

Magnetic Resonance Imaging and Breast Ultrasonography as an Adjunct to Mammographic Screening in High-Risk Patients

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Screening mammography remains the standard of care for breast cancer screening of the general population and is likely to remain so in the foreseeable future. We discuss the current role of breast ultrasound and magnetic resonance imaging (MRI) in screening for breast cancer in the high-risk population. Breast ultrasound finds small cancers not seen on mammography particularly in women with dense breasts. Breast MRI has sensitivity significantly higher than that of mammography, breast ultrasound, or a combination of mammography and breast ultrasound.

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Screening Breast Magnetic Resonance Imaging

The use of mammography as a breast cancer screening tool in the general population has been shown to reduce mortality associated with breast cancer by at least 24%.¹ In recent years, the United States and other countries have incorporated breast magnetic resonance imaging (MRI) into their annual screening mammography guidelines for selected groups of women at high risk for breast cancer.² The American Cancer Society has published guidelines for the use of MRI as an adjunct to annual screening mammography, recommending it for women with BRCA mutations, women who are first-degree relatives of BRCA carriers but have not undergone BRCA testing themselves, and women with a lifetime risk that is 20%-25% or greater than that of the average woman, as defined by risk prediction models.²

There are several risk-prediction models available such as the Gail model,³ Claus model,⁴ BRCAPRO,⁵ and Tyrer-Cuzick.⁶ The BRCAPRO Risk Prediction Model is one of the more commonly used models for estimating the probability of a person having a genetic mutation.⁵ The group of women with a lifetime risk that is 20%-25% or greater than average but who are without a genetic predisposition for developing

breast cancer is more heterogeneous than the group with the probability of having a genetic mutation such as BRCA mutations. Therefore, there are several commonly used models available to assess for such an individual's risk of breast cancer. At our institution, either the Gail or Claus model is used to calculate the lifetime risk of women without a known genetic predisposition to breast cancer and thus advise them as to the risks and benefits of yearly MRI screening.^{3,4}

Other groups for whom an annual MRI is recommended as an adjunct to screening with mammography include those women with Li-Fraumeni syndrome or Cowden/Bannayan-Riley-Ruvalcaba syndromes and their first-degree relatives.² The American Cancer Society also recommends screening MRI with mammography for women who received radiation therapy to the chest between the ages of 10 and 30 years.² This is especially recommended for survivors of Hodgkin's lymphoma who received the more traditional larger radiation doses routinely given before 1995, when radiotherapy was often the only primary curative modality.⁷⁻¹⁰ As a consequence of this irradiation, these women have a higher risk of developing breast cancer.⁷⁻¹⁰ In the past decade and a half, lower radiation doses and smaller radiation treatment volumes have been used in patients with Hodgkin's lymphoma than were used before 1995, seriously lessening this risk.⁹

Currently, there is insufficient evidence to recommend adjunctive MRI screening with annual screening mammography in women whose lifetime risk of breast cancer is estimated to be <20%, including those with biopsy-proven lobular carcinoma in situ or atypical lobular hyperplasia, atypical ductal hyperplasia, a mammographic appearance of heterogeneously or extremely dense breast tissue, and those with personal histories of breast cancer.

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Regardless of the models used to determine an individual's risk of breast cancer, aggressive surveillance and screening starting at a younger age are recommended for the high-risk populations, as defined by the guidelines from the American Cancer Society. Current surveillance protocols for breast cancer screening in women considered high risk include clinical breast examination (CBE) every 6 months and annual mammography and MRI.²

Prevention and/or early diagnosis are crucial methods for reducing morbidity and mortality in high-risk populations. In addition to increased screening for women deemed to be at high risk for breast cancer, there are prevention strategies, including the prescription of chemopreventive agents such as tamoxifen and the choice of surgical strategies such as prophylactic mastectomy. However, this article will focus on the efficacy of imaging surveillance and will review the literature and data regarding MRI screening in particular.

Sensitivity and Specificity of Breast MRI

Although comparisons are challenging because of the many variations among guidelines for breast cancer screening used in different screening programs and different countries, breast MRI has been shown consistently to have a higher sensitivity for detecting breast cancer (71%-91%) than does mammography (33%-50%) (Table 1).¹¹⁻²⁰ The populations studied in these multicenter trials have been heterogeneous and have ranged from women with moderate lifetime risk of developing breast cancer to those with high lifetime risk, including those with genetic predispositions for developing breast cancer such as BRCA mutation carriers.

