1- and T2-weighted images are obtained. Chemical fat suppression techniques and subtraction are often used. Kinetic curves are generated by measuring lesion enhancement at scan intervals separated by 3 minutes or less. Dynamic scanning is usually performed with T1-weighted images (with or without fat suppression). Both breasts should be imaged simultaneously unless the patient has undergone mastectomy. Gadolinium contrast (0.1 mmol/kg) is used unless the examination is performed solely for the evaluation of implant integrity, which does not require contrast enhancement.

MRI evaluation of breast lesions includes assessment of morphologic features, signal characteristics, and enhancement patterns. As with mammographic and sonographic lesions, morphology is described using a BI-RADS lexicon. Masses are described as round, oval, lobulated, or irregular, with smooth, irregular, or spiculated margins. Enhancement patterns are described as homogeneous, heterogeneous, central or rim enhancing, or with dark (nonenhancing) or enhancing internal septations. Generally, benign lesions such as cysts, lymph nodes, and fibroadenomas with myxomatous contents have high (bright) signal on T2-weighted images. Most malignant masses have low signal on T2-weighted images (Fig. 5A).

**Fig. 5.** (A) Irregular rim enhancing mass on MRI (IDC). (B) Stippled and clumped nonmass enhancement on MRI (DCIS).
Unlike the BI-RADS classification for mammographic and sonographic findings, the American College of Radiology (ACR) lexicon for MRI includes so-called nonmass enhancement. With nonmass enhancement, there is enhancement of the breast tissue without the presence of a defined mass. Nonmass enhancement can be symmetric or asymmetric. The distribution of nonmass enhancement is described as a focal area, linear, ductal, regional, segmental (triangular, apex toward the nipple), or diffuse. The pattern of nonmass enhancement is characterized as homogeneous, stippled, clumped, or reticular. Linear, clumped, or irregular nonmass enhancement suggests DCIS (see Fig. 5B).

Enhancement of lesions on dynamic MRI is quantified and displayed as kinetic curves, demonstrating initial uptake and subsequent washout or accumulation of contrast over time. Initial enhancement (within the first 2 minutes usually) is described as rapid, medium, or slow. Enhancement after the first 2 minutes follows a pattern of decreasing enhancement (washout), stable enhancement (plateau), or gradually increasing enhancement (persistent). Breast carcinomas typically demonstrate rapid uptake and washout. Normal tissue and benign lesions generally have slow uptake and persistent delayed enhancement (Fig. 6). There is considerable overlap between the enhancement curve characteristics of benign and malignant lesions, however, and use of both morphologic features and kinetic curves is thought to be preferable to relying solely on enhancement characteristics.

The sensitivity of MRI for detection of breast cancer is high, generally reported in the range of 90%. Nonetheless, the sensitivity is considerably lower for DCIS than for invasive carcinoma, and the specificity of breast MRI is only in the range of 50% to 70%.

Breast MRI has also been shown to be the best predictor of response in patients who have undergone neoadjuvant chemotherapy. In the American College of Radiology Imaging Network (ACRIN) 6657/I-SPY Trial, MRI imaging findings were found to be a stronger predictor of response to chemotherapy at pathologic evaluation than clinical assessment for locally advanced breast cancer. The most useful sign of response was change in volumetric measurement early in treatment.

**IMAGING-GUIDED BREAST INTERVENTIONAL PROCEDURES**

In the current practice of breast cancer diagnosis, one important objective is to reduce unnecessary surgical excisional biopsies. Percutaneous needle biopsies have become the procedure of choice for diagnosis of image-detected abnormalities. In addition to distinguishing benign from malignant causes, percutaneous biopsy facilitates surgical planning. In many cases, all necessary surgical procedures can be performed in a single setting with attention to surgical margins, appropriate selection of patients for breast conservation versus mastectomy, and performance of sentinel node biopsy, if indicated.

Interventional procedures can be guided by mammographic, ultrasonographic, or magnetic resonance images. Percutaneous sampling is conducted with core needle biopsy (using “gun type” or vacuum-assisted needles) or fine needle aspiration. Core biopsy needle sizes range from 7 to 14 gauge for most breast lesions. MRI-guided biopsies generally require intravenous gadolinium contrast to identify the lesion to be biopsied. With core needle biopsy, a radiopaque, usually metal marker is frequently placed at the biopsy site, particularly for small lesions, to document the location of the area sampled.

