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RISK AND PREVENTION (ME WOOD, SECTION EDITOR)

Screening Modalities for Women at Intermediate and High Risk for Breast Cancer

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Abstract

Purpose of Review Breast cancer screening is critically important to detect malignancy at an early stage. Annual mammography remains the gold standard as the imaging modality for patients with an average breast cancer risk. However, women with increased breast cancer risk benefit from supplemental screening using additional imaging modalities. This review summarizes the current recommendations within this patient population.

Recent Findings Analysis from ACRIN 6666 demonstrated that the cancer detection rate of ultrasound is comparable to mammography with an increased amount of invasive and node-negative cancers detected. Supplemental ultrasound increased the sensitivity and cancer detection rate in the J-START randomized controlled trial. Abbreviated breast MRI and ultrafast breast MRI have demonstrated effective cancer detection performance in the high-risk population.

Summary Women with increased breast cancer risk benefit from supplemental screening using digital breast tomosynthesis, ultrasound, and breast MRI. Molecular breast imaging may be considered in some patients.

Keywords Breast cancer · Breast cancer screening · High-risk screening · Mammography · Ultrasound · Magnetic resonance imaging

Introduction

Breast cancer is the most common cause of cancer mortality in women, most frequent cancer-related cause of death in women within less developed regions of the world, and remains the second most frequent cancer-related cause of death in the developed regions of the world despite advances in treatment and prevention [1]. Screening for breast cancer remains crucial to the early detection and treatment of malignancy before the involvement of the lymphatic system and distant metastasis occurs.

The benefit of screening and detecting malignancy at an early stage is weighed against the risk of false positives that result in additional imaging, potential biopsy, and emotional distress experienced by a patient. Currently, the American College of Radiology and the Society of Breast Imaging recommend women of average risk begin annual screening mammography at 40 years of age [2, 3•]. A woman of average risk is considered to have less than a 15% chance of developing breast cancer during her lifetime [4•].

A woman at intermediate risk is defined to have a 15–20% lifetime risk of breast cancer [4•]. These patients may have a family history of breast cancer or ovarian cancer, atypical ductal hyperplasia (ADH), or lobular neoplasia including lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH).

Several factors can elevate a woman's risk above average- and intermediate-risk categories where supplemental screening may provide benefit. A woman at high risk for developing breast cancer carries a lifetime risk greater than 20% [4•]. These patients may have a mutation in ATM, BRCA, CHEK2, PALB2, PTEN, TP53, or other highly penetrant gene placing them at increased risk for breast cancer. A patient who received chest or mantle radiation earlier in life for another condition is also considered to be at this level of risk [5]. In a review of childhood cancer survivors treated with chest radiation, the cumulative incidence of breast cancer by 50 years of

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age was found to be 30% and a breast cancer-specific mortality at 5 and 10 years was found to be 12% and 19%, respectively [5]. These women are recommended to begin screening 8 years after finishing their radiation treatment or at 25 years of age if they completed their treatment before the age of 17.

Multiple breast cancer risk assessment models have been developed to assist clinicians in properly assessing a patient's risk. The Cuzick-Tyrer, Gail, Claus, BRCAPRO, and BOADICEA models are commonly used to determine the lifetime risk of a patient by incorporating varying degrees of personal and family history [6, 7]. Regardless of assumed history, it is strongly recommended that all women, particularly black women or those with Ashkenazi Jewish heritage, be evaluated for their breast cancer risk by 30 years of age so that patients can be properly stratified and begin appropriate screening [8••]. Supplemental screening from a variety of imaging modalities can then be leveraged to detect malignancy at an earlier stage with the hope of offering a higher likelihood of cure, less extensive surgery, and better cosmetic outcomes (Table 1).

Mammography and Digital Breast Tomosynthesis

Screening mammography is the only imaging modality proven to decrease mortality from breast cancer and remains the gold standard for breast cancer screening. Regular screening mammography decreases the risk of death from breast cancer by 30–48% and the invitation to screening alone reduced mortality by 22% in women 50–74 years at entry and by 15% in women 39–49 years at entry across seven randomized controlled trials [9–15].