Despite the heterogeneity of these study populations, the sensitivity of MRI remains higher than that of mammography, ultrasound, or their combination¹⁵ (Fig. 1). In 2004, Kriege et al¹⁷ reported a sensitivity for breast MRI of 80%, compared with 33% and 18% for mammography and CBE, respectively. Their study population consisted of 1909 women with a breast cancer lifetime risk of 15% or more. During the study, 51 breast cancers were diagnosed, 44 of which were invasive carcinomas. MRI scanning detected 32 of these lesions, whereas mammography detected only 18.¹⁶ Six years later, the High Breast Cancer Risk Italian 1 Study also reported their results involving 18 centers and 501 women.¹⁹ They found that MRI scans were more sensitive (91%) than CBE (18%), mammography (50%), or ultrasound (52%).¹⁹

On the other hand, the specificity of MRI (79%-95%) was lower in 4 clinical trials than that of mammography (93%-99%) or ultrasound (88%-96%).^{15,17,18,20} However, in another prospective multi-institutional trial of 529 patients, the specificity of MRI (97%) was similar to that of mammography, and both modalities had higher specificities than ultrasound.¹⁶ With the advances in MRI technology in recent years, we might expect the specificity of MRI to improve if it were tested with today's imaging requirements and equipment.

Cancer Yield and Characteristics of MRI-Detected Cancers

In the last few decades, there have been several multi-institutional trials performed in several countries in North America and Europe. Despite the variation in these countries' medical practices, the number of screening-detected breast cancers ranged from 2%-9% in all of the women who participated within the published trials from several countries (Table 2) for all imaging modalities.¹⁴⁻²² When the cancers detected were categorized by imaging modalities used, MRI had the highest cancer detection rate compared with mammography and ultrasound. Unfortunately, MRI also had several drawbacks, which included a higher false-positive rate and a higher biopsy rate. For example, of the 195 individuals enrolled in one study, the biopsy recommendation rate was 8.5% in the MRI group compared with 2.2% for the mammography group.²¹ Nevertheless, MRI not only detected cancers that were mammographically or sonographically occult but also demonstrated an added cancer yield of 4%, none of which were detected by mammography, in the contralateral breast of women with recent unilateral breast cancer.²²

Most of the cancers detected by MRI screening were between 10 and 20 mm in size and were invasive carcinomas.²³ Despite the small size of the tumors, 12%-26% of these patients had node-positive disease at the time of detection.²³ This raises the question of whether the current annual screening interval is an inadequate frequency for the high-risk population or if the node-positive disease found at detection is related to the aggressiveness of breast cancer in this high-risk population.

There is frequently some overlap between benign and malignant morphologic and kinetic features seen on MRI scans of biopsy-proven breast cancer lesions. In a recent surveil-

Table 1 Sensitivity and Specificity of Mammography, Ultrasound, and MRI in Detection of Breast Cancer

Study	n	Sensitivity (%)			Specificity (%)		
		Mam	US	MRI	Mam	US	MRI
Warner (2004) ¹⁵	236	36	33	77	99	96	95
Kuhl (2005) ¹⁶	529	33	40	91	97	91	97
Kriege (2004) ¹⁷	1909	33	NA	80	95	NA	90
Leach (2005) ¹⁴	649	40	NA	77	93	NA	81
Sardanelli (2011) ¹⁹	501	50	52	91	99	98	97
Weinstein (2009) ²⁰	609	33	17	71	94	88	79

Mam, mammography; US, ultrasound; NA, not available.

