Breast Cancer Screening in Women at Higher-Than-Average Risk: Recommendations From the ACR

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Abstract

Early detection decreases breast cancer mortality. The ACR recommends annual mammographic screening beginning at age 40 for women of average risk. Higher-risk women should start mammographic screening earlier and may benefit from supplemental screening modalities. For women with genetics-based increased risk (and their untested first-degree relatives), with a calculated lifetime risk of 20% or more or a history of chest or mantle radiation therapy at a young age, supplemental screening with contrast-enhanced breast MRI is recommended. Breast MRI is also recommended for women with personal histories of breast cancer and dense tissue, or those diagnosed by age 50. Others with histories of breast cancer and those with atypia at biopsy should consider additional surveillance with MRI, especially if other risk factors are present. Ultrasound can be considered for those who qualify for but cannot undergo MRI. All women, especially black women and those of Ashkenazi Jewish descent, should be evaluated for breast cancer risk no later than age 30, so that those at higher risk can be identified and can benefit from supplemental screening.

Key Words: Breast cancer screening, breast cancer, higher risk populations, breast MRI, digital breast tomosynthesis, breast cancer risk assessment

INTRODUCTION

Early detection decreases mortality for women with breast cancer [1-3]. The ACR currently recommends annual mammographic screening beginning at age 40 for women at average risk for breast cancer, on the basis of extensive literature review [4]. Women with additional risk factors placing them at higher-than-average risk for developing breast cancer need further consideration for earlier and/or more intensive screening [5]. These women typically have, at age < 40 years, risk equivalent to or higher than that of an average-risk woman at age 40.

Breast imaging experts from the ACR Commission on Breast Imaging have reviewed a wide body of literature regarding the screening of higher-risk women. Our analysis again includes consideration of the ACR Appropriateness Criteria, which use robust strength-of-evidence...
methodology accepted by the National Guidelines Clear- inghouse [6,7]. Our recommendations for women in the higher-risk population are based on the latest data available regarding the use of MRI, ultrasound, molecular breast imaging (MBI), and digital breast tomosynthesis (DBT) in addition to digital mammography (DM).

**POPULATION SUBGROUPS AT HIGHER RISK**

There are several factors that increase a woman’s risk for breast cancer. Known genetic predisposition is found in about 5% to 10% of breast cancers [8], with the BRCA1 or BRCA2 mutation the most widely recognized [9]. The lifetime risk for breast cancer is 50% to 85% among BRCA1 carriers and approximately 45% among BRCA2 carriers [10,11]. Women of Ashkenazi Jewish descent are known to be at high risk for the BRCA1 mutation, although they may also have higher rates for other actionable mutations [12]. Other less common gene mutations include TP53 and CHEK2 (Li-Fraumeni syndrome), PTEN (Cowden and Bannayan-Riley-Ruvalcaba syndromes), CDH1 (hereditary diffuse gastric cancer), STK11 (Peutz-Jeghers syndrome), PALB2 (interacts with BRCA2), and ATM (ataxia-telangiectasia) genes.

Women with strong family histories are at higher risk, even in the absence of known genetic mutations. The number of family members with breast cancer, especially first-degree relatives, and their age at diagnosis are important considerations that add complexity to the assessment (see “Models for Risk Assessment” later in this article).

Women treated with chest or mantle radiation therapy at a young age, such as those with Hodgkin lymphoma, are at increased risk for developing breast cancer, starting approximately 8 years after the completion of radiation treatment [13,14]. The cumulative risk for a Hodgkin lymphoma survivor treated at age 25 will be 20% to 25% by age 45 [15,16]. This is similar to BRCA1/2 carriers, whose cumulative risk by age 40 is 15% to 18% [17]. Recipients of ≥20 Gy and those treated at younger ages (first and second decades of life) are at greatest risk. Any woman who has received a cumulative dose of 10 Gy or more before age 30 is considered high risk [18].

