Trends in breast cancer screening and diagnosis

ABSTRACT
Screening mammography is the single most effective method of early breast cancer detection and is recommended on an annual basis beginning at age 40 for women at average risk of breast cancer. In addition to traditional film-screen mammograms, digital mammograms now offer digital enhancement to aid interpretation, which is especially helpful in women with dense breast tissue. Useful emerging adjuncts to mammography include ultrasonography, which is particularly helpful for further assessment of known areas of interest, and magnetic resonance imaging, which shows promise for use in high-risk populations. Image-guided biopsy—directed by ultrasonography or stereotactic mammography views—plays a critical role in histologic confirmation of suspected breast cancer.

EARLY DETECTION OF BREAST CANCER IS VITAL TO REDUCING THE MORBIDITY AND MORTALITY ASSOCIATED WITH THIS DISEASE. After a brief overview of breast cancer epidemiology and risk assessment, this article describes screening and diagnostic imaging techniques as they are currently practiced to promote early breast cancer detection. We conclude with a review of image-guided needle biopsy techniques and a recommended approach to breast cancer screening in the general population.

EPIDEMIOLOGY OF BREAST CANCER: DAUNTING BUT SLOWLY IMPROVING

After nonmelanoma skin cancers, breast cancer is the most common form of cancer in women today, accounting for more than 1 in 4 cancers diagnosed in US women.1 If the current incidence of breast cancer remains constant, US females born today have an average risk of 12.7% of being diagnosed with breast cancer during their lifetime (ie, 1-in-8 lifetime risk), based on National Cancer Institute statistics.2,3 The American Cancer Society estimated that 178,480 new cases of invasive breast cancer and 62,030 new cases of in situ breast cancer would be diagnosed in the United States in 2007, and that 40,460 US women would die from breast cancer that year.1 Only lung cancer accounts for more cancer deaths in women.

The role of race and ethnicity
Breast cancer risk varies by race and ethnicity in the United States. After age 40 years, white women have a higher incidence of breast cancer compared with African American women; conversely, before age 40, African American women have a higher incidence compared with white women. African American women are more likely than their white counterparts to die from their breast cancer at any age. Incidence and death rates from breast cancer are lower among Asian American, American Indian, and Hispanic women compared with both white and African American women.1

Recent hopeful trends
Despite the daunting incidence numbers reviewed above, recent years have seen encouraging trends in US breast cancer epidemiology.

For invasive breast cancer, the growth in incidence rates slowed during the 1990s, and rates actually declined by 3.5% per year during the period 2001–2004.4 These changes are likely attributable to multiple factors, including variations in rates of mammography screening and decreased use of hormone replacement therapy after the 2002 publication of results from the Women’s Health Initiative trial. Still, the trend is encouraging.

Incidence rates of in situ breast cancer rose rapidly during the 1980s and 1990s, largely due to increased diagnosis by mammography, but have plateaued since 2000 among women aged 50 years or older while continuing to rise modestly in younger women.1

Meanwhile, the overall death rate from breast cancer in women declined by 2.2% annually from 1990 to 2004.1

RISK FACTORS AND RISK MODELING

Risk factors for breast cancer have been well described and include the following:

- Age (≥ 65 years vs < 65 years, although risk increases across all ages up to 80 years)
- Family history of breast cancer
• Late age at first full-term pregnancy (> 30 years)
• Never having a full-term pregnancy
• Early menarche and/or late menopause
• Certain genetic mutations for breast cancer (eg, in the BRCA1, BRCA2, ATM, and CHEK2 genes)
• Certain breast disorders, such as atypical hyperplasia or lobular carcinoma in situ
• High breast tissue density
• High bone density (postmenopausal)
• High-dose radiation to the chest.

The above risk factors are, in general, fixed. More elusive risk factors, in that they are variable and modifiable, include obesity, use of exogenous hormones (recent and long-term hormone replacement therapy; recent oral contraceptive use), alcohol use, tobacco use, diet, and a low level of physical activity. Breast implants are not a risk factor for breast cancer, though their presence does obscure breast tissue on imaging, limiting the detectability of a tumor when it does develop (see “Screening the Surgically Altered Breast” below).

