Breast Cancer Screening With Imaging: Recommendations From the Society of Breast Imaging and the ACR on the Use of Mammography, Breast MRI, Breast Ultrasound, and Other Technologies for the Detection of Clinically Occult Breast Cancer

Carol H. Lee, MD, D. David Dershaw, MD, Daniel Kopans, MD, Phil Evans, MD, Barbara Monsees, MD, Debra Monticciolo, MD, R. James Brenner, MD, Lawrence Bassett, MD, Wendie Berg, MD, Stephen Feig, MD, Edward Hendrick, PhD, Ellen Mendelson, MD, Carl D'Orsi, MD, Edward Sickles, MD, Linda Warren Burhenne, MD

Screening for breast cancer with mammography has been shown to decrease mortality from breast cancer, and mammography is the mainstay of screening for clinically occult disease. Mammography, however, has well-recognized limitations, and recently, other imaging including ultrasound and magnetic resonance imaging have been used as adjunctive screening tools, mainly for women who may be at increased risk for the development of breast cancer. The Society of Breast Imaging and the Breast Imaging Commission of the ACR are issuing these recommendations to provide guidance to patients and clinicians on the use of imaging to screen for breast cancer. Wherever possible, the recommendations are based on available evidence. Where evidence is lacking, the recommendations are based on consensus opinions of the fellows and executive committee of the Society of Breast Imaging and the members of the Breast Imaging Commission of the ACR.

Key Words: Screening, breast cancer, recommendations, mammography, breast ultrasound, breast MRI

J Am Coll Radiol 2010;7:18-27.

INTRODUCTION

The significant decrease in breast cancer mortality, which amounts to nearly 30% since 1990, is a major medical success and is due in large part to the earlier detection of breast cancer through mammographic screening. Nevertheless, major efforts continue to build on this success by developing additional methods to screen for early breast cancer. Consequently, recommendations for breast cancer screening with imaging technologies have become increasingly complex. Several organizations, most notably the American Cancer Society (ACS) [1], have guidelines that are largely evidence-based, for how screening mammography should be used. In addition, the ACS has issued guidelines, also based predominately on existing evidence, for the use of magnetic resonance imaging of the breast to screen for breast cancer [2]. However, there are gaps in these guidelines, undoubtedly due to a lack of data concerning many aspects of the optimal

Department of Radiology, Memorial Sloan-Kettering Cancer Center, New York, New York.

Corresponding author and reprints: Carol H. Lee, Memorial Sloan-Kettering Cancer Center, Department of Radiology, 300 E 66th Street, Room 729, New York, NY 10021; e-mail: leec1@mskcc.org.

Disclosures: P. Evans, Hologic, Inc., consultant, Scientific Advisory Board. B. Monsees, Hologic, Inc., member, Advisory Board. L. Bassett, Hologic, Inc., consultant, Research Advisory Committee. W. Berg, Naviscan, Inc., consultant; Medipattern, Inc., consultant. E. Hendrick, GE Healthcare, consultant, member, Advisory Board; Koning, Corp., member, Advisory Board; Bracco Imaging, SpA, member, Advisory Board. E. Mendelson, Hologic, Inc., member, Medical Advisory Board; Siemens Medical Systems, investigator; Supersonic Imaging, investigator and speaker; Toshiba Ultrasound, speaker. C. D'Orsi, Hologic, Inc., consultant. L.W. Burhenne, Hologic, Inc., member, Advisory Committee.

0091-2182/10/$36.00 • DOI 10.1016/j.jacr.2009.09.022

utilization of available screening tests. To address some of these gaps, the Society of Breast Imaging (SBI) and the ACR, whose members are directly responsible for performing these screening tests, have performed and analyzed many of the trials establishing appropriate screening algorithms, and have the most expertise in these technologies, are issuing these guidelines and recommendations for breast cancer screening. Whenever possible, these are based on peer-reviewed published scientific data. Where data are lacking, the recommendations reflect expert consensus opinions by the fellows of the SBI and the members of the Breast Imaging Commission of the ACR. These guidelines and recommendations are intended to suggest appropriate utilization of imaging modalities for screening. They are not intended to replace sound clinical judgment and are not to be construed as representing the standard of care. It should be remembered that mammography is the only imaging modality that has been proven to decrease mortality from breast cancer.

The SBI and the ACR also wish to remind women and their physicians that in those instances in which there is a concern that risk for developing breast cancer is considerably elevated above that of the general population, consultation with appropriate experts in breast cancer genetics or high-risk management is desirable.

SOCIETY OF BREAST IMAGING AND AMERICAN COLLEGE OF RADIOLOGY RECOMMENDATIONS FOR IMAGING SCREENING FOR BREAST CANCER

A. BY IMAGING TECHNIQUE

1. Mammography

- Women at average risk for breast cancer
  - Annual screening from age 40

- Women at increased risk for breast cancer
  - Women with certain *BRCA1* or *BRCA2* mutations or who are untested but have first-degree relatives (mothers, sisters, or daughters) who are proved to have *BRCA* mutations
    - Yearly starting by age 30 (but not before age 25)

  - Women with ≥20% lifetime risk for breast cancer on the basis of family history (both maternal and paternal)
    - Yearly starting by age 30 (but not before age 25), or 10 years earlier than the age of diagnosis of the youngest affected relative, whichever is later

  - Women with mothers or sisters with pre-menopausal breast cancer
    - Yearly starting by age 30 (but not before age 25), or 10 years earlier than the age of diagnosis of the youngest affected relative, whichever is later

