REVIEW

CME CREDIT

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How should we screen for breast cancer? Mammography, ultrasonography, MRI

ABSTRACT

Of the imaging techniques currently available to evaluate women for breast disease, mammography remains the mainstay of breast cancer screening, but recent guidelines have included magnetic resonance imaging (MRI) for the screening of some women at high risk. Whole-breast ultrasonography for screening has not been established as useful and so should not be offered routinely to patients.

KEY POINTS

Most major medical organizations recommend starting routine screening mammography for women at age 40.

If a *screening* mammogram is abnormal or has findings of unclear significance, the patient should be referred for *diagnostic* mammography.

If a palpable breast mass is discovered, the patient should be referred for diagnostic mammography and ultrasonography.

Breast MRI can be considered in addition to mammography for screening in high-risk patients, such as women with a BRCA gene mutation, a strong family history of breast cancer or a personal history of ovarian cancer, or women who have received high-dose chest radiation, such as mantle radiotherapy for Hodgkin disease. Other high-risk groups in which breast MRI is currently being studied are women with a personal history of breast cancer, women with a history of atypical duct hyperplasia or lobular carcinoma in situ, and women with an elevated Gail breast cancer risk assessment score.

THE ANSWER TO HOW WE should screen for breast cancer is, "Very carefully." No screening procedure is perfect, women vary greatly in their breast cancer risk, and screening may lead to unnecessary procedures and alarm. Therefore, physicians must carefully consider which screening regimen is right for each patient.

While many issues surrounding breast cancer screening are still unresolved, general guidelines have now been implemented on the basis of data accrued over many years.

In this article, we summarize the most current guidelines and also comment briefly on screening examinations that hold promise but have not yet earned a place in routine breast cancer screening.

Breast cancer survival has improved over the past few decades. In the 1940s, the 5-year survival rate for early-stage localized disease (no lymph node involvement or metastasis) was 72%, which has improved to 97% today.[1] This improvement in survival is in large measure attributable to the increased and effective use of screening mammography in asymptomatic patients, with improved treatment protocols also playing a role. Early detection of breast cancer, ie, before it is clinically apparent, is important both to patients and to their physicians. In this article, we also examine how the careful use of breast imaging techniques—mammography, ultrasonography, and magnetic resonance imaging (MRI)—can improve breast cancer detection in women.

WHO SHOULD UNDERGO MAMMOGRAPHIC SCREENING?

Experts have long agreed that screening mammography reduces the rate of death

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Current breast biopsy techniques

CORE NEEDLE BIOPSY

A large-bore automated cutting needle is used to remove three to five solid cylindrical tissue samples ("cores"). For adequate samples, a 14-gauge or larger needle is used. These procedures are performed with guidance by ultrasonography, stereotactic imaging, or MRI. In most cases this is the preferred method of biopsy, since it usually provides adequate tissue for tumor grading and performance of receptor studies, both of which are important in formulating the patient's treatment plan.

FINE-NEEDLE ASPIRATION

A smaller-bore (usually 18- or 20-gauge) needle is used to obtain cytologic samples from a suspicious breast mass. This is technically easy to perform but is less used by radiologists now that automated core-biopsy instruments are more widely available. Fine-needle aspiration can often make the diagnosis of malignancy but does not provide sufficient tissue for more detailed studies, and thus generally necessitates obtaining a second (core) biopsy specimen for study before definitive treatment can be planned. In addition, the satisfactory interpretation of cytologic specimens requires pathologists with special expertise in cytopathology. Fine-needle aspiration is not recommended for the evaluation of suspected ductal carcinoma in situ.

EXCISIONAL BIOPSY

This procedure is performed by a surgeon in the operating room, usually to remove the entire mass or suspicious area. Excisional biopsy requires preoperative wire localization if the lesion is not palpable.

Screening mammography lowers the mortality rate by about 20%

from breast cancer in women who begin screening in their 50s and 60s. These conclusions are supported by results from eight randomized clinical studies of the efficacy of screening mammography. For women ages 50 to 69, screening mammography decreased the death rate from breast cancer by 20% to 35%.[2,3]

The value of screening mammography for women in their 40s has been more recently addressed; meta-analyses now reveal that screening mammography decreases breast cancer death rates by about 20%.[2,4]

For women over age 70 there are fewer studies. One study in the Netherlands found that mammographic screening in women over age 65 led to a 55% decrease in the breast cancer death rate.[5]

Annual screening mammography for women age 40 and older is covered by major insurance carriers in the United States. In 2007, the Medicare reimbursement for bilateral screening mammography was $93.03.