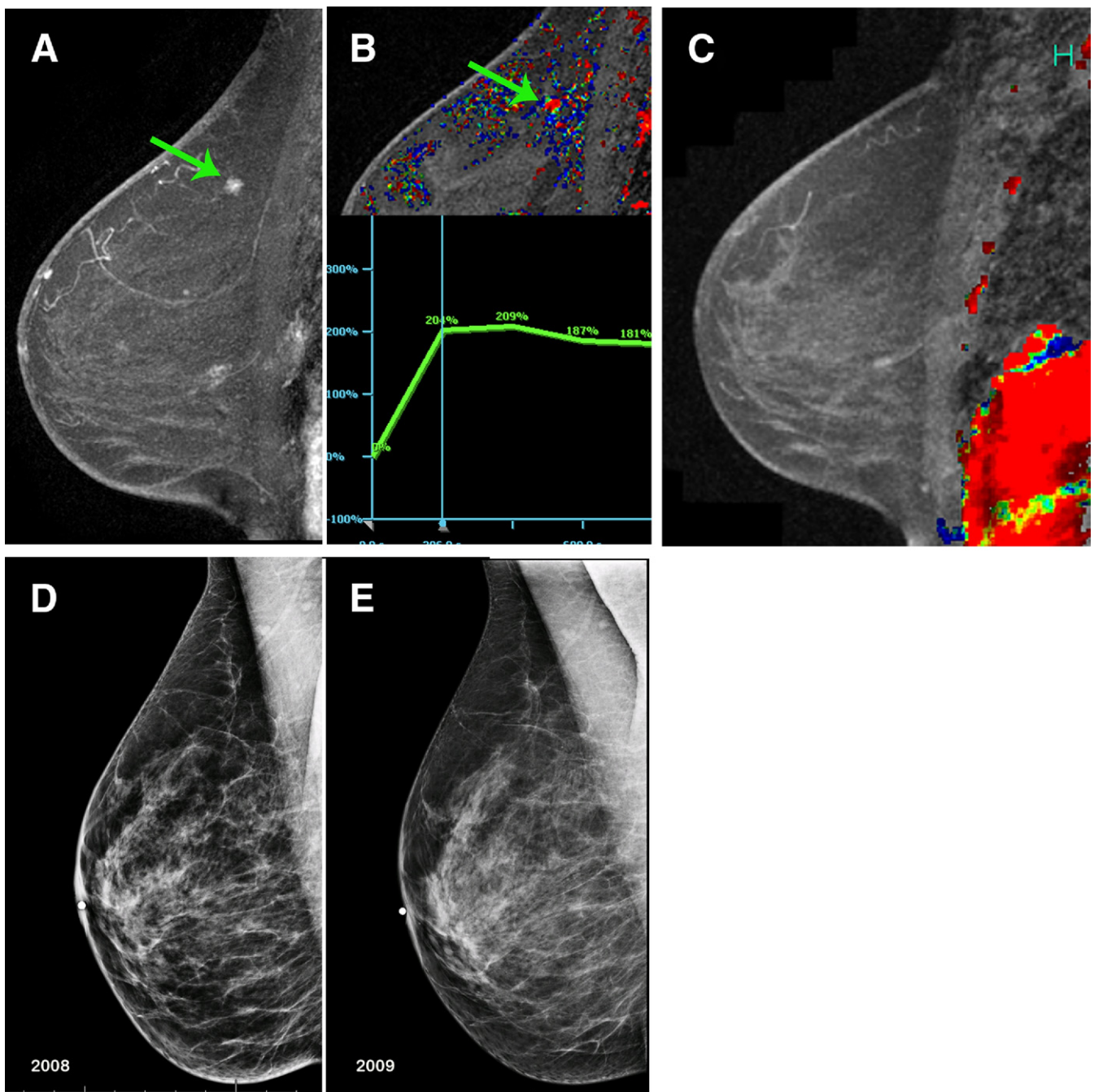


Figure 1 A 46-year-old woman with strong family history for breast cancer who received mammography and MRI screening. Sagittal maximum intensity projection image (A) with corresponding kinetic curve analysis (B) demonstrates a new 0.6-cm irregular enhancing focus with linear distribution (arrow) at the 1 o'clock position of the left breast. This lesion was subsequently biopsied, with final diagnosis of intraductal carcinoma. This lesion was not present on the MRI examination performed 1 year earlier (C) or detected on the screening mammography (E) performed 6 months earlier, with prior mammography comparison (D). (Color version of figure is available online.)

lance program of 629 women with either a personal or familial history of breast cancer, 68 women had an MRI-detected cancer. Twenty percent of the MRI-detected invasive carcinomas (13 of 64) present as non-mass-like enhancement on the scan as opposed to the typical malignant-appearing mass; indeed, 92% of the intraductal carcinomas presented as non-mass-like asymmetric enhancement.²⁴ Half of these intraduc-

tal carcinomas had kinetic patterns suggestive of benign lesions. This observation that cancerous lesions might have non-mass-like morphologic features and benign kinetic features has also been described by others.^{25,26} This overlap between the features traditionally associated with benign and malignant lesions makes the detection of cancers under such circumstances all the more challenging.