  - Women with histories of mantle radiation (usually for Hodgkin's disease) received between the ages of 10 and 30
    - Yearly starting 8 years after the radiation therapy, but not before age 25

  - Women with biopsy-proven lobular neoplasia (lobular carcinoma in situ and atypical lobular hyperplasia), atypical ductal hyperplasia (ADH), ductal carcinoma in situ (DCIS), invasive breast cancer or ovarian cancer
    - Yearly from time of diagnosis, regardless of age

a. Screening Mammography by Age

i. Age at Which Annual Screening Mammography Should Start

Age 40

- Women at average risk

Younger Than Age 40

- *BRCA1* or *BRCA2* mutation carriers: by age 30, but not before age 25
- Women with mothers or sister with pre-menopausal breast cancer: by age 30 but not before age 25, or 10 years earlier than the age of diagnosis of relative, whichever is later
- Women with ≥20% lifetime risk for breast cancer on the basis of family history (both maternal and paternal): yearly starting by age 30 but not before age 25, or 10 years earlier than the age of diagnosis of the youngest affected relative, whichever is later
- Women with histories of mantle radiation received between the ages of 10 and 30: beginning 8 years after the radiation therapy but not before age 25
- Women with biopsy-proven lobular neoplasia, ADH, DCIS, invasive breast cancer, or ovarian cancer regardless of age

ii. Age at Which Annual Screening With Mammography Should Stop

- When life expectancy is <5 to 7 years on the basis of age or comorbid conditions
- When abnormal results of screening would not be acted on because of age or comorbid conditions

2. Ultrasound (in Addition to Mammography)

- Can be considered in high-risk women for whom magnetic resonance imaging (MRI) screening may be appropriate but who cannot have MRI for any reason
- Can be considered in women with dense breast tissue as an adjunct to mammography

3. MRI

- Proven carriers of a deleterious *BRCA* mutation
  - Annually starting by age 30
- Untested first-degree relatives of proven *BRCA* mutation carriers
  - Annually starting by age 30
- Women with >20% lifetime risk for breast cancer on the basis of family history
  - Annually starting by age 30
- Women with histories of chest irradiation (usually as treatment for Hodgkin's disease)
  - Annually starting 8 years after the radiation therapy
- Women with newly diagnosed breast cancer and normal contralateral breast by conventional imaging and physical examination
  - Single screening MRI of the contralateral breast at the time of diagnosis
- May be considered in women with between 15% and 20% lifetime risk for breast cancer on the basis of personal history of breast or ovarian cancer or biopsy-proven lobular neoplasia or ADH

B. BY RISK FACTOR

1. Average Risk

- Annual mammogram starting at age 40

2. High Risk

- *BRCA1* or *BRCA2* mutation carriers, untested first-degree relatives of *BRCA* mutation carrier
  - Annual mammogram and annual MRI starting by age 30 but not before age 25
- Women with ≥20% lifetime risk for breast cancer on the basis of family history
  - Annual mammography and annual MRI starting by age 30 but not before age 25, or 10 years before the age of the youngest affected relative, whichever is later
- History of chest irradiation received between the ages of 10 and 30
  - Annual mammogram and annual MRI starting 8 years after treatment; mammography is not recommended before age 25
- Personal history of breast cancer (invasive carcinoma or DCIS), ovarian cancer, or biopsy diagnosis of lobular neoplasia or ADH
  - Annual mammography from time of diagnosis; either annual MRI or ultrasound can also be considered; if screening MRI is performed in addition to mammography, also performing screening ultrasound is not necessary
- Women with dense breasts as the only risk factor
  - The addition of ultrasound to screening mammography may be useful for incremental cancer detection

DISCUSSION

RECOMMENDATIONS FOR SCREENING MAMMOGRAPHY

Screening Annually Beginning at Age 40

Evidence to support the recommendation for regular periodic screening mammography comes from the results of several randomized controlled trials (RCTs) conducted in Europe and North America [3-10] that included a total of nearly 500,000 women. The trials varied in age of included women and in screening frequency, but all but 1 demonstrated statistically significant decreases in breast cancer mortality among the populations invited to screening. Overall, on the basis of a meta-analysis of the RCTs, there was a 26% reduction in mortality [11]. More recent studies of the effect of screening mammography in routine use (service screening) have demonstrated an even greater benefit [12,13]. Duffy et al [13] reported a 39% reduction in breast cancer mortality when comparing the period before the advent of population-based screening in screening to the period after its introduction. They estimated that three quarters of this reduction was due to mammographic screening.

There has been some controversy about the age at which regular screening with mammography should start [14]. Originally chosen as a surrogate for menopause, it has been argued that the effectiveness of screening changes at the age of 50, and some have suggested that the data do not support screening before this age [15,16]. The evidence in fact does not support this opinion. A careful review of the arguments shows that the suggestion that the age of 50 has any biologic or screening relevance is nothing more than an artifact of inappropriate subgroup analysis of data that were never designed to permit such analysis [17,18]. The RCTs did not have sufficient sta-

tistical power to permit analysis of this subgroup, yet the results of analyzing women aged 40 to 49 years as a subgroup led to the misinterpretation that screening was inherently different among them, when in fact the data show that they benefit in the same way as do women aged ≥50 years [19-23].