Three-dimensional digital breast tomosynthesis (DBT) is an imaging modality that can be utilized for screening that consists of a series of multiple low-dose radiographic images of a stationary compressed breast. The images are obtained at multiple angles along an arc, reconstructed into a three-dimensional dataset, and then viewed as multiple individual sequential thin slices. Synthetic two-dimensional digital mammographic images can also then be generated from the acquired dataset. This imaging technique allows the interpreting reader to evaluate varying regions of the breast and conclude if a conspicuous finding may be generated from superimposed benign tissue.

The adjunct use of DBT has shown an increase in cancer detection rate, decrease in the recall rate, and an increase in the positive predictive value of recalls [16, 17]. Friedewald and colleagues analyzed the performance of digital mammography alone and when used in combination with DBT from 13 academic and nonacademic breast centers and found an overall increase in the cancer detection rate by 1.2 per 1000 screens performed when DBT was added [17].

Women at intermediate risk of breast cancer will often benefit from mammographic screening beginning at a younger age than 40. A recent cohort study found a breast cancer incidence of 9.9% within 7 years following a diagnosis of ADH, ALH, or LCIS by core-needle biopsy [18]. Patients placed within this category from a biopsy-proven diagnosis of atypical hyperplasia or LCIS should begin annual screening when diagnosed or once they reach 30 years of age if diagnosed earlier [8••].

Ultrasound

Ultrasound provides a supplemental screening imaging modality alongside mammography without the risk of additional radiation and at a relatively low cost. Furthermore, dense breast tissue is not a hindrance to the ability of ultrasound to detect malignancy in the same manner that dense breast tissue can partially limit mammography. Mandelson and colleagues found reduced mammographic sensitivity to be strongly associated with increased breast density [19]. Not only does dense breast tissue decrease the effectiveness of mammography by masking cancer but it also serves as a risk factor for breast cancer itself [20, 21].

Table 1 Imaging modality recommendations for breast cancer screening

Patient history	Recommend screening imaging modality	Age to begin screening
Average breast cancer risk (< 15% LTR)	Annual MG ± DBT	40 years of age
Patient of average risk with dense breast tissue	Annual MG ± DBT US may be considered	40 years of age
Diagnosis of ADH, ALH, or LCIS	Annual MG ± DBT US and MRI may be considered	30 years of age or at diagnosis, whichever occurs later
History of chest radiation as a child	Annual MG ± DBT with MRI concurrently or alternating every 6 months	8 years after treatment No earlier than age 25
High risk of breast cancer due to gene mutation or medical history (> 20% LTR)	Annual MG ± DBT with MRI concurrently or alternating every 6 months	25–30 years of age

LTR, lifetime risk; *MG*, mammography; *DBT*, digital breast tomosynthesis; *US*, ultrasound; *MRI*, magnetic resonance imaging

Ultrasound as a primary screening modality in heterogeneously or extremely dense breast tissue has demonstrated comparable detection rates as screening mammography with an increased number of invasive and lymph node-negative cancers discovered. In reviewing the data from ACRIN 6666, Berg and colleagues found comparable detection rates between screening mammography and ultrasound, 80.2% of cancers detected were invasive, and invasive cancers detected by ultrasound were 20.3% more frequently node negative [22••]. Supplemental ultrasound screening also provides increased sensitivity to detect malignancy and increases the cancer detection rate in the setting of dense breast tissue compared to mammographic screening alone [23••]. Supplemental sonographic screening has also been shown to yield better incremental breast cancer detection than supplemental DBT, while maintaining a similar false-positive recall rate [24]. Unfortunately, screening ultrasound is accompanied by an increase in the false-positive rate, resulting in potential unnecessary biopsy procedures [22••, 25, 26]. Currently, supplemental screening ultrasound remains an optional consideration for patients with dense breast tissue or women at intermediate risk for breast cancer [4•, 27].