Women with a genetic predisposition to breast cancer merit special consideration. Hereditary breast cancers account for about 5% to 10% of breast cancer cases, and the BRCA1 and BRCA2 mutations are responsible for 80% to 90% of these cases, while other gene mutations (noted above) or genetic syndromes account for the rest. Clinical options for managing women with a genetic predisposition include surveillance, chemoprevention, and prophylactic surgery. Detailed discussion of the management of these women is beyond the scope of this article, but readers are referred to http://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf for practice guidelines from the National Comprehensive Cancer Network.

Tools for risk assessment
Several tools are available to predict a woman’s risk of developing breast cancer. Probably the most widely used is the Gail model, which was published in 1989 and forms the statistical basis for the National Cancer Institute’s Breast Cancer Risk Assessment Tool, which is available for downloading at http://www.cancer.gov/bcrisktool. The model uses a woman’s personal medical and reproductive histories and her family history of breast cancer to predict her 5-year and lifetime risk of developing invasive breast cancer. Factors included in the risk calculation are age, race, number of first-degree relatives with a history of breast cancer, age at first live birth (or nulliparity), age at menarche, number of breast biopsies, and presence or absence of a history of atypical hyperplasia. The relative risk for each of these factors is multiplied to generate a composite risk. The Gail model has been validated for white women but has been shown to underestimate breast cancer risk in African American women; it remains to be validated for Hispanic women, Asian women, and other subgroups of women.

The commonly taught “triple test” for palpable breast lesions is another risk model that incorporates clinical findings. It consists of a physical examination, mammography, and fine-needle aspiration (in the “modified triple test,” ultrasonography replaces mammography). When all three elements of the test are concordant (either all benign or all malignant), the triple test has been reported to have 100% diagnostic accuracy.

A WORD ABOUT BREAST EXAMINATION

Breast self-examination
The role of breast self-examination is controversial in the literature. There are currently no data to support the contention that it increases detection of breast cancer.
cancer. As a result, the American Cancer Society no longer recommends that all women perform monthly breast self-exams, although it advises that all women be told about the potential benefits and limitations of breast self-examination (Table 1). Research suggests that structured breast self-examination is less important than self-awareness. Women who detect breast tumors themselves typically find them outside of a structured examination, such as when bathing or getting dressed.

Clinical breast examination
As noted in Table 1, regular clinical breast examinations are recommended by the American Cancer Society for asymptomatic women at average risk for breast cancer, with the recommended frequency depending on the woman’s age. The US Preventive Services Task Force takes the stance that there is insufficient evidence to recommend for or against breast cancer screening with clinical breast examination alone. While it is unclear precisely what contribution clinical breast exams make to the detection of breast cancer, they certainly provide clinicians an opportunity to raise awareness about breast cancer and educate patients about breast symptoms, risk factors, and new detection technologies.

### SCREENING MAMMOGRAPHY

Screening mammography is the single most effective method of early breast cancer detection, and the American Cancer Society recommends that women at average risk for breast cancer have annual screening mammograms beginning at age 40 years (Table 1).

#### The evidence base

The primary evidence supporting the recommendation for screening mammography comes from eight randomized trials that studied the effectiveness of screening mammography for cancer detection in Sweden, the United States, Canada, and the United Kingdom. Overall, breast cancers detected by screening mammography are smaller and have a more favorable history and tumor biology than those detected clinically without the use of imaging. A pooled analysis of the most recent data from all randomized trials of screening mammography in women aged 39 to 74 years showed a 24% reduction in mortality (95% CI, 18% to 30%) in women undergoing screening mammography, although not all individual trials showed a statistically significant mortality reduction.

#### The screening procedure at a glance

A screening mammogram, as distinguished from a diagnostic mammogram (Table 2), consists of two standard radiographic views of each breast (mediolateral oblique and cranio-caudal). The woman being screened is advised to wear no powders or deodorants and should be asymptomatic. Women with symptoms (eg, breast lump, focal tenderness, nipple discharge) should be scheduled for a diagnostic mammogram (Table 2), not a screening mammogram.