Recently, the United States Preventive Services Task Force (USPSTF), an independent government agency consisting of 16 primary care physicians and public health specialists issued revised recommendations for screening [24,25]. Whereas they had formerly recommended routine screening every one to two years starting at age 40, they are now recommending against routine screening for women aged 40 to 49 and biennial rather than annual screening for women aged 50 to 74. They make no recommendation for women over age 74, citing insufficient evidence.

In their meta-analysis of the randomized controlled trials, they acknowledge a statistically significant 15% reduction in mortality among women aged 40 to 49 who are screened but state that the "harms" associated with screening, including anxiety over false positive results, need for additional testing or biopsy, and the possibility of overdiagnosis and overtreatment outweigh the benefits. They also used mathematical modeling to predict the mortality reduction achieved with various screening strategies and determined through these models that screening biennially would preserve 81% of the mortality reduction of annual screening and starting at age 40 rather than age 50 would result in additional mortality reduction of only 3% [26]. They also stated that screening at age 50 rather than 40 would sacrifice 33 years of life per 1000 women. Despite these analyses, they concluded that biennial screening beginning at age 50 would achieve most of the benefit of annual screening starting at age 40 with substantially less harm.

In their 2009 recommendations, the USPSTF suggest that women aged 40 to 49 years might want to consider their personal risk for developing breast cancer before deciding to participate in screening [24]. This has also been suggested by the American College of Physicians [27]. Not only does this recommendation ignore the basic fact that the age of 50 has no meaning, but there is no direct evidence that screening women with mammography, on the basis of their individual risk for breast cancer, will have the same mortality decrease as screening the general population. None of the RCTs of screening mammography stratified women by risk. Despite the identification of factors that increase a woman's risk for developing breast cancer, most women who develop breast cancer have no demonstrable risk other than they are women and they are aging. It is estimated that approximately 70% to 80% of breast cancers occur in women with no identifiable risk factors [28,29]. Therefore, if only high-risk women are screened, the majority of breast cancers would be missed, because most breast cancers occur among the very large population of women who are not at increased risk.

The revised USPSTF recommendations were met with widespread concern among the breast imaging community and the public. The ACR and SBI along with the ACS and other organizations strongly criticized the USPSTF recommendations, disagreeing with the conclusions reached by their analysis of the existing data and with the method by which their recommendations were formulated. Amidst all the furor, the ACR and SBI firmly stand behind their recommendation that screening mammography should be performed annually beginning at age 40 for women at average risk for breast cancer.

Screening With Digital Mammography

Several studies comparing the performance of digital mammography and film-screen techniques for screening have found equivalent sensitivity for breast cancer detection [30-34]. The Digital Mammographic Imaging Screening Trial, a multicenter study that enrolled >49,000 women at 33 centers across the United States and Canada, found no significant difference between digital and film-screen mammography in sensitivity among the entire cohort [32]. However, digital mammography performed significantly better than analog mammography in premenopausal and perimenopausal women, those aged <50 years, and those with dense breasts [32,34]. For these women, digital mammography might be preferred. However, the RCTs that have demonstrated mortality reduction from screening mammography have been based on film-screen mammography, and the ACR and SBI feel that women should continue to be screened, even if digital mammography is not available in their communities.

Screening Women With Mammography Before Age 40

Randomized controlled trials have not been performed to test the impact of mammographic screening on mortality reduction in high0risk women of any age, including those aged <40 years. However, if the level of risk for developing breast cancer in a high-risk woman aged <40 years is the same or greater than the level of risk of a 40-year-old in the general population, it is reasonable to offer screening to these younger women. Because no data exist on the optimum age to start screening mammography in women at increased risk for breast cancer, the recommendations in this document are based on consensus opinions by the members of the ACR Breast Imaging Commission and the fellows of the SBI. A discussion of

the risk associated with various conditions is presented below.

Women who have undergone breast conservation have a recurrence rate in the treated breast of 0.5% to 1% per year [35]. The risk for all women with personal histories of breast cancer (at any age) to develop a second cancer is 5% to 10% in the first decade after their diagnoses [36]. For any woman with histories of breast cancer, mammographic screening should be performed annually after the diagnosis of breast cancer, whatever the age of the patient.

Similarly, women with personal histories of ovarian cancer have a 3-fold to 4-fold increased risk for the subsequent development of breast cancer [37], and it is the opinion of the SBI and ACR that they should have screening mammography yearly from the time of diagnosis of the ovarian cancer.

Women with histories of mediastinal radiation are at increased risk for breast cancer due to scatter radiation to the breasts. The largest group of these women is those treated for Hodgkin's disease with mantle radiation to the mediastinum [38]. It is acknowledged that the relative risk for developing breast cancer in these women is high, estimated between 4 and 75 times, particularly when the radiation was delivered between the ages of 10 and 30 or was >4 Gy [39-42]. In one study, 35% of women with mediastinal radiation for Hodgkin's disease developed breast cancer by age 40 [40]. Breast cancers have been diagnosed as early as 10 years after Hodgkin's disease has been cured. Therefore, mammographic screening is recommended to begin 8 to 10 years after treatment but not before age 25 [43,44].

High-risk histopathologies found at the time of breast biopsy are premalignant changes and convey an increased risk for developing breast cancer. They include lobular neoplasia and ADH. Annual mammographic screening after these diagnoses is indicated.