Women with personal histories of breast cancer are at risk for recurrence or a second breast cancer. A meta-analysis of 10,801 women treated with breast-conserving therapy found a 10-year recurrence rate of 19.3% and a 15-year cancer death rate of 21.4% [19]. The risk for contralateral cancer is 0.5% to 1% per year during the 10 years after diagnosis [20]. Although hormone therapy and/or chemotherapy lowers this risk, women diagnosed with early estrogen receptor–positive cancers remain at increased risk for future cancer (approximately 10% and 20% at 5- and 10-year follow-up, respectively) [21-24]. Age at diagnosis matters. Risk analysis shows that all women diagnosed at or before age 50 and treated with breast-conserving therapy have a 20% or higher lifetime risk for a new breast cancer [25].

Women with lobular neoplasia—atypical lobular hyperplasia or lobular carcinoma in situ (LCIS)—have a lifetime risk of 10% to 20% [26]. For women with LCIS at biopsy, breast cancer risk is bilateral, and most cancers occur more than 15 years after the diagnosis. Atypical ductal hyperplasia (ADH) confers increased risk but to a lesser degree than LCIS. At a median follow-up of 17 years, the relative risk for invasive cancer is 4- to 5-fold for women with ADH and 6- to 10-fold for women with LCIS [27]. Recent work shows the cumulative risk for invasive cancer 10 years after a diagnosis of ADH was 2.6 times higher than without ADH [28].

White and black women have the highest incidence rates of breast cancer of any group, and their occurrence rates are now similar [29]; however, a meta-analysis found that black women were 19% more likely to die of their disease [30]. Recent data from the American Cancer Society show that non-Hispanic black women have death rates 39% higher than non-Hispanic whites [31]. Reasons may include access to mammography, health care delivery patterns, and tumor biology [32]. Black women experience delays in diagnosis and treatment initiation, which negatively affect survival [33-36]. Although stage at diagnosis, tumor characteristics, and body mass index contribute to racial differences in survival, disparities persist after accounting for those factors [37]. Black women are less likely to be diagnosed with stage I cancer but are twice as likely to die of early breast cancers [38]. This difference may be attributed to the higher incidence of triple-negative (estrogen receptor, progesterone receptor, and Her2 receptor negative) breast cancer among black women. In fact, intrinsic differences in tumor aggressiveness may exist [38]. Recent data show a 2-fold higher population-based incidence rate of triple-negative breast cancer in African American women compared with white American women in all age categories [39–41]. Among 46,276 women, BRCA1 and BRCA2 mutation prevalence, respectively, was 10.2% and 5.7% with African ancestry, compared with 6.9% and 5.2% with
Western European ancestry [42]. Use of next-generation sequencing found that 65 of 289 black women with breast cancer (22%) had inherited mutations [43]. This might explain the increased risk for young-onset aggressive breast cancers in black women.

There is an increased risk for developing breast cancer among women with dense breasts, usually defined as having either heterogeneous dense or extremely dense breasts [44]. Density assessment may vary by radiologist and from year to year, and apparent changes may be affected by weight loss or gain and use or withdrawal of endocrine therapy [45]. More objective qualitative measurements are possible with the transition to DM and DBT but need validation [46,47]. Currently, 43% to 46% of US women older than age 40 have dense breasts [44,48]. The relative risk depends on which groups are compared. For example, the relative risk between women at the extremes shows 4 times higher risk among women with extremely dense breasts versus those with fatty breasts. However, most risk estimates involve comparison with the average woman, and because 79% of women lie in the two middle categories [48], a more suitable comparison is between those with dense breast parenchyma to those with scattered fibroglandular density. When that comparison is made, the relative risk for breast cancer associated with dense tissue is about 1.45 [49].