Table 2 Rates and Numbers of Breast Cancers Detected by Imaging Screening Modality

Study	n	No. of Cancer Cases Detected	Rate of Cancer Detection (%)	Cancer Detected by*		
				Mam	US	MRI
Warner (2004) ¹⁵	236	22	9	8 (36%)	7 (33%)	17 (77%)
Kuhl (2005) ¹⁶	529	43	8	14 (33%)	17 (40%)	39 (91%)
Lehman (2007) ²¹	171	6	3.5	2 (33%)	1 (17%)	6 (100%)
Kriege (2007) ²²	1909	45	2.4	18 (40%)	NA	32 (71%)
Leach (2005) ¹⁴	649	35	5	14 (40%)	NA	27 (77%)
Sardanelli (2007) ¹⁸	278	18	7	10 (56%)	11 (61%)	15 (83%)
Weinstein (2009) ²⁰	609	20	3	6 (30%)†	3 (15%)	12 (60%)

NA, not available.

*Number of cancer cases that were seen on each of these imaging modalities. If a cancer was seen on 2 imaging modalities, then that case was counted under both imaging modalities.

†This study used digital mammography.

Interval Cancers and Contralateral Cancers

Despite the addition of MRI to mammography screening, some published trials still report cancers developing between the screening intervals (ie, interval cancer) at a rate of 2%-9%.^{14-17,27} The screening regimens commonly had 1-year intervals, with MRI and mammography performed within 90 days of one another. However, some experts recommend—and some centers throughout the United States already perform—annual MRI and mammographic examinations staggered at 6-month intervals. The rationale behind this screening regimen is to decrease the incidence of interval cancers as well as to offer the patient the psychological reassurance of being observed every 6 months. However, some patients might prefer concurrent screening with both modalities because of the convenience of scheduling them together as well as the opportunity given for treating physicians to correlate the 2 examinations.

In addition, most of the data published has been from breast screening MRIs performed with a 1.5 tesla magnetic system. In the United States, many private practices and academic centers routinely use magnetic systems with higher field strengths such as 3.0 tesla. The impact of these higher-field magnetic systems on the specificity and sensitivity of diagnosis remains unclear and is a promising area for further research.

The studies discussed herein describe the role of breast MRI on today's practice as well as providing possible insight into future trends. Some of the challenges still to be addressed include the fact that a large proportion of women at high risk are not identified for screening purposes until after they present with a newly diagnosed breast cancer. Other challenges specific to breast MRI screening include delays in receiving an MRI examination and the higher cost of MRI, which can be as much as 10 times that of mammography or ultrasound.

In addition, breast MRI cannot replace mammography, especially in the detection of ductal carcinoma in situ (DCIS). This is because mammography is superior in the detection of microcalcifications (although MRI has been shown to enable the detection of noncalcified DCIS).²⁸ Therefore, mammography should not be removed from the screening regimen, and the addition of screening MRI to mammography screen-

ing for the detection of noncalcified DCIS requires further systematic evaluation with a multi-institutional trial.

Providing MRI in addition to mammographic screening has many advantages, including the added cancer yield, earlier detection (which leads to cancer being caught at a smaller size and lower stage), and the potentially lower rate of interval cancers. However, the impact of MRI screening on mortality is still not known. Therefore, patients and health care providers should be informed of the current data before patients are offered screening MRIs or physicians adopt this modality into routine practice.

The potential for false-positive findings because of the higher sensitivity but lower specificity of MRI also might lead to additional scans and biopsies, with their attendant risks, which include cost and patient anxiety. Other disadvantages of MRI include the accessibility of the examination and the psychological impact of additional testing and biopsies on patients and their families. Informing patients of all the benefits and risks of these imaging modalities involves considerable time spent counseling, which might not be practical in all screening programs.