Lobular carcinoma in situ is found incidentally in about 1% of breast biopsies. It is associated with 6% of breast cancers. Ninety percent of women diagnosed with lobular carcinoma in situ are premenopausal. The risk for breast cancer is estimated at 0.5% to 1.0% per year [45], and breast cancers can develop in either breast. Routine annual mammography and clinical surveillance have reduced mortality at a rate comparable to that achieved with bilateral mastectomy. These women should be screened annually with mammography after the diagnosis of lobular carcinoma in situ is made. Atypical ductal hyperplasia is the nonobligate precursor lesion to DCIS. It has a relative risk for developing breast cancer for women aged 20 to 30 years of 7.0; for women with positive family histories, the risk increases to 9.7 [46]. The mean time to developing cancer is 8.2 years. These women should be screened annually with mammography after this diagnosis is made.

Several genes and numerous mutations have been shown to be responsible for hereditary breast cancer. Of these the most common are mutations on *BRCA* genes. The *BRCA1* mutation conveys a 19% risk for breast cancer by age 40, with the lifetime risk estimated as high as 85%. Mutations to *BRCA2* convey a similar lifetime risk, although cancer seems to develop later in these women. Both genes also increase risk for ovarian cancer, and this risk should also be addressed in these women. These women reach a risk for developing breast cancer comparable with that of an average 40-year-old woman at a young age [47]. By expert consensus, screening of these women should not begin before age 25, because breast cancers rarely develop in these women before then, breast tissue in very young women is often dense and difficult to screen, and breast tissue in young women has increased sensitivity to radiation. The optimum age to start screening these high-risk women has not been established. Most government-sponsored high-risk screening programs outside the United States start screening with mammography and MRI at age 25 or 30, sometimes with the addition of ultrasound.

The PTEN gene, associated with Cowden's syndrome, the p53 gene of Li-Fraumeni syndrome, and Muir-Torres syndrome (the MSH2 and MLH1 genes) are rare and seem to convey increased breast cancer risk [48]. The risk is also elevated in Peutz-Jeghers syndrome (STK11 gene), although the exact risk has not been calculated. Because of the rarity of these syndromes and the paucity of clinical experience with mammographic screening among such women, recommendations for early screening cannot be made at this time.

At What Age Should Breast Cancer Screening End?

None of the RCTs included women aged >74 years. Consequently, there are no data to prove mortality reduction for women aged >74 years. However, there is no reason to expect that mammographic screening would be any less effective among older women. It has been shown that the sensitivity and positive predictive value of mammography in diagnosing breast cancer increases with increasing age [19,49,50]. In a retrospective study of >690,000 women aged 66 to 79 years, the incidence of metastatic breast cancer was reduced by 43% in the screened versus nonscreened population [51]. Although actual mortality from breast cancer could not be gauged from this study, metastatic breast cancer seems a reasonable surrogate for mortality and lends evidence to the effectiveness of screening in the older age group.

It is the general consensus that the potential benefit of

early detection should be weighed against the risks of false-positive results, the quality of life, and life expectancy. It has been shown from the RCTs that it takes approximately 5 to 7 years for the benefit of mortality reduction from screening to become evident [52]. Women in average health aged 70 to 74 years can expect to live an additional 13.4 years [53]. Life expectancy for women with average health aged 75 to 79 years is approximately 10 years, nearly 8 years for women aged 80 to 84 years, and 6.6 years for women aged ≥85 years [53]. However, women of these ages who have health problems might have substantially shorter life expectancies. Therefore, universal upper age limits for screening mammography may not be justified. In deciding who should be screened, it seems reasonable to take into account a woman's life expectancy on the basis of age and comorbid conditions, as well as an individual woman's preference regarding the potential benefit of diagnosing an occult breast cancer versus the disadvantage of additional testing that screening mammography may generate.

Given the competing causes of morbidity and mortality that increase with age, the ACR and SBI suggest that screening with mammography should continue as long as a woman has a life expectancy of ≥5 to 7 years on the basis of age and health status, is willing to undergo additional testing including biopsy, if indicated by findings on mammography, and would be treated for breast cancer if diagnosed.

HIGH-RISK SCREENING

Risk Assessment

There are a variety of risk assessment tools available to calculate a woman's breast cancer risk, including the Gail, Claus, BRCAPRO, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BODAICEA), and Tyrer-Cuzick models [54-58]. Each of these models is based on different data sets and takes into account different risk factors. The first to be widely used is the Gail model, which includes race, age at menarche, age at first live birth, number of previous breast biopsies, and number of first-degree relatives with breast cancer [54]. This is the model that is available on the National Cancer Institute's online breast cancer risk assessment tool and is the one incorporated into some automated mammography reporting systems. The Gail model is the only one of the various risk assessment models that has been validated for African American as well as white women. However, it does not take into consideration the ages at diagnosis of the first-degree relatives, paternal family history, or second-degree relatives and is not recommended by the ACS for use in assessing whether a woman should receive supplemental screening with MRI.

The Claus model is based on the number of relatives with breast cancer, which relatives have breast cancer, and the ages at diagnosis of these relatives [55]. It includes paternal family history but includes information only from white women.

The BRCAPRO model determines the probability that a woman is carrying a mutation of the *BRCA1* or *BRCA2* gene [56]. This model is based on whether the woman has a personal history of breast cancer or a history of breast or ovarian cancer among her first-degree and second-degree relatives. It also considers Ashkenazi Jewish ancestry.

The BOADICEA is also used to estimate the likelihood of carrying a *BRCA1* or *BRCA2* mutation as well as the risk for developing breast or ovarian cancer [57].