The mammography technologist obtains the standard radiographs of each breast, and computer-assisted detection software can be applied to the mammogram films to aid in the identification of abnormalities as a computer-generated second opinion. Although com-

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**TABLE 2**

<table>
<thead>
<tr>
<th>Screening mammogram</th>
<th>Diagnostic mammogram</th>
</tr>
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<tbody>
<tr>
<td>• Annual examination</td>
<td>• Performed as a follow-up to an abnormal screening mammogram or when patient is symptomatic (lump, pain, or nipple discharge)</td>
</tr>
<tr>
<td>• Patient is asymptomatic</td>
<td>• Examination is tailored to the patient’s issue and directed by an on-site radiologist</td>
</tr>
<tr>
<td>• Two standard views (mediolateral oblique and cranio-caudal) obtained of each breast</td>
<td>• Batch-read later by radiologist</td>
</tr>
<tr>
<td>• Batch-read later by radiologist</td>
<td>• Ultrasonography may be added, if necessary</td>
</tr>
</tbody>
</table>

**TABLE 3**

<table>
<thead>
<tr>
<th>BI-RADS categories for mammography reporting</th>
<th>Assessment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Incomplete</td>
<td>Further diagnostic imaging and/or review of prior studies needed</td>
<td></td>
</tr>
<tr>
<td>1 Negative</td>
<td>Routine yearly screening</td>
<td></td>
</tr>
<tr>
<td>2 Benign findings</td>
<td>Routine yearly screening</td>
<td></td>
</tr>
<tr>
<td>3 Probably benign findings</td>
<td>Short-term imaging follow-up at 6 months</td>
<td></td>
</tr>
<tr>
<td>4 Suspicious abnormality</td>
<td>Recommend biopsy</td>
<td></td>
</tr>
<tr>
<td>5 Highly suspicious of malignancy</td>
<td>Biopsy and treatment, as necessary</td>
<td></td>
</tr>
<tr>
<td>6 Known biopsy-proven malignancy</td>
<td>Continue ongoing treatment</td>
<td></td>
</tr>
</tbody>
</table>

BI-RADS = Breast Imaging Reporting and Data System
puter-assisted detection is not currently standard of
care, it is available at most institutions. The films are
read later by a radiologist who will interpret them
according to the American College of Radiology’s stan-
dard system of describing mammogram findings, called
the Breast Imaging Reporting and Data System (BI-
RADS). In this system, results are assigned a category
rating on a scale from 0 to 6 (Table 3). This standard-
ization allows physicians to use consistent language,
ensures better follow-up of suspicious findings, and
reduces interobserver variability.

**Analog vs digital**

Breast radiographs can be obtained by the traditional film-
screen (analog) method or obtained digitally (Figure 1).

Digital mammograms are radiographs that are
acquired digitally and allow digital enhancement to
aid in interpretation. When receiving a digital mam-
ogram, the woman being screened still undergoes
compression and positioning as for a conventional
film-screen mammogram, and the images are still pro-
duced with x-rays. However, digitization allows manip-
ulation of the images as they are being interpreted,
abling the radiologist to focus on areas of interest or
to "window" and "level" the image, similar to adjusting
the tint and contrast on a television set.

Research trials comparing digital and film mammogra-
phy, such as the Digital Mammographic Imaging Screen-
ing Trial (DMIST), have found digital mammomgra-
phy to be especially helpful in women with extremely
dense breasts, who have an elevated risk for breast can-
cer. For women with fatty breasts the differences
between the types of mammogram are less significant.

The type of mammogram a woman receives gener-
ally depends on the equipment available at the site
she visits. Digital mammography units currently cost
approximately 3 times as much as corresponding film-
screen units, yet digital mammograms command
reimbursement rates only about 1.6 times higher than
those for film mammograms (Table 4). A hard copy
of the digitized image can be printed, although the
hope is that eventually fewer mammogram images
will be printed and space-saving electronic storage
will supplant storage of printed films.

For further detail on digital mammography, readers
are referred to the recent review by D’Orsi and Newell.