Screening Breast Ultrasound

Mammography is likely to remain the gold standard for breast cancer screening of the general population. Breast MRI and whole breast ultrasound survey have been shown to be of greater sensitivity than mammography in the early detection of breast cancers.^{11-20,29-31} However, unlike mammography, these 2 modalities have not been proved to reduce breast cancer mortality. Proof of mortality rate reduction will require a randomized controlled clinical trial involving a large number of women receiving screening with the new modality, who will then have to be followed for at least 15 years and be matched with a control group of women who receive the current standard care. The new modality being tested would have to show mortality rate reduction over and above what has been achieved with screening mammography; this is unlikely to be the case anytime in the near future.²⁹

In North America, breast ultrasound has been predominantly used as a targeted examination for a clinical or mammographic problem, whereas in Europe whole breast ultra-

sound survey has been more prevalent.³² It is not uncommon to identify incidental nonpalpable cancers during diagnostic sonographic evaluation of a mammographic or physical finding.³² Mammography is known to have a limited sensitivity in women with dense breast tissue. The use of breast ultrasound as a supplemental modality for breast cancer screening has been studied in women with dense breast tissue and in those with an elevated risk for breast cancer. Dense breast tissue is by itself considered a risk factor for breast cancer.³³ It has been suggested that in women with a 3-fold relative risk compared with women without any known risk factors, it is enough to be categorized in the high-risk group.³⁴ To date, none of the major professional societies in the United States or elsewhere recommend the use of screening ultrasound for breast cancer.³¹

Clinical Efficacy of Supplemental Screening Ultrasound

A systematic search and review of studies involving mammography and ultrasound performed for screening of breast cancer found 6 cohort studies, of which only 2 had follow-up on patients with negative or benign findings. Screening ultrasound performed in women with American College of Radiology breast density types 2-4 identified primarily invasive cancers in 0.32% of women. The mean tumor size was 9.9 mm, and 90% of the cancers were node negative. Biopsy rate was high at 2.3%-4.7%, with positive predictive value of 8.4%-13.7% for those biopsied because of an abnormal finding on the ultrasound examination. The added benefit of using ultrasound to screen for breast cancers in women with a negative mammogram might be lower in women aged 50-69 years.³¹

The most notable and the largest clinical trial of screening ultrasound to date is the American College of Radiology Imaging Network trial³⁵ (ACRIN 6666). This study was a prospective multicenter trial randomized to a group receiving ultrasound and mammographic screening and one to mammographic screening alone to compare the diagnostic yield of performance of breast ultrasound and mammography versus mammography alone in women with elevated risk of cancer. The criteria used in this study to determine an elevated risk for breast cancer included a personal history of breast cancer, prior atypical biopsy, elevated risk based on the Gail or Claus model or both. A standard protocol and interpretive criteria were used. Mammography and ultrasound were performed and read independently, allowing for reducing potential biases in patient recruitment and interpretation. Data were analyzed from 2637 patients who underwent imaging. Thirty-one cancers were detected in the study group, 11.8 per 1000 women; the increase in the cancer detection rate because of addition of ultrasound was 4.2 per 1000 women. The diagnostic accuracy for mammography was 0.78, for ultrasound was 0.80, and for combined mammography and ultrasound was 0.91. Ultrasound hence proved a useful supplemental modality, identifying additional small node-negative invasive cancers in this cohort of women at an elevated risk for breast cancer.