The principal aim of screening mammography is the same for all age groups: to detect breast cancer at an early stage, before it becomes clinically apparent, and thereby to avoid the illness and death that accompany locally advanced or widespread breast cancer.

A recent study[6] considered the separate effects of screening mammography and of adjuvant therapy on the breast cancer death rate, drawing on the experience of multiple institutions. From 1975 to 2000, the overall reduction in breast cancer deaths was 24%. The study estimated that the portion of the reduction attributed to screening mammography ranged from 28% to 65% (median 46%), with the rest attributed to the use of adjuvant therapy.[6] The variability in the reduction of the death rate was attributed to variations in the inclusion criteria of the participating groups: eg, some groups included patients with ductal carcinoma in situ, and other studies included only patients with invasive carcinoma.

General recommendations for mammographic screening

Screening mammography should begin at age 40. This recommendation is supported by major medical organizations, including the American Cancer Society, the American College of Radiology, the National Cancer Institute, the American College of Obstetricians and Gynecologists, and the American Medical Association.[7] In our practice, we follow the American College of Radiology recommenda-

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tions for routine screening at yearly intervals.

Screening mammography is most effective between ages 50 and 59 and should be routinely recommended.

There is no established upper age limit to the beneficial use of screening mammography. According to the 2004 revised American College of Radiology guidelines,[8] "It is unclear at what age, if any, women cease to benefit from screening mammography. Because this age is likely to vary depending on the individual's overall health, the decision as to when to stop routine mammography screening should be made on an individual basis by each woman and her physician."[8] The American Cancer Society further recommends that "as long as a woman is in reasonably good health and would be a candidate for treatment, she should continue to be screened with mammography."[9]

Special recommendations

If a patient has a first-degree relative who has had breast cancer, screening mammography should commence 10 years earlier than the age at which that relative was diagnosed, or at age 25, whichever is older. For example, if the patient's mother was diagnosed with breast cancer at age 39, screening mammography for her daughters should begin at age 29.

Patients with a personal history of atypical duct hyperplasia or lobular carcinoma in situ are candidates for increased surveillance, usually including a clinical breast examination and mammography every 6 months. (High-risk patients may also be candidates for breast MRI, as discussed later in this article).

Patients who have received high-dose chest radiation (mantle radiotherapy) are at increased risk of developing radiation-induced breast cancer. For this reason, a woman with a diagnosis of Hodgkin lymphoma for example, who received mantle radiotherapy, should begin mammographic screening 8 years after her radiation treatment.

'Mammogram density' is now considered a risk factor for breast cancer. In fact, the risk associated with mammogram density may be greater than the risk from many other risk factors.[10–13] Mammogram density is thought to be an inherited phenomenon,[14] but it can also be caused by hormone therapy. Women on long-term hormone therapy are called back more often for further evaluation and have a higher rate of benign breast biopsies carried out to evaluate suspicious findings.[15]

The addition of breast ultrasonography or MRI in selected cases of mammogram density may be useful. Digital mammography may also play a role in patients with mammogram density and is currently undergoing evaluation in large-scale trials.[16] Its clinical usefulness has yet to be fully elucidated.

WHAT HAPPENS IF THE MAMMOGRAM SHOWS AN ABNORMALITY?

Screening mammography may detect a mass lesion, suspicious microcalcifications, focal asymmetry, or architectural distortion. It may detect lymph nodes of abnormal size, contour, or density. It may also detect more subtle changes such as skin thickening. If any of these findings is noted, diagnostic mammography is recommended.

About 10% of women who undergo screening mammography are called back for further evaluation. Of these patients, around 10% will have a breast biopsy, of which 25% to 40% will be positive for breast cancer.[17,18] Using estimates from the Mammography Quality Standards Act guidelines, of 1,000 asymptomatic patients screened by mammography, 2 to 10 patients will be shown to have breast cancer. This range allows for variations encountered in different screening populations.

There is as yet no upper age limit to the beneficial use of screening mammography

WHEN SHOULD WE ORDER DIAGNOSTIC MAMMOGRAPHY?