**SCREENING THE SURGICALLY ALTERED BREAST**

Following surgical cancer treatment or reconstructive
surgery, screening of remaining breast tissue for cancer is
still performed and is just as essential to patient care as
presurgery screening. The first line of defense for any
patient with a surgically altered breast is mammography.

When a patient has had breast reconstruction fol-
lowing mastectomy, it is presumed that very little
breast tissue remains. There is no standard of care for
screening the nonbreast tissue introduced by the
reconstructive procedure. Nonetheless, at our institu-
tion we perform a single mediolateral oblique projec-
tion on any flap-reconstructed breast in light of rare
anecdotal accounts of cancer found in and around the
reconstructed breast. When problem-solving is needed
to evaluate a new palpable abnormality, special angled
views (tangential) and directed ultrasonography can be
used. We do not routinely perform screening mam-
mography on mastectomy patients who have had
reconstruction with implants, but we can investigate
areas of clinical concern (eg, due to palpable masses)
with directed ultrasonography.

The cosmetically altered breast presents its own
issues in cancer detection. Both silicone-gel and saline
implants obscure breast tissue that could contain can-
cer. For this reason, special implant-displaced views
are performed that allow visualization of a larger por-
tion of breast tissue beyond that allowed by standard mammograms. Therefore, an asymptomatic patient with implants who presents for screening mammography will have eight mammography views obtained instead of the routine four views.22

Patients who have had breast reduction, excisional biopsy, or prior breast conservation surgery (lumpectomy and radiation) are screened in a routine manner with mammography.23 Patients who have had prior surgical procedures often have architectural distortion at the surgical site, which is generally stable over time. Any prior surgical procedure can predispose the patient to the development of fat necrosis, which is a benign entity but can mimic cancer in its early phases through the development of calcifications and, occasionally, a new palpable lump. We most commonly confront this issue in the period 2 to 4 years after the operation.24 Occasionally the findings are such that a biopsy is needed to determine whether fat necrosis is the cause. In this population, magnetic resonance imaging (MRI) can also be used as an adjunctive tool, and can sometimes clarify the presence of fat necrosis and other postoperative findings, such as seroma, hematoma, or inflammation. In other instances, only a biopsy can determine what a particular finding represents.

**DIAGNOSTIC MAMMOGRAPHY**

Any mammography performed for a problem-solving purpose is considered diagnostic mammography (Table 2); the exam is tailored to the patient’s individual issue.25 Diagnostic mammography requires the presence of a qualified radiologist at the time of imaging. The goal is to come to a final conclusion about the mammographic or clinical finding at the time of the patient’s visit. Special views are usually performed that include, but are not limited to, spot-compression or spot-magnification views, depending on the finding.26 The patient is then given a same-day written account of the results at the conclusion of the study.

Examples of problems that may prompt diagnostic mammography include patient-reported palpable findings, screening mammography findings that are recalled for further investigation, or physician-detected findings. Often, ultrasonography is also used at the same visit and its results are integrated with the mammography findings to arrive at the final impression.

**BREAST ULTRASONOGRAPHY AND BREAST MRI**

Ultrasonography and MRI are two very useful adjunctive tools for breast lesion detection and analysis. At this time, however, neither is a replacement for screening mammography as a primary screening modality; rather, each is used in a complementary fashion for lesion analysis and biopsy guidance.10,27

**Ultrasonography: Best for further study of areas of interest**

Ultrasonography uses high-frequency sound waves to create a picture using a probe directed to an area of interest in the breast. The optimal probe for breast imaging is one typically operating in a frequency of 12 to 18 MHz and 4 cm in scanning width. Because ultrasonography provides views of only a small area of breast tissue at a time, it is operator and patient dependent. It is best used when a known area of interest needs further evaluation, such as when a patient reports a palpable abnormality or when a mass is detected on mammography.

Ultrasonography uses no ionizing radiation, so it is especially helpful in young or pregnant women who present with a palpable abnormality. It is also useful for patients who have recently undergone a surgical procedure. As ultrasonography is currently used, no compression is needed and it can be performed easily in patients with limited mobility. Needle biopsies are most easily performed using ultrasonographic guidance.