Image guidance is also used for preoperative needle localization. With needle localization, a hook wire is placed at the area of interest. Surgical removal of the lesion is confirmed with a radiographic or sonographic image of the specimen.
Correlation of imaging and pathologic findings is necessary for all image-guided percutaneous biopsies to ensure radiologic-pathologic correlation. Presuming there is no discordance, surgical removal of lesions found to be benign at core needle biopsy is usually unnecessary.

Breast cancer is most likely to spread to the ipsilateral axillary lymph nodes first (Fig. 7). Pathologic evaluation of axillary lymph nodes is necessary to stage breast cancer. Image-guided breast biopsy can be used to perform fine or core needle biopsies on suspicious axillary node identified by imaging. A positive finding on image-guided axillary biopsy can be incorporated into the selection and sequencing of multidisciplinary treatment planning.

Fig. 6. (A) Washout enhancement curve on MRI. (B) Persistent enhancement curve on MRI.
NEW TECHNOLOGIES IN BREAST CANCER IMAGING

Tomosynthesis

Digital breast tomosynthesis (DBT) is a 3-dimensional (3D) technique in which radiographic images are acquired at multiple angles during a sweep of the x-ray tube. DBT uses FFDM units as a platform. Much like conventional tomography, DBT produces thin slices at different depths through the breast tissue, removing normal overlying structures that can overlap and obscure abnormal tissue on standard, 2-dimensional (2D) mammograms. Compression is required for DBT, and the radiation dose from the combination of DBT and mammography is higher than that from mammography alone. If DBT is used for screening, the radiation dose should decrease for those patients who avoid being recalled. Most women are not recalled from screening mammography, however.

The FDA approved the first DBT device as an adjunct to mammography for diagnostic and screening breast imaging in 2011. The use of 2D and 3D images has been shown to improve the radiologists’ ability to differentiate cancerous from noncancerous lesions and to reduce the number of patients recalled from screening studies when compared with mammography alone.25

Lack of reimbursement has prevented large-scale adoption of DBT in the United States at the current time. In addition, the larger number of images when DBT is added to mammography may be a challenge for radiologists, for whom it takes more time to review images from both the mammogram and the DBT.

Contrast-enhanced Mammography

Contrast-enhanced mammography, like contrast-enhanced MRI, uses both anatomic and physiologic information based on enhancement with contrast. Neovascularity in malignancies leads to rapid uptake and washout of contrast in both MRI and contrast-enhanced mammography. In 2011, contrast-enhanced mammography received approval from the FDA. Originally, contrast-enhanced mammography was envisioned as an alternative to MRI in places where MRI is not readily available or in patients for whom there is a contraindication to MRI.

Like DBT, contrast-enhanced mammography is performed using digital mammographic technology. The same type and dose of iodinated contrast are used for

Fig. 7. (A) Axillary adenopathy on ultrasound imaging. (B) Axillary adenopathy on mammography.
contrast-enhanced mammography as for computed tomography. With contrast-enhanced mammography, 2 images of each breast are acquired in the standard CC and MLO positions, a low-energy image and a high-energy image. The 2 images are combined and processed. Then, the background, nonenhancing structures are subtracted, making areas of enhancement more conspicuous (similar to subtracted images from MRI studies). The radiation dose is 20% greater than a standard mammogram. Sensitivity is higher than mammography (93% compared with 78% for mammography alone), with no loss of specificity.

Radionuclide Breast Imaging—Positron Emission Mammography and Breast-specific Gamma Imaging

Over the years, many breast cancers were incidentally identified on nuclear medicine studies of other parts of the body (such as cardiac studies) using the radionuclide Technetium 99m (Tc 99m). In the past, however, breast cancer detection with nuclear medicine imaging was limited by poor spatial resolution. The recent development of higher-resolution detectors has made nuclear medicine imaging a viable option for breast cancer diagnosis.

Breast-specific gamma imaging (BSGI) uses a scintillating crystal detector to identify uptake of Tc 99m in breast lesions. Two views of each breast are obtained. Studies report an overall high sensitivity (91%–96%) for detection of breast cancer, although sensitivity is less for small lesions measuring less than 1 cm. The specificity (in the range of 60%) is not a significant improvement over MRI.