The Tyrer-Cuzick model takes into account family and reproductive history as well as Ashkenazi Jewish ancestry, reproductive history, and other personal factors such as rf height and weight [58]. None of the models include third-degree relatives or breast density as a factor. The result of the risk assessment can vary a great deal in any one individual, depending on which model is used. Because of this complexity, women who are potentially at increased risk for breast cancer are best served by having formal risk assessments performed by trained health professionals. However, for some women, their radiologists may be the health care providers who are most aware of the possibility that they are at increased risk for breast cancer. A mechanism by which this information is conveyed to patients so that appropriate risk assessment, counseling, screening, and prevention options can be determined needs to be established by the health care community. Radiologists are encouraged to have a basic understanding of risk assessment to understand when the request for a screening examination may or may not be appropriate. An excellent review of screening high-risk women was recently published by Berg [59] and provides an overview and foundation for a rational approach to this issue.

Screening With Breast MRI

For women with the highest risk for developing breast cancer, screening technologies in addition to mammography have been adopted. These have been particularly sought after for those women at risk for hereditary breast cancer, for which mammographic screening may have relatively low sensitivity. Recently, the ACS issued recommendations for screening breast MRI among certain high-risk women [2]. The ACR and SBI endorse these recommendations. Several prospective trials of MRI screening of women at risk for familial breast cancer have shown increased detection of breast cancer with the use of this modality compared to mammographic screening

[60-65]. All of these studies have demonstrated higher sensitivity for breast MRI screening compared with mammography and breast ultrasound in this group of high-risk women, and the ACR and SBI suggest that annual screening MRI be performed in addition to annual mammography for women with >20% lifetime risk for the development of breast cancer.

In addition to having the *BRCA1* or *BRCA2* mutation, a family history that may suggest a genetic predisposition to breast cancer includes having ≥2 first-degree relatives with breast cancer, a first-degree relative with premenopausal breast cancer, a family history of breast and ovarian cancer, a first-degree relative with more than one independent cancer, and having a male relative with breast cancer. Whether women who have a 15% to 20% lifetime risk for developing breast cancer, such as those with biopsy proven lobular neoplasia, ADH, or prior breast cancer, should be screened with MRI is still in question. In its recently issued guidelines, the ACS did not recommend either for or against screening of women in these groups [2]. It may be best for an individual breast imaging facility to decide, after consultation with referring clinicians, whether these women will be screened with MRI and to be rigorous in risk assessment and consistent in the choice of populations that undergo MRI screening at their facilities.

The ACS guidelines state that screening with MRI is inappropriate for women at <15% lifetime risk for breast cancer, and the ACR and SBI concur with this conclusion.

It is important to emphasize that breast MRI is not meant to replace mammography. There are cases, particularly of DCIS, that are detectable by mammography but not by MRI. In performing screening MRI and mammography, they can either be done concurrently or staggered by 6 months. The advantage of staggering is that patients have some form of screening every 6 months. The advantage of concurrent screening is that correlation between the two examinations is facilitated, especially if there is an abnormality on one of the studies. The timing of the screening examinations, whether they should be concurrent or staggered, is a matter to be determined by individual facilities.

For women with newly diagnosed breast cancer, there is evidence that a single round of screening of the contralateral breast with MRI at the time of diagnosis will detect otherwise occult malignancy in approximately 3% to 9% of these women [66-68].

The addition of breast MRI to the screening algorithm for women at greatest risk adds considerable cost. Studies have suggested that for those at the greatest risk, carriers of the *BRCA1* mutation, adding MRI to mammography increases screening cost by >$50,000 per cancer [69]. These costs increase considerably as the risk for developing cancer diminishes. It is to be expected that as women with decreasing risk undergo MRI, this will also increase the false-positive biopsy rate and other parameters of false-positive image interpretation. This is the rationale for limiting MRI screening to those women at the greatest risk for developing breast cancer.

Screening With Ultrasound

Several published papers from independent breast imaging facilities have reported that breast ultrasound screening in women with dense breasts and negative mammograms and clinical examinations yielded an incremental cancer detection rate of 2.8 to 4.6 cancers per 1,000 women [70-74]. A recent multi-institutional study of screening breast ultrasound sponsored by ACRIN® included women who not only had dense breasts but who were also at increased risk for breast cancer [75]. The ACRIN® study reported results similar to those of the single-institution studies with an incremental cancer detection rate of 4.2 per 1,000 women screened. In all of the studies, breast cancers detected by ultrasound only have been reported to be small invasive cancers, with a high proportion of node-negative cases.

With the release of the first results of the ACRIN® trial, more attention is being paid to the use of supplemental screening with ultrasound, particularly in women with dense breasts. Breast density in and of itself has been shown by several studies to be an independent risk factor for the development of breast cancer, with the relative risk for women with the most dense breasts 2 to 6 times that of women with the least dense breasts [76-78]. There is some controversy over the methodology of these density studies, raising the question of the true relationship between density and risk [79]. However, it has been demonstrated that the sensitivity of mammography is lower in women with dense breasts, and regardless of whether women with dense breasts are at increased risk or not, it has been shown that the use of supplemental ultrasound screening will result in the detection of otherwise occult cancers.

There are several challenges associated with the widespread adoption of screening ultrasound. All published screening ultrasound studies have reported high false-positive rates. In the ACRIN® study, in which experienced radiologists specializing in breast imaging followed a standard protocol, the positive biopsy rate was 8.8%, or 6.7% if cyst aspirations are included among biopsy cases. The screening ultrasound examinations in all but one of the reported studies were performed by the radiologist, and the mean examination time has been on the order of 10 to 20 minutes.