**MRI: An emerging adjunct under study in high-risk patients**

Breast MRI is an emerging modality under active research that shows promise for adjunctive breast imaging. It is commonly being used as a tool for local staging in women with newly diagnosed breast cancer.28,29 Current research is focused on its suitability as a screening modality, in conjunction with mammography, in high-risk populations based on family his-

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**TABLE 4**

<table>
<thead>
<tr>
<th>Screening option</th>
<th>Approved by FDA?</th>
<th>HCPSC code</th>
<th>Medicare reimbursement*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analog screening mammography</td>
<td>Yes</td>
<td>77057</td>
<td>$78.13</td>
</tr>
<tr>
<td>Digital screening mammography</td>
<td>Yes</td>
<td>G0202</td>
<td>$124.50</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>No</td>
<td>77059</td>
<td>$933.77</td>
</tr>
<tr>
<td>Computer-aided detection</td>
<td>Yes</td>
<td>77051</td>
<td>$16.07</td>
</tr>
<tr>
<td>Clinical breast exam</td>
<td>N/A</td>
<td>G0101</td>
<td>$33.94</td>
</tr>
<tr>
<td>Breast self-exam</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*2007 Medicare reimbursement for Cleveland, Ohio.
FDA = US Food and Drug Administration; HCPSC = Healthcare Common Procedure Coding System; N/A = not applicable.
and other factors addressed in the Gail model and similar risk models.

The limitations of breast MRI include its high cost, unsuitability for some patients (eg, the obese [due to table weight constraints], patients with pacemakers, patients with renal failure), the potential for unnecessary biopsies due to decreased specificity, lack of portability, and the length of time required for imaging.

Breast MRI is a four-dimensional study, with time as the fourth dimension (in addition to length, width, and depth). The patient receives an intravenous line and is given gadolinium for contrast enhancement. Imaging time depends on the protocol used and is specific to the imaging center, but it typically involves approximately 20 minutes of motionless scan time for the patient. Lesions are detectable by their level of vascularity, and diagnostic images are dependent on adequate contrast enhancement (Figure 2). Several software packages are commercially available that perform post-processing of breast MRI data. Although cancer on MRI has a characteristic enhancement curve, there is much overlap with benign entities; as a result, morphologic characteristics of the lesion—such as size, shape, and borders—are paramount.

When a lesion is initially detected with MRI, an attempt is usually made to identify it with ultrasonography as well, owing to the ease of ultrasonography-guided biopsy. It is important, however, for an imaging center that performs breast MRI to be able to perform biopsies using MRI guidance since not all lesions are identifiable by other modalities. Breast MRI studies are not easily portable between imaging facilities since a typical study contains a thousand or more images that are best viewed on a site-specific workstation monitor.

**HISTOLOGIC CONFIRMATION**

Once an abnormality is detected on imaging, a confirmatory histologic diagnosis is needed before embarking on medical or surgical treatments. Image-guided biopsy plays a critical role in this regard. In our breast imaging section, we perform ultrasonography-guided core needle biopsy and aspiration, stereotactic needle biopsy, and MRI-guided needle biopsy, as well as wire localizations on the day of surgery. All procedures performed are considered minimally invasive and are suitable for a vast majority of patients for whom they are recommended.

**Ultrasonography-guided procedures**

Ultrasonography-guided core needle biopsy is the modality of choice for most patients when a suspicious abnormality is visible on ultrasonography. Generally, the patient is placed in an angled supine position, with her arm elevated for optimal lesion accessibility. Following administration of a local anesthetic, a small nick is made in the skin and a specialized 14- or 18-gauge spring-loaded core biopsy needle is inserted during real-time imaging with the ultrasonographic probe (Figure 3). Several samples are obtained, and the pathologic diagnosis is generally available within a few working days. Breast core biopsy needles are also commercially available as handheld vacuum-assisted devices, which can sample larger amounts of tissue in a short time but are more expensive and often accompanied by a noisy vacuum device.
TABLE 5
Recommendations for breast MRI screening as an adjunct to mammography

Recommend annual MRI screening (based on evidence *)
- BRCA mutation
- First-degree relative of BRCA carrier, but untested
- Lifetime risk ~20%–25% or greater, as defined by BRCAPRO† or other models that are largely dependent on family history