Screening ultrasound for patients carrying a high risk of breast cancer is an option for women who cannot undergo magnetic resonance imaging (MRI) evaluation. Berg and colleagues found that screening ultrasound added to annual mammography added detection of 5.3 cancers per 1000 women screened in the first year and 3.7 cancers per 1000 women screened in the second and third years [27]. These patients often need an alternative to MRI evaluation as symptoms of claustrophobia and anxiety can be prohibitive for patients to complete an MRI examination. Several socioeconomic factors may limit the ability of women to seek adjunctive MRI screening due to issues relating to cost, insurance status, or access to facilities. Patients with poor renal function are also restricted from receiving intravenous gadolinium contrast agents necessary for the examination. In these settings, supplemental ultrasound screening can be employed when MRI is not available [28].

Automated whole-breast ultrasound (ABUS) addresses many concerns and limitations of handheld sonographic evaluation. ABUS acquires a three-dimensional sonographic dataset of the breasts without the need of a radiologist or trained breast ultrasound technologist to complete the imaging portion of the exam. This frees the radiologist to focus on study interpretation, decreases study variability dependent on operator expertise, and can increase patient throughput [29]. The addition of ABUS to mammographic screening has demonstrated a 26.7% increase to cancer detection sensitivity and an increase in cancer detection rate by 1.9 cancers detected per 1000 women screened but at a cost of an increased false-positive rate that is also seen with handheld ultrasound [30].

Magnetic Resonance Imaging

Contrast-enhanced breast MRI has consistently demonstrated high sensitivity to detect cancer in women with an elevated breast cancer risk compared with mammography and ultrasound, despite variations in screening programs and different imaging techniques [31–34]. Breast MRI exhibits excellent sensitivity of 81–98.4% and specificity of 77–92.6% across multiple studies investigating the performance of the imaging modality in women at increased risk without the use of additional ionizing radiation [35].

Although a decrease in mortality due to breast MRI screening has not been directly demonstrated by a randomized control trial, the combination of mammography and breast MRI for annual screening in women of high risk has been demonstrated to be effective in detecting small invasive cancers that are node negative. Sung and colleagues evaluated the imaging and histopathologic features of breast malignancy detected by screening mammography and MRI and found that lesions detected by screening breast MRI were 71% more likely to be invasive [36]. Additionally, Berg and colleagues found a supplemental yield of 14.7 cancers per 1000 women screened with an elevated breast cancer risk when breast MRI was utilized [27].

Interval cancer rates have also been noted to decrease with the addition of MRI to annual screening mammography. This might suggest that the annual screening schedule may be too long for high-risk populations. Common intervals include annual screening for both modalities occurring at the same date or alternating annual MRI and mammography every 6 months [37, 38]. The rationale behind an alternating screening regimen is to potentially 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 may prefer concurrent screening with both modalities because of the convenience of scheduling them together as well as the opportunity for treating physicians to correlate the two examinations.

Additional techniques within magnetic resonance imaging that are being evaluated for purposes of breast cancer screening include abbreviated breast MRI and ultrafast breast MRI. Abbreviated breast MRI focuses on reducing the length of a diagnostic breast MRI experienced by the patient and a reduction in the number of images required to be interpreted by the reader. An abbreviated protocol will usually incorporate a T2-weighted sequence, dynamic post-contrast sequence, possible diffusion-weighted sequence, and maximum-intensity projected (MIP) images generated from the dynamic post-contrast sequence. Panigrahi and colleagues evaluated the use of an abbreviated protocol to screen women with a high risk of breast cancer and found no significant difference in the sensitivity and specificity as compared to the full diagnostic protocol in this demographic [39•]. An ultrafast breast MRI