Models for Risk Assessment

Many statistical models have been developed to estimate the risk for developing breast cancer as well as the probability of carrying a deleterious mutation in genes such as BRCA1 and BRCA2. The modified Gail model incorporates age, ethnicity, hormonal and reproductive history, history of breast disease, and the number of first-degree female relatives with breast cancer to estimate the risk for invasive breast cancer over varying time periods [50-52]. The modified Gail model includes invasive breast cancer incidence rates for African American, Asian, and Pacific Islander women; however, the model requires additional validation for other racial or ethnic groups, including Hispanic women [51,53]. BRCAPRO (an Internet-based statistical model developed at academic breast centers, free for research and counseling use) assesses the probability of carrying germline BRCA1 mutations, as well as the risk for developing invasive breast cancer [54]. BRCAPRO excludes nonhereditary risk factors and genetic mutations other than BRCA, so the model is expected to underestimate risk [55]. Limited data suggest that BRCAPRO underpredicts BRCA mutation carriage in Hispanics [56]. The Tyrer-Cuzick, or IBIS, model is the most comprehensive but is also the most time intensive. The Tyrer-Cuzick model assesses the probability of carrying a BRCA mutation and the risk for developing in situ or invasive breast cancer. The model incorporates nonhereditary risk factors and detailed first- and second-degree family history, including unaffected relatives, and allows for multiple genes with variable penetrance [57]. To determine screening breast MRI eligibility, the American Cancer Society recommends models that incorporate first- and second-degree family history, such as Claus, Tyrer-Cuzick, BRCAPRO, and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm [9,58-60].

These statistical models use different input parameters and different outcomes and were developed and validated in different populations. Therefore, the performance of the models among individuals and across populations varies considerably. Despite good calibration (the ability to correctly estimate expected events compared with observed events in a population), existing models discriminate an individual’s risk with only moderate accuracy [55,61]. Limited prospective comparative data of model performance in clinical practice suggest that the Tyrer-Cuzick model is the most consistently accurate for predicting breast cancer risk [62,63]. However, density as a risk factor is not well validated in any of the currently used models. Research efforts are under way to better identify determinants of risk and incorporate novel risk factors to optimize future models [64,65].

IMAGING HIGHER-RISK WOMEN

DM and DBT

Screening mammography reduces breast cancer mortality by more than 40% in women aged 40 years and older [2,66-69]. In general, women of higher-than-average risk should begin screening at an earlier age.

Breast density tends to be higher at younger ages; for some at higher risk (ie, those with genetic predisposition or family histories with early breast cancer cases), this is coupled with biologically more aggressive tumors [70-74]. The sensitivity of mammography is 25% to 59% in higher-risk women [75-81]. Compared with the general population, these higher-risk women are more likely to be diagnosed with larger, node-positive malignancies on screening mammography and experience higher interval cancer rates [72,82-86].
DM improves cancer detection in dense tissue compared with previous film-screen techniques [87,88]. DBT detects significantly more cancers and decreases false-positive recalls compared with DM alone [89-103]. The largest performance improvements occur in women <50 years of age and those with higher breast density [96,104-107]. Because younger women generally have denser breasts [71], higher-risk women who begin screening at an earlier age would be expected to benefit from DBT.

Limited published data exist regarding DBT performance, specifically with higher-risk women. In one study of 2,673 higher-risk women, the DBT cancer detection rate was 8.6 of 1,000 in higher-risk versus 5.1 of 1,000 in average-risk women, an increase that was not statistically significant [104]. The small sample size and the underlying prevalence of disease are considerations in viewing these results.

A UK randomized trial of higher-risk 40- to 49-year-old women found no significant decrease in recall rate with DM plus DBT compared with DM alone [108]. However, the DM recall rate (2.8%) was very low, making any further reduction difficult to achieve. In a single study of breast cancer survivors, surveillance DBT significantly decreased recall rate [109].

The effects of DM and DBT in higher-risk women are similar to those described in average-risk women [4]. Because higher-risk women frequently begin screening at an earlier age, each woman may undergo a greater number of screening examinations and therefore may experience an increased number of false-positive recalls and biopsies. Although *BRCA* mutation carriers may be particularly susceptible to radiation, the low radiation dose from screening mammography does not demonstrably increase their breast cancer risk [110]. *BRCA1* carriers receive less benefit from mammography before age 40, but a significant proportion of breast cancers detected in *BRCA2* carriers are found only on mammography [111]. Heijnsdijk et al [112] found that mammography starting at age 30 was slightly better than no mammography for *BRCA1* mutation carriers undergoing MRI but much better for *BRCA2* carriers. Likewise, mammography remains important for early detection in women treated at a young age with chest radiation therapy [18,113-115]. By the age of 40 to 45 years, 13% to 20% of women treated as children or adolescents with mantle radiation therapy will develop breast cancer [13,14,114,116]. This population should begin screening at age 25 or 8 years after the completion of therapy, whichever is later.