Positron emission mammography (PEM) uses 18F fluorodeoxyglucose (18F FDG), the same agent used for whole-body positron emission tomography (PET). Unlike whole-body PET, PEM studies are imaged with a special detector whose design mimics a mammographic unit. A total of 12 images of each breast are acquired. Originally, the same dose of FDG was used as for whole-body PET. This method showed high sensitivity and specificity (both exceeding 90%) for breast cancer detection. In general, PEM has been shown to be as sensitive as MRI for detection of breast cancer with better specificity. Widespread acceptance of both BSGI and PEM has been limited by the high radiation dose associated with these studies, 50 mGy to the lower colon and 59 mGy to the bladder for PEM. Research has been directed to reducing the radiation dose for PEM and BSGI.

SCREENING MAMMOGRAPHY CONTROVERSIES

Since the early 1990s, when mammographic screening was widely adopted, the mortality rate from breast cancer has dropped more than 30% in the United States. The largest and longest studies of breast cancer screening with mammography have demonstrated a reduction in breast cancer deaths in women starting at age 40 years. In June 2012, the American Medical Association joined the American Congress of Obstetricians and Gynecologists, American Society of Breast Surgeons, American Cancer Society, and the American College of Radiology in endorsing mammographic screening for women with average risk of breast cancer starting at age 40 years.

Nonetheless, these recommendations have frequently been challenged, particularly for women from ages 40 to 49 years. In November 2009, the United States Preventive Services Task Force (USPSTF) recommended against routine mammographic screening in women of average risk of breast cancer before age 50 years. Instead, the USPSTF recommended screening between the ages of 50 and 74 years and only every other year. In making this recommendation, the USPSTF reviewed
randomized controlled trials on screening mammography but not any information from other peer-reviewed studies, including service screening trials.\(^{32,36}\) The USPSTF cited the potential harms from screening mammography including radiation exposure, pain during procedures, anxiety and other psychological responses, consequences of false-positive and false-negative findings, and overdiagnosis of breast cancer.

It has been demonstrated that roughly 6500 additional women would die each year in the United States if USPSTF guidelines were used.\(^{97}\) In June 2012, Mayo Clinic researchers presented data indicating that the USPSTF recommendation had resulted in a 5.72% decrease in mammograms performed in women aged 40 to 49 years. Mammography rates in almost 8 million women were reviewed before and after the announcement of the USPSTF guidelines.\(^{38}\)

**Screening with Ultrasonography**

The limitations of mammography are well documented, with false-negative rates as high as 20%.\(^{39–48}\) Cancers are more difficult to detect on mammography if the breast tissue is dense, which is more common in younger women. In addition, the density of breast tissue on mammography may be an independent risk factor for the development of breast cancer. Increased breast density is associated with a higher risk of the proliferative lesions that are precursors of breast cancer.\(^{49–52}\) Thus, much effort has been spent trying to find more accurate methods to detect breast cancer either in addition to or in the place of mammography.

ACRIN trial 6666 is the largest study to date of screening ultrasonography.\(^{53}\) A total of 2637 women at high risk for breast cancer were screened with mammography and ultrasonography. Forty breast cancers (in 1.5% of participants) were diagnosed. Twenty of the cancers were found with mammography alone (cancer detection rate of 7.6 per 1000 women screened; diagnostic accuracy, 78%). The combination of ultrasound imaging and mammography detected 31 cancers (a detection rate of 11.8 cancers per 1000 women screened; diagnostic accuracy, 91%). Of the 40 total cancers, 8 identified were not seen on initial mammographic or sonographic screening but were identified later in the 12-month period of the study. Both modalities together detected 28% more breast cancers than were identified by mammography alone.

The false-positive rate for findings seen only on ultrasound imaging was greater than for findings seen only on mammography. More than routine follow-up was recommended in 13% of the mammographic screening examinations and 28% of combined mammographic and sonographic screening examinations.

Biopsy was recommended in 241 cases. Findings identified on mammography alone resulted in an unnecessary biopsy for 1 in every 40 women in the study. Findings identified with the combination of mammography and ultrasound screening resulted in an unnecessary biopsy for 1 in 10 women in the study. A total of 168 biopsies were recommended for findings seen with ultrasound imaging only (results: 7.1% carcinoma, 3.6% atypical, 89% benign); 46 biopsies were recommended for findings seen with mammography only (results: 26% carcinoma, 2% atypical, 72% benign).