Breast sonography has never been studied or been advocated to be used as the only modality to screen for breast cancer. The rationale against such an approach is sound; not the least is the low yield of ultrasound alone detected breast cancers. There is, however, some data from a study in Japan that demonstrate the value of sonography when used as the only modality for screening of breast cancer in women <40 years of age.³⁶ This study was undertaken in the Ibaraki prefecture of Japan where the breast cancer screening recommendations include performing annual screening ultrasound and CBE in women of ages 30 through 56 and biannual mammography in women of ages 40 through 65. There were 12,359 women in the age group of 30-39 years who received annual screening breast ultrasound and did not undergo mammographic screening. Of these, 4501 women also received annual CBE in addition to whole breast screening ultrasound. In young women, ie, younger than the age of 40 years, as expected, the cancer yield was low, with a cancer detection rate of 0.04%-0.07%.³⁶ In those women between the ages of 40-56 years in whom both mammography and ultrasound were used, the cancer detection rate ranged from 0.13%-0.16% for sonography and 0.1%-0.22% for mammography. Overall, 41,653 women underwent mammography, and 48,294 women underwent CBE and breast ultrasound. The rate of detection of stage I cancers was 72% by ultrasound, 66% by mammography, and 42% by CBE.³⁶ Cancer detection by mammography and ultrasound was complementary. Approximately one-third of cancers would have been missed if only 1 of these modalities were used, which once again proves the value of supplementing ultrasound with mammography, as has been shown in the ACRIN 6666 trial. There have been other studies conducted in Japan, where a significant proportion of women tend to have small breasts with dense parenchyma and are better suited for whole breast ultrasound survey. These studies have also validated the use of ultrasound in the detection of small cancers in women with dense breasts.^{37,38}

Breast Ultrasound: Pros and Cons

The benefits of ultrasound as a screening modality are that it does not use ionizing radiation, is well-tolerated, does not require intravenous contrast administration, and is optimally amenable for percutaneous biopsy guidance. Ultrasound is able to identify small nonpalpable masses while undeterred by presence of dense breast tissue, which is an inherent limitation of mammography. More than 90% of cancers identified at sonography are in women with >50% of dense breast tissue.^{39,40} However, unlike mammography, the vast majorities of cancers that are seen on ultrasound are invasive cancers; DCIS is not usually identified by sonography.³⁵ On the other hand, MRI has been shown to readily identify DCIS.⁴¹ Nevertheless, it is debatable whether a screening examination that identifies small node-negative cancers is adequate or whether detection of DCIS is a more critical requirement of a screening test.

There are limitations for the use of ultrasound in screening for breast cancer. Ultrasound has never been proved to re-

duce mortality from breast cancer. Because the incidence of cancers seen on ultrasound is low, to prove mortality rate reduction, a large cohort will have to be studied in a randomized blinded controlled clinical trial.³² These studies are unlikely to be conducted anytime in the near future, leaving this important question of whether ultrasound screening will lead to breast cancer mortality rate reduction unanswered. Ultrasound is an operator-dependent examination; standardization of the examination and having a skilled, adequately trained sonologist are critical for performance of a whole breast ultrasound.³² This is compounded by intraobserver and interobserver variability when follow-up for probably benign lesions is recommended. Perhaps one of the most significant drawbacks for the use of ultrasound is the time that it takes to perform a high-quality bilateral breast ultrasound, which was reported to be a median of 19 minutes.³⁵ That compares very poorly with mammographic interpretation time. A breast radiologist might read up to 50 mammograms in the time taken to perform 3 breast ultrasounds.³⁰ Another limitation of ultrasound is the high rate of false-positive studies; the positive predictive value in those cases in which biopsy was performed was 8.8%-8.9%, compared with 23% with mammography.³⁵ In this context it is worthwhile keeping in mind that a false-positive ultrasound might not have the same consequence as that of a false-positive mammogram. As Kuhl³⁰ points out in an editorial, a suspicious finding on a mammogram requires a much more expensive and time-consuming biopsy procedure than an ultrasound-guided core biopsy or a fine-needle aspiration biopsy that can be performed often immediately after the ultrasound examination.

Conclusions

At the present time, mammography remains the standard of care for screening for breast cancer. MRI and ultrasonography have been studied as supplemental methods for screening of women at an elevated risk for breast cancer. Although breast MRI has been shown to be superior to both mammography and ultrasound in identifying breast cancers, it is limited by its cost and availability. The use of breast MRI in women with low to moderate risk of developing breast cancer is not recommended because widespread or unlimited use of MRI would lead to higher false-positive rates and increased costs. Ultrasound is limited by the time it takes to perform an examination and the high false-positive rate. The appropriate screening and management strategy is still best determined for each individual patient. Currently, there is no universal recommendation for the frequency of ultrasound or MRI as an adjunct to the mammographic screening protocol. In addition, the optimal age at which to start screening high-risk women and the optimal screening regimen remain unanswered questions, despite multiple published trials over several countries.

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