**Contrast-Enhanced Breast MRI**

Contrast-enhanced breast MRI (ie, breast MRI, with and without gadolinium-based contrast; hereafter MRI) is known to increase cancer detection in higher-risk women and is more sensitive than either mammography or ultrasound in high-risk populations [75,76,115,117-123]. In a recent study of *BRCA2* mutation carriers and women of 20% or higher lifetime risk for breast cancer, sensitivity for breast cancer detection was 90.0% using MRI versus 37.5% for mammography and 37.5% for ultrasound [120]. Similarly, in a study limited to *BRCA1* and *BRCA2* mutation carriers, MRI sensitivity was 68%, compared with 37% for mammography and 32% for ultrasound [122]. MRI has consistently been shown to outperform mammography and ultrasound, even when these latter modalities are used together [118] and in mixed high-risk populations [118,123].

Recommendations have been established supporting the use of MRI in women with genetics-based increased risk and their untested first-degree relatives, women who received chest radiation therapy before age 30, and women with a calculated risk of 20% or more [9,124,125]. Data continue to accumulate to support these recommendations, as well as some refinements to them [118,120,122,123,126-130]. In previous recommendations, less certainty was expressed for the use of MRI in women of intermediate risk: those with personal histories of breast cancer, with LCIS or atypia at biopsy, with a calculated risk of 15% to 20%, or with dense breast tissue. Newer data are available to clarify MRI use in some of these groups.

For *BRCA* gene mutation carriers, MRI was initially recommended as a supplemental screening modality starting at age 25, to be obtained in addition to annual mammography at and beyond age 30. That recommendation remains solid. Since our previous recommendations, there are additional outcome data confirming the high cancer detection rate using MRI in this population [79,111,122,129,130]. However, recent studies also suggest that mammography adds only a small amount of increased cancer detection in *BRCA1* carriers under age 40, if MRI is used regularly [111,122,123,126]. These studies are somewhat limited by small sample sizes. A modeling study by Obdeijn et al [130,131] showed that the benefit of mammography in addition to MRI for *BRCA1* mutation carriers under age 40 could be positive or neutral; it is dependent largely on underlying assumptions and the balance of benefit and risk, as *BRCA1* carriers are thought to be more
susceptible to the effects of radiation. More evidence is needed to assess the role of mammography in BRCA1 carriers. BRCA2 carriers benefit more from mammography in addition to MRI [112]; about a third of cancers in these women are found only on mammography [111].

Patients with histories of chest or mantle radiation therapy under the age of 30 benefit from annual MRI screening [113-115,119]. The incremental cancer detection rate has been demonstrated to be approximately 4% in these patients, similar to that found for genetic mutation carriers [113,114]. Breast cancer risk increases substantially approximately 8 years after the completion of therapy, so surveillance is recommended to begin at that time but not before age 25 [18,115,119].

Personal history of breast cancer has been shown to confer higher risk than solely family history in the absence of a known genetic mutation [132]. Mammography has been shown to be less sensitive in those with histories of breast cancer [133-135]. Weinstock et al [133] found MRI sensitivity for cancer at 85% versus 23% for mammography; no tumors were found only by mammography in this population. Early work in patients whose sole risk factor is a personal history showed that the cancer detection rate with MRI was high, at 10.6 [136,137], although isolating personal history as the sole risk factor was difficult and resulted in small study numbers. Newer studies reaffirm those early results, showing a consistently high cancer detection rate with MRI (range, 10-29 cancers/1,000) in patients with personal histories of breast cancer [132,133,138-140]. MRI in the group with histories of breast cancer performed better than in patients with genetic or family histories, with fewer false positives, higher specificity, and equivalent sensitivity and cancer detection rates [140]. MRI surveillance is beneficial for women diagnosed with breast cancer before age 65 [25] and especially before age 50 [25,134,139]. A multi-institutional study involving 754 women with breast-conserving therapy at age 50 or younger showed that the addition of MRI improves the detection of early-stage but biologically aggressive tumors and decreases interval cancers [134]. Women with personal histories of breast cancer and dense tissue also benefit from MRI, which is expected, as this combination of risk factors is likely to indicate a lifetime risk of 20% or higher [141-143].