In a follow-up study, Berg and colleagues\(^{54}\) examined the impact of adding yearly screening ultrasonography or a single screening MRI to mammography in women at high risk for breast cancer. In 2662 women, 111 breast cancers were detected in 110 women. Of the breast cancers identified on imaging screening studies, there were 33 detected by mammography only, 32 detected by ultrasound imaging only, 26 detected by both mammography and ultrasound imaging, and 9 detected by MRI only (after negative mammography and ultrasound imaging). Eleven breast cancers were not detected by any screening imaging modality.
The increase in cancer detection with supplemental annual screening ultrasound imaging persisted after the first screening ultrasound imaging. With subsequent annual screening ultrasound imaging, the risk of false-positive results decreased but remained higher than for mammography. The positive predictive value (PPV) for lesions seen only on ultrasonography was 9% for the first screening ultrasound imaging and 11.7% for the second and third. The PPV for lesions seen only with mammography was 29.2% for the first screening study and 38.1% for the second and third.

The addition of ultrasound imaging to mammographic screening increased cancer detection by 5.3 cancers per 1000 women in the first year and 3.7 cancers per 1000 women in the second and third years. The addition of MRI screening resulted in a supplemental cancer detection of 14.7 cancers per 1000 women screened. Although the addition of MRI to screening with mammography alone or to mammography plus ultrasonography significantly increased detection of early breast cancer, there was a low rate of interval cancers (8%) in the main ACRIN 6666 study and all interval cancers were node negative. Thus, the benefit of adding screening MRI (rather than ultrasound imaging) to mammographic screening was unclear in patients who are not at high risk.

Under MQSA, all mammography reports sent to clinicians are required to include one of the 4 categories addressing the density of the breast parenchyma. In 2009, Connecticut became the first state to require that all mammography reports given to patients include information regarding the density of the breast tissue also. Since then, other states have followed suit. Almost certainly, this will lead to increased demands for nonmammographic screening tests. These additional tests (most commonly ultrasonography and MRI) may not be readily available and could also result in a high number of false-positive examinations, generating unnecessary follow-up studies and biopsies. Supplemental screening studies may not be cost-effective or reimbursed by insurers. In addition, there may be insufficient resources (equipment and personnel) to implement large-scale screening with modalities other than mammography.

Breast ultrasound imaging is traditionally performed using hand-held equipment, which is time and labor intensive. In ACRIN Trial 6666, physicians performed the screening ultrasound examinations. Reproducibility of that study’s results using technologists or automated breast ultrasound systems (although certainly feasible) is still under investigation. In June 2012, an automated breast ultrasound machine was approved by the FDA for use in breast cancer screening.

Screening with MRI

In March 2007, the American Cancer Society recommended that women with an especially high risk (greater than 20% lifetime) of developing breast cancer undergo screening with MRI in addition to mammography. Women were considered to meet the criteria for additional screening with MRI if they had a BRCA1 or 2 mutation, a first-degree relative with a BRCA1 or 2 mutation and had not undergone genetic testing, a greater than 20% lifetime risk of breast cancer based on risk-assessment tools that take family history and other factors into consideration, undergone radiation therapy to the chest between ages 10 and 30 years, or a history of Li-Fraumeni, Cowden, or Bannayan-Riley-Ruvalcaba syndrome.

There was not believed to be sufficient evidence to recommend for or against screening with MRI in women with a 15% to 20% lifetime risk of breast cancer. Women with a 15% to 20% lifetime risk of breast cancer include those with lobular carcinoma in situ or atypical lobular hyperplasia, atypical duct hyperplasia, very dense or unevenly
dense breasts, and a personal history of breast cancer. Finally, the American Cancer Society did not recommend screening for breast cancer with MRI in women with a lifetime risk of breast cancer less than 15%. In addition, although ultrasound can detect additional cancers, it should not take the place of screening with MRI in addition to mammography in women at very high risk of developing breast cancer.

SUMMARY
Multidisciplinary care requires careful integration of imaging and pathologic information both prospectively and throughout the course of treatment of the patient with breast cancer. A thorough understanding of the appropriate strategies for breast cancer screening based on risk factors is essential for identifying breast cancer in its earliest and most-treatable stages. Although mammography remains the cornerstone imaging study for breast cancer diagnosis, other examinations, currently in use and still in development, may provide additional information that results in earlier detection, better staging and surgical planning, more precise assessment of response to treatment, earlier identification of recurrent carcinoma, and, hopefully, better patient outcomes.

REFERENCES