Several studies comparing mammography, breast ultrasound, and breast MRI for screening have demon-

strated superior sensitivity of MRI for cancer detection in high-risk women [61,63,80]. Performing supplemental screening with ultrasound in these women adds no additional benefit over screening with mammography and MRI. However, screening breast ultrasound may have a role as a supplemental screening tool for high-risk women who have contraindications to MRI or in those whose levels of risk do not reach the level recommended for breast MRI screening by the ACS.

Clearly, it would not be feasible, given the current shortage of radiologists who perform breast imaging, for all women whose only risk factor is breast density to undergo radiologist-performed supplemental ultrasound screening. Issues related to reproducibility, high false-positive rates, low positive predictive value for biopsy recommendations, operator dependency of the examination, inability to image most DCIS cases, and lack of agreement on which solid or complex lesions found at screening require biopsy have resulted in a failure of widespread acceptance of breast ultrasound screening [81]. Because of the demonstrated superior sensitivity of breast MRI for screening high-risk women, the disadvantages associated with screening ultrasound and constraints of a limited number of radiologists who perform breast imaging, many facilities have chosen not to offer ultrasound screening. The ACR and SBI consider such a choice to be acceptable within the standard of care.

Screening With Other Imaging Technologies

There are no large, peer-reviewed published studies that support the routine use of other imaging techniques such as thermography, sestimibi, PET, transillumination, electrical impedance scanning, or optical imaging for breast cancer screening. Of these alternate screening modalities, thermography is the most widely studied. It was initially included in the Breast Cancer Detection Demonstration Project but was dropped after experience during the first 4 years of the project showed a sensitivity of only 43% for the detection of breast cancer [82]. The ACR and SBI do not endorse thermography or any of these other modalities for screening for breast cancer.

ACKNOWLEDGMENTS

We gratefully acknowledge the assistance received from Dr Robert Smith of the ACS and from the fellows of the SBI in formulating these recommendations. We also acknowledge the help of Pamela Wilcox of the ACR and Michele Wittling of the SBI, without whose assistance this document would not have been possible.

REFERENCES

1. Smith RA, Saslow D, Sawyer KA, et al. American Cancer Society guidelines for breast cancer screening: update 2003. CA Cancer J Clin 2003; 53:141-69.
2. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 2007;57:75-89.
3. Verbeek ALM, Hendricks JHCL, Holland R, Mravunac M, Sturmans F. Screening and breast cancer mortality, age specific effects in Nijmegen project, 1975-82. Lancet 1985;l:865-6.
4. Shapiro S, Venet W, Strax P, Venet L. Periodic screening for breast cancer: the Health Insurance Plan Project and its sequelae, 1963-1986. Baltimore, Md: Johns Hopkins University Press; 1988.
5. Nystrom L, Rutqvist LE, Wall S, et al. Breast cancer screening with mammography: overview of Swedish randomized trials. Lancet 1993; 341:973-8.
6. Roberts MM, Alexander FE, Anderson TJ, et al: Edinburgh trial of screening for breast cancer: mortality at seven years. Lancet 1990;335: 241-6.
7. Miller AB, Baines CJ, To T, et al. Canadian national breast screening study: 1: breast cancer detection and death rates among women aged 40 to 49 years. CMAJ 1992;147:1459-76.
8. Miller AB, Baines CJ, To T, et al. Canadian national breast screening study: 2: breast cancer detection and death rates among women aged 50 to 59 years. CMAJ 1992;147:1477-88.
9. Moss SM, Summerley ME, Thomas BT, Ellman R, Chamberlain JOP. A case-control evaluation of the effect of breast cancer screening in the United Kingdom trial of early detection of breast cancer. J Epidemiol Commun Health 1992;46:362-4.
10. Otto SJ, Fracheboud J, Looman CWN, et al; National Evaluation Team for Breast Cancer Screening. Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. Lancet 2003;361:411-7.
11. Kerlikowske K, Grady D, Rubin SM, et al. Efficacy of screening mammography. A metaanalysis. JAMA 1995;273:149-54.
12. Tabar L, Vitak B, Tony HH, Yen MF, Duffy SW, Smith RA. Beyond randomized controlled trials: organized mammographic screening substantially reduces breast carcinoma mortality. Cancer 2001;91:1724-31.
13. Duffy SW, Tabar L, Chen H, et al. The impact of organized mammography service screening on breast carcinoma mortality in seven Swedish counties. Cancer 2002;95:458-69.
14. Fletcher SW. Breast cancer screening among women in their forties: an overview of the issues. J Natl Cancer Inst Monogr 1997;22:5-9.
15. Shapiro S. Screening: assessment of current studies. Cancer 1994;74: 231-8.
16. Sox H. Screening mammography in women younger than 50 years of age. Ann Inter Med 1995;122:550-2.
17. Kopans DB. Informed decision making: age of 50 is arbitrary and has no demonstrated influence on breast cancer screening in women. AJR Am J Roentgenol 2005;185:177-82.
18. Kopans DB, Moore RH, McCarthy KA, et al. Biasing the interpretation of mammography screening data by age grouping: nothing changes abruptly at age 50. Breast J 1998;4:139-45.
19. Kerlikowske K, Grady D, Barclay J, Sickles EA, Eaton A, Ernster V. Positive predictive value of screening mammography by age and family history of breast cancer. JAMA 1993;270:2444-2450.
20. Evans AJ, Kutt E, Record C, Waller M, Moss S. Radiological findings of screen-detected cancers in a multi-centre randomized, controlled trial of

mammographic screening in women from age 40 to 48 years. Clin Radiol 2006;61:784-8.