If a patient presents with a breast complaint, or if an abnormality is noted on the clinical breast examination, then diagnostic mammography should be ordered. In contrast to screening mammography, which consists of two standard views of each breast, diagnostic mammography includes extra views or studies tailored to evaluate the finding in question.

Reasons to refer a patient for diagnostic mammography include an abnormal screening mammogram, a breast mass or thickening on palpation, focal breast pain, clear or bloody

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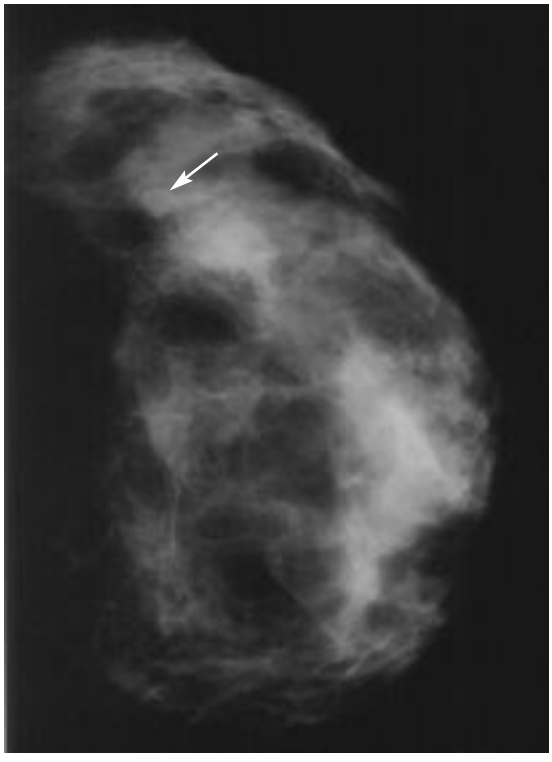

FIGURE 1. Screening mammography reveals a mass (arrow).

FIGURE 2. Diagnostic mammography magnifies the mass (arrow).

Screening for breast cancer should begin with mammography

nipple discharge, nipple retraction, a concerning palpable lymph node, or abnormal skin changes such as erythema or peau d'orange. If a breast mass is palpated, an ultrasonographic examination is ordered in addition to diagnostic mammography (FIGURES 1–3).

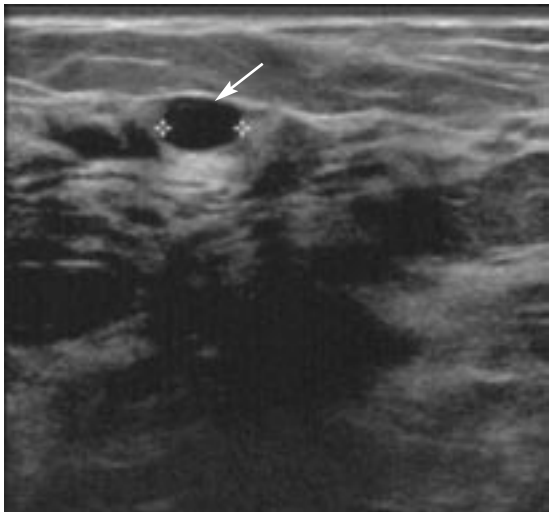

FIGURE 3. Ultrasonography further defines the mass (arrow) as a simple cyst.

If diagnostic mammography or ultrasonography reveals suspicious findings, biopsy is recommended (see "Current breast biopsy techniques," page 898). In a small number of cases in which suspicion of cancer is very low, a conclusion of "probably benign" may be given, with recommendations for short-term follow-up.

A PALPABLE MASS WITH NEGATIVE MAMMOGRAPHIC AND ULTRASONOGRAPHIC STUDIES

What should be done when a mass is palpable, but mammographic and ultrasonographic studies are negative? This will depend on the situation. Often, ultrasonography will show the palpable lump to be a normal fibrous ridge or a region of benign asymmetry that corresponds definitely to the palpable findings. In these cases, no further workup is needed. But if clinical suspicion remains high despite the negative imaging results, biopsy should be considered.

Fine-needle aspiration is an easy, minimally invasive way to obtain a sample of a palpable mass. It can be performed in the office. Core biopsy can be carried out on a palpable mass using imaging guidance in order to assure a safe trajectory for the cutting needle.