Recommend annual MRI screening (based on expert consensus opinion)
- Radiation to chest between age 10 and 30 years
- Li-Fraumeni syndrome§ (patient or first-degree relatives)
- Cowden and Bannayan-Riley-Ruvalcaba syndromes¶ (patient or first-degree relatives)

Insufficient evidence to recommend for/against MRI screening#
- Lifetime risk 15%–20%, as defined by BRCAPRO or other models that are largely dependent on family history
- Lobular carcinoma in situ or atypical lobular hyperplasia
- Atypical ductal hyperplasia
- Heterogeneously or extremely dense breast on mammography
- Personal history of breast cancer, including ductal carcinoma in situ

Recommend against MRI screening (based on expert consensus opinion)
- Lifetime risk < 15%

* Evidence from nonrandomized screening trials and observational studies.
† A statistical model and software package for genetic counseling of women at high risk of hereditary breast or ovarian cancer.
‡ Based on evidence of lifetime risk for breast cancer.
§ A rare disorder that greatly increases the risk of developing several types of cancer, including breast cancer, particularly in children and young adults.
¶ Hamartoma syndromes associated with increased incidence of several malignancies, especially a marked increase in the incidence of breast carcinoma in women.
# Payment should not be a barrier. Screening decisions should be made on a case-by-case basis, as there may be particular factors to support MRI. More data on these groups is expected to be published soon.


Stereotactically guided procedures
Stereotactic core biopsy is performed when lesions—usually calcifications, but sometimes masses—are visible only on mammography. Stereotactic refers to the means by which the target is localized, ie, with a “stereo pair” of digital mammogram pictures with a small field of view. The patient is placed in a prone position with the breast of interest placed through a hole at the undersurface of the table in a light compression. The biopsy unit is attached to a dedicated computer that calculates coordinates. The needle is then brought to the coordinate position for sampling to take place.

The biopsy needle used for this procedure is vacuum-assisted, which means the needle is placed only one time, and samples in the vicinity of the target are vacuumed into a reservoir for retrieval. If the target is calcifications, a specimen radiograph is routinely performed to verify adequate sample acquisition before the patient leaves the biopsy table. When the original target is no longer visible, a titanium marker clip is often placed. This facilitates localization of the biopsied area should surgery be needed.

Stereotactic biopsy has several limitations that ultrasonography-guided biopsy does not. The patient must be cooperative and mobile enough to get on the table and hold a prone position for the duration of the procedure (about 45 minutes). If the patient is taking warfarin or has a bleeding diathesis, preprocedure steps such as clinical evaluation to check the international normalized ratio and prothrombin time, or even stopping the warfarin temporarily, may be needed to minimize bleeding during the procedure, as a 9- or 12-gauge needle is used.

Stereotactic biopsy is also limited by lesion position. A far posterior lesion may not be accessible if it does not reach through the hole in the table. Also, there is a limit to the compressed thinness of breast tissue that can be biopsied. Finally, most tables used for stereotactic biopsy have a functioning weight limit of 300 pounds.

Open surgical biopsy
A final option is open surgical biopsy, which is used when the more minimally invasive techniques are equivocal, discordant, or impossible due to the limitations noted above, or when atypical cells are found.

HOW SHOULD WE SCREEN OUR PATIENTS?
The various screening options for breast cancer are listed in Table 4, along with their market approval status and Medicare reimbursement levels.

For women at average risk for breast cancer, the American Cancer Society recommends an annual mammogram and clinical breast examination by a
For women at high risk for developing breast cancer (>20% to 25% lifetime risk, based on the Gail model or similar risk models), breast MRI should be considered as an adjunct to annual screening mammography (Table 5). Evidence is currently insufficient, however, to support the adjunctive use of breast MRI for women with other risk factors (Table 5), although studies are ongoing.

In conclusion, the process of finding breast cancer includes regular screening with mammography and clinical breast examination (plus MRI in high-risk women) and the diagnostic modalities of ultrasonography, MRI, and diagnostic mammography. Our ultimate goal is to find cancer at the earliest time possible by all means necessary for the individual patient.

REFERENCES