21. de Koning HJ, Boer R, Warmerdam PG, Beemsterboer PMM, van der Maas PJ. Quantitative interpretation of age-specific mortality reductions from the Swedish breast cancer-screening trials. J Natl Cancer Inst 1995; 87:1217-23.
22. Hendrick RE, Smith RA, Rutledge JH, Smart CR. Benefit of screening mammography in women ages 40-49: a new meta-analysis of randomized controlled trials. Monogr Natl Cancer Inst 1997;22:87-92.
23. Moss SM, Cuckle H, Evans A, Johns L, Waller M, Bobrow L. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial. Lancet 2006;368:2053-60.
24. U.S. Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2009;151:716-26.
25. Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L. Screening for breast cancer: An update for the U.S. Preventive Services Task Force. Ann Inter Med 2009;151:727-37.
26. Mandelblatt JS, Cronin KA, Bailey D, et al. Effects of mammography screening under different screening schedules: Model estimates of potential benefits and harms. Ann Intern Med 2009;151:738-47.
27. Qaseem A, Snow V, Sherif K, Aronson M, Weiss KB, Owens DK, for the Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Screening mammography for women 40 to 49 years of age: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2007;146;511-5.
28. Burstein HJ, Harris JR, Morrow M. Malignant tumors of the breast. In: Devita VT, Lawrence TS, Rosenberg SA, eds. Cancer: principles and practice of oncology. 8th ed. Philadelphia: Lippincott, Williams & Wilkins; 2008:1606-54.
29. Seidman H, Stellman SD, Mushinski MH. A different perspective on breast cancer risk factors: some implications of nonattributable risk. CA Cancer J Clin 1982;32:301-13.
30. Lewin JM, D'orsi CJ, Hendrick RE, et al. Clinical comparison of full-field digital mammography and screen-film mammography for detection of breast cancer. AJR Am J Roentgenol 2002;179:671-7.
31. Skaane P, Skjennald A, Young K, et al. Follow up and final results of the Oslo I study comparing screen-film mammography and full-field digital mammography with soft copy reading. Acta Radiol 2005;46:679.
32. Pisano ED, Gatsonis C, Hendrick E, et al. Diagnostic performance of digital versus film mammography for breast cancer screening. N Engl J Med 2005;353:1773-83.
33. Skaane P, Hofvind S, Skjennald A. Randomized trial of screen-film versus full-field digital mammography with soft-copy reading in population based screening program: follow-up and final results of Oslo II study. Radiology 2007;244:708-17.
34. Pisano ED, Hendrick RE, Yaffe MJ, et al. Diagnostic accuracy of digital versus film mammography: exploratory analysis of selected population subgroups in DMIST. Radiology 2008;246:376-83.
35. Dershaw DD. Breast imaging and the conservative treatment of breast cancer. Radiol Clin N Am 2002;40:501-16.
36. Fowble B, Hanlon A, Freeman G, et al. Second cancers after conservative surgery and radiation for stages I-II breast cancer: identifying a subset of women at increased risk. Int J Radiat Oncol Biol Phys 2001;51:679-90.
37. Travis LB, Curtis RE, Boice JD, et al. Second malignant neoplasms among long-term survivors of ovarian cancer. Cancer Res 1996;56:1564-90.
38. Yahalom J, Petrek JA, Bidinger P, et al. Breast cancer in patients irradiated for Hodgkin's disease: a clinical and pathological analysis of 45 events in 37 patients. J Clin Oncol 1992;10:1674-81.
39. Hancock SL, Tucker MA, Hoppe RT. Breast cancer after treatment of Hodgkin's disease. J Natl Cancer Inst 1993;85:25-31.
40. Bhatia S, Robison LL, Oberlin O, et al. Breast cancer and other second neoplasms after childhood Hodgkin's disease. N Engl J Med 1996;334: 745-51.
41. Wolden SL, Hancock SL, Carlson RW, Goffinet DR, Jeffrey SS, Hoppe RT. Management of breast cancer after Hodgkin's disease. J Clin Oncol 2000;18:765-72.
42. Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA 2003;290:465-75.
43. Dershaw DD, Yahalom J, Petrek JA. Mammography of breast carcinoma developing in women treated for Hodgkin's disease. Radiology 1992;184: 421-3.
44. Henderson TO, Amsterdam A, Bhatia S, et al. Narrative review: surveillance for breast cancer in women treated with chest radiation for a childhood, adolescent or young adult cancer. In press.
45. Arpino G, Laucirica R, Elledge RM. Premalignant and in situ breast disease: biology and clinical implications. Ann Intern Med 2005;143:446-57.
46. Page DL, Dupont WE, Rogers LW, Rados MS. Atypical hyperplastic lesions of the female breast: a long-term follow-up study. Cancer 1985; 55:2698-708.
47. Burke W, Daly M, Garber J, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer II. BRCA1 and BRCA2. JAMA 1997;277:997-1003.
48. Garber JE, Offit K. Hereditary cancer predisposition syndromes. J Clin Oncol 2005;23:276-92.
49. Kerlikowske K, Grady D, Barclay J, et al. Effect of age, breast density, and family history on the sensitivity of first screening mammography. JAMA 1996;276:33-8.
50. Kopans DB, Moore RH, McCarthy KA. Positive predictive value of breast biopsy performed as a result of mammography: there is no abrupt change at age 50 years. Radiology 1996;200:357-60.
51. Smith-Bindman R, Kerlikowske K, Gebretsadik T. Is screening mammography effective in elderly women? Am J Med 2000;108:112-9.
52. Kerlikowske K, Salzmann P, Phillips KA, et al. Continuing screening mammography in women aged 70 to 79 years—impact on life expectancy and cost-effectiveness. JAMA 1999;282:2156-63.
53. Mandelblatt JS, Wheat ME, Monane M. Breast cancer screening for elderly women with and without comorbid conditions—a decision analysis model. Ann Intern Med 1992;116:722-30.
54. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 1989;81:1879-86.
55. Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. Cancer 1994; 73:643-51.
56. Berry DA, Iversen ES Jr, Gudbjartsson DF, et al. BRCAPRO validation, sensitivity of genetic testing of BRCA1/BRCA2, and prevalence of other breast cancer susceptibility genes. J Clin Oncol 2002;20:2701-12.
57. Antoniou AC, Cunningham AP, Peto J, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. Br J Cancer 2008;98:1457-66.
58. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med 2004;23:1111-30.
59. Berg WA. Tailored supplemental screening for breast cancer: what now and what next? AJR Am J Roentgenol 2009;192:390-9.