If the palpable mass is not easily accessible (eg, if it is close to the chest wall or in the axil-

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la), or if the patient is very anxious, an excisional biopsy can be performed to remove the entire mass.

No imaging technique can exclude breast cancer with 100% accuracy. This is true for mammography, ultrasonography, and MRI.

ULTRASONOGRAPHY IN BREAST CANCER SCREENING: ADJUNCTIVE ROLE ONLY

Should we use ultrasonography to screen for breast cancer? In a word, no. The rationale and limitations summarized below—from the Position Statement on Screening Breast Sonography in Dense Breasts, promulgated by the Society of Breast Imaging[19]—reflect the expert consensus on this issue.

Screening mammography is an important tool, but it can miss some breast cancers, especially in women with dense breast tissue. For this reason, it was thought that ultrasonographic screening might improve breast cancer detection rates.[20] Indeed, breast ultrasonography can detect some invasive cancers that mammography and physical examination miss, but the number of cancers found with ultrasonography alone remains small. Also, ultrasonography does not detect most microcalcifications, which are the typical findings in ductal carcinoma in situ. In fact, 75% of cancers missed by ultrasonography were ductal carcinoma in situ and 25% were invasive carcinomas.

In addition, the results of ultrasonography can vary widely, depending on the expertise of the technician. Indeterminate findings can lead to the increased use of costly and perhaps unnecessary interventions. There are at present no data to support whole-breast ultrasonographic screening to decrease breast cancer death rates. A study by the American College of Radiology Imaging Network (called ACRIN Study 6666) is under way to investigate this issue.

Screening for breast cancer should begin with mammography. Ultrasonography can be added to evaluate a mass or to clarify focal mammographic findings. According to a position statement of the Society of Breast Imaging,[19] it "has not been established that women will benefit from the incorporation of sonography into routine breast cancer screening programs… At the present time, it is not the standard of care to offer or perform this examination." In our practice, we do not recommend or offer screening with breast ultrasonography.

MAGNETIC RESONANCE IMAGING AND BREAST CANCER SCREENING

What is breast MRI?

MRI uses magnetic fields along with radiofrequency transmitters and receivers to produce cross-sectional images of the human body. To image the breast, specialized imaging receivers ("coils") that encompass each breast are used.

For cancer detection protocols, a contrast agent that contains gadolinium is injected intravenously to help identify tissues that "handle" the agent in an abnormal way, which is a possible sign of the neovascularity seen in many breast cancers. MRI involves no ionizing radiation, and most patients tolerate the contrast agent well.

The procedure. The patient lies prone on a padded table that contains the two breast coils. The breasts are positioned within the coils, sometimes with mild compression to maintain constant positioning. The table is advanced into the magnet and a preselected series of scans is carried out, both before and after the injection of contrast material. The entire study takes about 40 to 50 minutes, with about half of that time devoted to patient preparation, placement of a small-gauge intravenous catheter, and patient positioning. The scans are acquired rapidly, but image reconstruction and post-processing continue after the patient has left the scanner.

Contraindications to MRI include implant expanders, cardiac pacemakers, neurostimulator devices, extreme claustrophobia, and morbid obesity.

No imaging study can exclude breast cancer with 100% accuracy

What are the disadvantages of breast MRI?

An important disadvantage of breast MRI is the rate of false-positive results. The sensitivity of breast MRI is high but the specificity is low. Breast cysts, fibroadenomas, papillomas, and fibrocystic changes may all appear as abnormalities on contrast images, resulting in unnecessary biopsies. In a study of breast MRI in high-risk women, many of whom were

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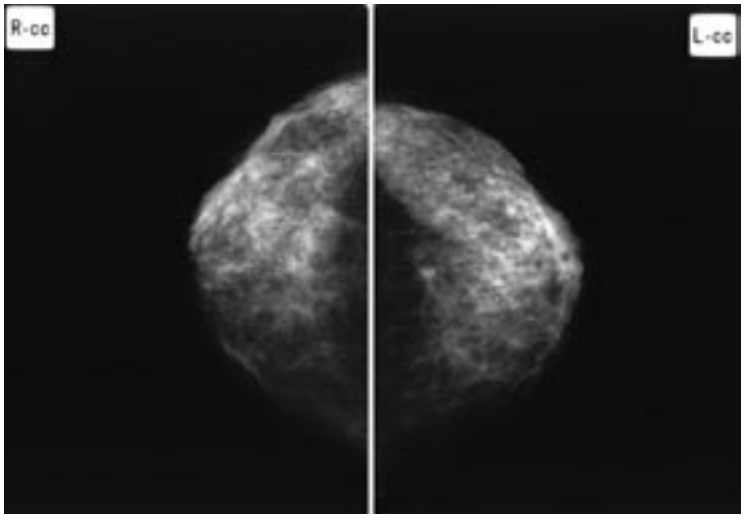