For women with LCIS, MRI has been shown to increase cancer detection to a level similar to other higher risk populations for which MRI is recommended [144,145]. Others have questioned its use, although without long-term follow-up [146]. Similar to those with personal histories of breast cancer, women with dense tissue and LCIS can benefit from MRI [143]. Whether having dense tissue alone would warrant additional surveillance with MRI has not been studied widely; the Dutch Dense Tissue and Early Breast Neoplasm Screening trial should provide data in this regard [147].

Ultrasound

Multiple studies confirm the incremental cancer detection capabilities of whole-breast ultrasound in women at elevated risk. For women whose only risk was dense breast tissue, a systematic review showed an incremental cancer detection rate of 3.2 per 1,000 [148]. Review of ultrasound screening performance after the adoption of Connecticut breast density legislation showed an incremental cancer detection rate of 3.1 to 4.0 per 1,000 over its initial 4 years [149]. ACRIN® 6666, a large prospective multicenter study evaluating women at elevated risk (most having dense breasts in combination with other risk factors), found a supplemental cancer detection rate of 4.3 per 1,000 [150]. The cancers found by ultrasound tended to be invasive, small (median size, 10 mm), and node negative (96%) [81,150].

However, this supplemental detection of clinically favorable cancers is accompanied by an increase in false-positive findings and lower positive predictive value (PPV) for biopsy compared with mammography or MRI [81,149,151-153]. In ACRIN 6666, the false-positive rate of ultrasound alone was 8.1% (versus 4.4% for mammography), and the PPV2 for ultrasound-only lesions was 8.9% in the prevalence round (mammography, 22.6%), increasing minimally in the incidence rounds (PPV3 of 11.7% versus mammography PPV3 of 38.1%) [81]. Short-term follow-up was recommended at an undesirably high rate as well (8.6% for ultrasound versus 2.2% for mammography) [150,154]. Other factors that have dampened enthusiasm for handheld whole-breast ultrasound screening include its operator dependence and time- and labor-intensive nature.

Recent studies suggest that as supplemental ultrasound screening matures as a technology, some of its drawbacks may diminish. Weigert [140] noted that PPV3 increased from 7.3% in year 1 to 20.1% by year 4, with a stable cancer detection rate. The Adjunct Screening With Tomosynthesis or Ultrasound in Women With Mammography-Negative Dense Breasts trial demonstrated a PPV3 of 48%, attributable to high physician
expertise and experience as well as availability of prior examinations for comparison [107]. Advances in automated breast ultrasound may address constraints of operator dependence and labor intensity. At this time, concerns around complete breast coverage (large breasts may be incompletely examined), as well as lack of robust screening data for automated breast ultrasound, preclude widespread adoption.

The effect of DBT, compared with DM alone, with supplemental ultrasound screening should be considered. DBT detects approximately half of the additional cancers detected by whole-breast ultrasound compared with DM, with fewer false positives [92,101,107]. If DBT is used instead of DM, the benefit of whole-breast ultrasound is reduced, whereas the elevated false-positive rate from sonography becomes relatively higher. In addition, if screening involves MRI and mammography, there is no incremental benefit but a substantial increase in false positives by also using ultrasound [75,76,120,122].

**MBI**

MBI involves intravenous injection of a radiopharmaceutical agent (technetium-99m sestamibi) and subsequent imaging using a dedicated breast-specific camera, preferably dual headed [155], to detect abnormal accumulation of radioactivity that could signal the presence of breast cancer. It shows excellent sensitivity (95%) and good specificity (80%), albeit somewhat lower for cancers <1 cm and ductal carcinoma in situ (84% and 86%, respectively [156]). Additionally, its performance is not hampered by breast density, and its performance is comparable with that of MRI [150,157-159]. Although to date there are no large trials to validate the efficacy of MBI for screening, several studies have shown that a significant incremental cancer detection rate can be realized when it is used to supplement mammography. Recent studies, in which breast density was exclusively [160] or mainly [161] the conferring risk factor, showed incremental cancer detection rates of 7.7 to 8.8 per 1,000, with median tumor sizes of 0.9 to 1.0 cm [155,160,161]. In patients with elevated risk related to family and personal breast cancer histories, Brem et al [162] showed an incremental cancer detection rate of 16.5, although higher administered activity was used in this study compared with the current desired dose of 300 MBq (8 mCi). However, these studies represent prevalence round—only data, so it is uncertain if these high supplemental cancer detection rates would persist over time [155].