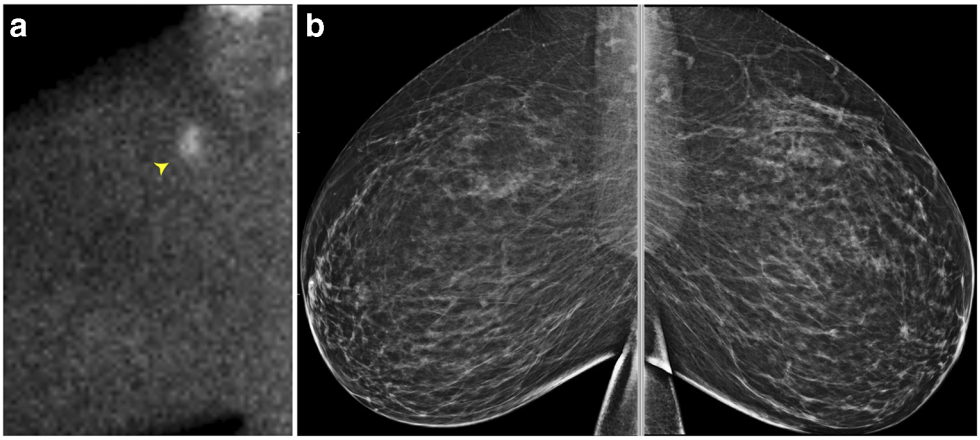

Fig. 1 48-year-old woman with a history of left breast ductal carcinoma in situ who was unable to tolerate a breast MRI, an MBI exam was performed instead. Suspicious focal non-mass uptake (arrowhead) observed on right mediolateral oblique view from molecular breast imaging examination (**a**) was identified, without any correlate seen by digital mammography (**b**). Subsequent ultrasound-guided biopsy demonstrates an occult high-grade invasive ductal carcinoma

focuses on analyzing the inflow of contrast into breast lesions while maintaining a spatial resolution that allows characterization of the lesion morphology. Van Zelst and colleagues examined the performance of ultrafast breast MRI in a high-risk breast cancer population and found an increased specificity and equal sensitivity of ultrafast breast MRI as compared to a full diagnostic protocol [40•]. Additionally, it should be noted that these techniques are not mutually exclusive and a hybrid approach by incorporating ultrafast breast MRI into an abbreviated or full diagnostic protocol can be pursued [41].

Molecular Breast Imaging

Molecular breast imaging (MBI) is an emerging functional imaging technique that uses technetium (Tc-99m) sestamibi to detect malignancy (Fig. 1). Images of the compressed breast are acquired in craniocaudal and mediolateral oblique views after patients are administered Tc-99m sestamibi intravenously. Tc-99m sestamibi then collects preferentially within cancer cells due to increased angiogenesis associated with the malignancy [42•]. The radiation dose received by the patient is approximately 2.3–2.5 mSv which is comparable to the dose administered by screening and diagnostic mammography [43, 44].

The ability of MBI to detect malignancy in a patient with dense breast tissue can make MBI an attractive option for high-risk breast cancer patients who cannot obtain a breast MRI due to anxiety, renal concerns, or weight concerns. MBI has demonstrated a reported sensitivity to detect malignancy of 92–96% and a specificity of 71–80% [45]. MBI as a supplemental screening modality has also demonstrated an incremental cancer detection rate of 7.7% in a community practice environment [46].

MRI remains the preferred imaging modality over MBI for supplemental screening in high-risk patients. While the radiation dose is low and comparable to other imaging modalities, MBI lacks comparable anatomy that would be included within an MRI examination and is currently not widely available [47].

Conclusions

Breast cancer screening in women of intermediate and high risk remains of crucial importance to detect and treat malignancy while it remains in the most optimal stages for treatment. Multiple imaging modalities are now available for clinicians to employ at varying patient ages depending on the patient's medical and family history. Mammography, digital breast tomosynthesis, ultrasound, and traditional diagnostic breast MRI remain at the forefront of breast cancer screening in elevated breast cancer risk populations. New developments are now being studied within abbreviated breast MRI, ultrafast breast MRI, and molecular breast imaging which may be incorporated into the standard screening recommendations in the near future.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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