FIGURE 4. This mammogram shows mild asymmetry of the left breast.

young and had very dense breast tissue, screening MRI led to three times as many benign breast biopsies as mammography.[21] However, one could argue that in high-risk populations the sensitivity of mammography is quite low and may be of limited value, making MRI an imperfect but better tool.[22]

Ultrasonography can clarify a focal finding on the clinical exam or mammogram

Another disadvantage of breast MRI is that it does not detect microcalcifications, which are often associated with ductal carcinoma in situ. These calcifications are readily apparent on mammography. Breast MRI is also not sensitive in detecting lobular cancers.

A recent study in Germany in high-risk women found breast MRI to have a sensitivity of 92% in detecting ductal carcinoma in situ (DCIS),[23] but in general DCIS remains a mammographic diagnosis.

Other major drawbacks to using breast MRI include cost and limited access. Fees for breast MRI range from $3,000 to $4,000, which is 10 times that of mammography. Unlike mammography, breast MRI is not routinely covered by insurance. Screening MRI protocols have yet to be developed, and access to breast MRI remains limited.

Who is a candidate for screening with MRI?

The average lifetime risk of breast cancer for an American woman is now one in seven.[17] However, the risk of breast cancer in women with a BRCA1 gene mutation is 3.2% by age 30, 19% by age 40, 50% by age 50, and 85% by age 70. The lifetime risk for carriers of BRCA1 or BRCA2 mutations is 50% to 85%.[24] Breast cancers in women with a mutation often occur at a young age, are "aggressive" with a high nuclear grade, and lack estrogen receptors.[25] At the time of diagnosis, half of these breast cancers have already spread to axillary lymph nodes.[22]

Up to this point, strategies to follow these patients have included bilateral prophylactic mastectomy, prophylactic chemotherapy with tamoxifen, and early surveillance, ie, beginning clinical breast examinations and mammographic screening at age 25 to 30.

The usefulness of breast MRI in these high-risk patients is now being studied. Investigators in the United Kingdom looked at mammography vs contrast-enhanced MRI in 649 asymptomatic women with a known BRCA1, BRCA2, or TP53 mutation or a strong family history of breast cancer. MRI was significantly more sensitive (77% vs 40%) but less specific (81% vs 93%) than mammography. In particular, MRI was significantly more sensitive than mammography in patients with a BRCA1 mutation and their first-degree relatives (92% vs 23%).[21,26]

Screening breast MRI is proving to be a useful adjunct to mammography in patients with a BRCA mutation. In addition to these patients, the American Cancer Society has recently recommended that other high-risk patients pursue breast MRI. These include women with a 20% to 25% or greater lifetime risk of breast cancer: ie, women with a strong family history of breast cancer or ovarian cancer and women with a history of mantle radiotherapy for Hodgkin disease.[27]

Insurance often covers the cost of breast MRI for patients in these high-risk groups. High-risk patients can also obtain breast MRI under research protocols in which there is no charge to the patient.

In our practice, candidates for annual screening breast MRI include:

- Women who carry a BRCA mutation
- Women with a strong family history of breast cancer
- First-degree relatives of a BRCA carrier, but untested
- Women with a strong family history or a personal history of ovarian cancer

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- Women who were treated for Hodgkin disease with radiation to the chest.
- Women known to have a hereditary breast cancer syndrome and their first-degree relatives.

Screening MRI is currently under investigation in patients with a history of atypical duct hyperplasia or lobular carcinoma in situ or with an elevated Gail score (ie, a 5-year risk of developing breast cancer ≥ 1.7%).

In carefully selected cases, MRI may be helpful in the evaluation of equivocal or suspicious mammographic findings; however, detailed mammographic evaluation and ultrasonography should be done first.