Because the biodistribution of radioactive substances results in whole-body radiation exposure (rather than breast only, as with mammography) and resultant higher estimated lifetime attributable risk, dose must be carefully considered when evaluating MBI for screening. An analysis comparing the benefit-to–radiation risk ratio of mammography versus a 300-MBq (8-mCi) MBI examination showed higher benefit ratios with mammography for all 10-year age intervals examined (13 versus 5 for age 40-49 years; 82 versus 37 for age 70-79 years) [163]. It is estimated that an administered dose of 75 to 150 MBq (2-4 mCi) is required to achieve a benefit-risk ratio comparable with that of mammography [164].

Further advances in detector technology to allow lower dosing, more widespread penetration of MBI-guided biopsy capabilities, and additional large prospective trials (to include incidence screening results) will be needed before MBI can be embraced as a screening tool, even in women at elevated risk [165].

**SUMMARY**

All women, especially black women and those of Ashkenazi Jewish descent, should be evaluated for breast cancer risk no later than age 30, so that those at higher risk can be identified and can benefit from supplemental screening.

**Recommendations for DM With or Without DBT**

For women with genetics-based increased risk (and their untested first-degree relatives) or with a calculated lifetime risk of 20% or more, DM, with or without DBT, should be performed annually beginning at age 30.

BRCA1 carriers may consider delaying the start of mammography screening until age 40 only if they are imaged yearly with contrast-enhanced breast MRI starting at age 25.

For women with histories of mantle or chest radiation therapy who received a cumulative dose of 10 Gy or more before the age of 30, DM, with or without DBT, should be performed annually beginning at age 25 or 8 years after radiation therapy, whichever is later.

For women diagnosed with breast cancer, ADH, or lobular neoplasia before age 40, annual screening should begin at the time of diagnosis.

**Recommendations for Breast MRI**

For women with genetics-based increased risk (and their untested first-degree relatives), history of chest radiation
(cumulative dose of $\geq 10\, \text{Gy}$ before age 30), or with a calculated lifetime risk of 20% or more, breast MRI should be performed annually beginning at age 25 to 30.

For women with personal histories of breast cancer and dense breast tissue, or those diagnosed before age 50, annual surveillance with breast MRI is recommended.

For women with personal histories of breast cancer not included in the above, or with LCIS or atypia on prior biopsy, MRI should be considered, especially if other risk factors are present.

Recommendations for Ultrasound

For women with elevated risk who would qualify for but cannot undergo breast MRI, adjunctive screening with ultrasound should be considered.

For women with elevated risk limited to increased breast density, ultrasound can be considered for adjunctive screening, after weighing benefits and risks.

Recommendations for Molecular Imaging

MBI is not recommended for screening surveillance in any higher-risk population.

TAKE-HOME POINTS

- For women with genetics-based increased risk (and their untested first-degree relatives) or with a calculated lifetime risk of 20% or more, DM, with or without DBT, should be performed annually beginning at age 30.
- For women with histories of chest radiation therapy before the age of 30, DM, with or without DBT, should be performed annually beginning at age 25 or 8 years after radiation therapy, whichever is later.
- For women with genetics-based increased risk (and their untested first-degree relatives), histories of chest radiation (cumulative dose of $\geq 10\, \text{Gy}$ before age 30), or a calculated lifetime risk of 20% or more, breast MRI should be performed annually beginning at age 25 to 30.
- For women with personal histories of breast cancer and dense breast tissue, or those diagnosed before age 50, annual surveillance with breast MRI is recommended.
- For women with personal histories not included in the above, or with ADH, atypical lobular hyperplasia, or LCIS, MRI should be considered, especially if other risk factors are present.
- All women, especially black women and those of Ashkenazi Jewish descent, should be evaluated for breast cancer risk no later than age 30, so that those at higher risk can be identified and can benefit from supplemental screening.

ADDITIONAL RESOURCES

Additional resources can be found online at: https://doi.org/10.1016/j.jacr.2017.11.034.