60. Kriege M, Brekelmans CT, Boetes C, et al. Efficacy of MRI and mammography for breast-cancer screening in women with familial or genetic predisposition. N Engl J Med 2004;351:427-37.

61. Warner E, Plewes DB, Hill KA, et al. Surveillance for BRCA 1and BRCA 2 mutation carriers with magnetic resonance imaging, ultrasound mammography, and clinical breast examination. JAMA 2004;292:1317-25.

62. Leach MO, Boggis CR, Dixon AK, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study. Lancet 2005;365:1769-78.

63. Kuhl C, Schrading S, Leutner CC, et al. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. J Clin Oncol 2005;23:8469-76.

64. Lehman CD, Blume JD, Weatherall P, et al. Screening women at high risk for breast cancer with mammography and magnetic resonance imaging. Cancer 2005;103:1898-905.

65. Sardanelli F, Podo F, D'Agnolo G, et al. Multicenter comparative multimodality survey of women at genetic-familial high risk for breast cancer (HIBCRIT study): preliminary results. Radiology 2007;242:698-715.

66. Lee SG, Orel SG, Woo IJ, et al. MR imaging screening of the contralateral breast in patients with newly diagnosed breast cancer: preliminary results. Radiology 2003;226:773-8.

67. Liberman L, Morris EA, Kim CM, et al. MR imaging findings in the contralateral breast of women with recently diagnosed breast cancer. AJR Am J Roentgenol 2003;180:333-41.

68. Lehman CD, Gatsonis C, Kuhl CK, et al. MRI evaluation of the contralateral breast in women with recently diagnosed breast cancer. N Engl J Med 2007;356:1295-303.

69. Griebsch I, Brown J, Boggis C, et al. Cost effectiveness of screening with contrast enhanced magnetic resonance imaging vs X-ray mammography of women at a high familial risk of breast cancer. Br J Cancer 2006;95:801-10.

70. Gordon PB, Goldenberg SL. Malignant breast masses detected only by ultrasound. A retrospective review. Cancer 1995;76:626-30.

71. Kaplan SS. Clinical utility of bilateral whole-breast US in the evaluation of women with dense breast tissue. Radiology 2001;221:641-64.

72. Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. Radiology 2002;225:165-75.

73. Buchberger W, Niehoff A, Obrist P, DeKoekkoek-Doll P, Dunser M. Clinically and mammographically occult breast lesions: detection and classification with high resolution sonography. Semin Ultrasound CT MR 2000;21:325-36.

74. Crystal P, Strano SD, Shcharynski S, Koretz MJ. Using sonography to screen women with mammographically dense breasts. AJR Am J Roentgenol 2003;181:177-82.

75. Berg WA, Blume JD, Cormack JB, et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA 2008;299:2151-63.

76. Harvey JA, Bovbjerg VE. Quantitative assessment of mammographic breast density: relationship with breast cancer risk. Radiology 2004;230:29-41.

77. Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. N Engl J Med 2007;356:227-36.

78. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidem Biomarkers Prev 2006;15:1159-69.

79. Kopans DB. Basic physics and doubts about the relationship between mammographically determined tissue density and breast cancer risk. Radiology 2008;246:348-53.

80. Lehman CD, Isaacs C, Schnall MD, et al. Cancer yield of mammography, MR, and US in high-risk women: prospective multi-institution breast cancer screening study. Radiology 2007;244:381-8.

81. Gordon PB. Ultrasound for breast cancer screening and staging. Radiol Clin N Am 2002;40:431-41.

82. Beahrs OH, Shapiro S, Smart CR. Report of the working group to review the National Cancer Institute-American Cancer Society Breast Cancer Detection Demonstration Projects. J Natl Cancer Inst 1979;62:641-709.

To access the article and take the exam, log in to **www.acr.org** and click on the CME icon located next to the *JACR* cover. Follow the instructions and answer 3 questions to complete the requirement for CME. Claim the credit and print your CME certificate online. *Note: CME for ACR members is free, however you will need to click on the "Buy Now" button and proceed through the shopping cart process in order to receive the credit.*

The American College of Radiology is accredited by the Accrediation Council for Continuing Medical Education to provide continuing medical education for physicians. The American College of Radiology designates this educational activity for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.