Important note: Breast MRI may not detect some in situ carcinomas and other low-grade benign or malignant lesions and is only an *adjunct* to mammography. Breast MRI should *never* be offered as a substitute for conventional screening mammography.

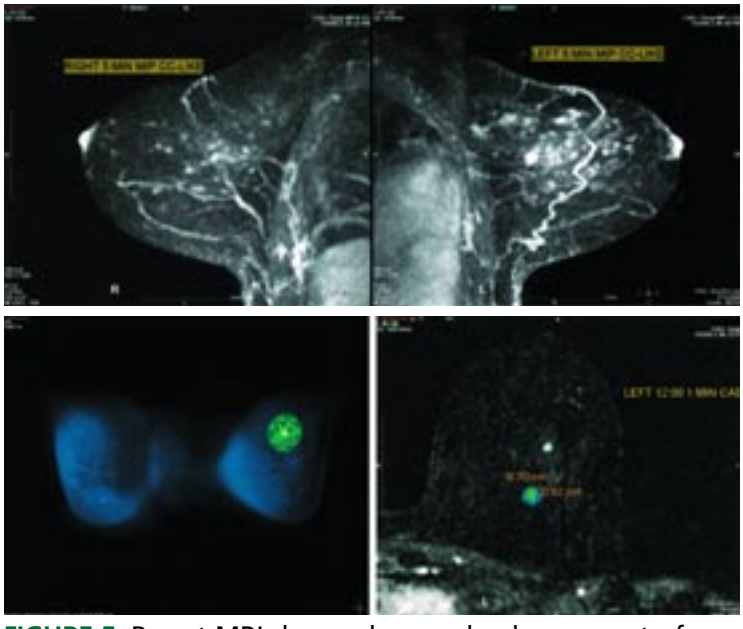

FIGURE 5. Breast MRI shows abnormal enhancement of a single lesion corresponding in size and location to the left mammographic asymmetry.

BREAST CANCER SCREENING GUIDELINES AS APPLIED IN DAILY PRACTICE

A 56-year-old white woman is seen at the breast center for her annual examination and mammographic evaluation. She is considered at high risk because of a family history of breast cancer—her mother and sister—and her elevated 5-year Gail score (5.0%).

Her breast examination is negative and her mammogram shows mild asymmetry on the left (FIGURE 4). Because she is at high risk, breast MRI is ordered and reveals a small mass on the left near the area of asymmetry (FIGURE 5).

She is taken to surgery and is found to have a 5-mm breast cancer with negative axillary lymph nodes. She undergoes radiation therapy and begins anastrozole (Arimidex) therapy. Cytotoxic chemotherapy was not necessary.

PATIENTS WITH BREAST CANCER: ANOTHER HIGH-RISK GROUP

No discussion of breast MRI would be complete without mentioning another high-risk group: patients with breast cancer.

A study of breast MRI in women recently diagnosed with breast cancer[28] found that MRI detected contralateral breast cancer in up to 10% of women initially diagnosed with unilateral breast cancer. The contralateral breast cancers in these women were missed by both clinical and mammographic evaluation.

These results suggest that breast MRI may be a valuable tool in evaluating women at the time of the initial breast cancer diagnosis. However, more evidence is needed from large-scale clinical trials before clinicians can recommend routine screening MRI for long-term follow-up of patients with a personal history of breast cancer.

MRI is not a substitute for conventional screening mammography

MUCH WORK IS YET TO BE DONE

In a report just released by the American Cancer Society, the breast cancer mortality rate decreased by 2.2% per year between 1990 and 2004.[29] However, in African American women the breast cancer death rate declined by only 1.6% per year and remained unchanged among Asian Americans/Pacific Islanders and Alaskans/Native Americans. Reasons for the differences in mortality rates remain unclear, and further research is needed. In the same report, it appears that breast cancer incidence is more complex than previously thought. Access to mammography and the

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decline in hormone therapy use may be contributing factors.

The decrease in screening mammogram rates is also of concern. Almost one-third of American women are not undergoing mammographic screening at appropriate intervals.[30] Most women who are not having routine mammograms are not receiving a recommendation for mammography from their physician. We must continue to communicate to our patients the importance of routine screening mammography and offer our high-risk patients additional breast imaging when appropriate. ■

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