The Role of MRI in Breast Cancer Screening

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Key Words
Breast cancer, screening, MRI, high-risk

Abstract
The 2009 NCCN Clinical Practice Guidelines in Oncology for Breast Cancer Screening and Diagnosis include significant updates for the role of MRI in screening women at increased risk for breast cancer. The NCCN now recommends considering breast MRI as an adjunct to annual mammography and clinical breast examination for women who have a BRCA1 or -2 mutation or who have a first-degree relative who has a BRCA1 or -2 mutation but who have not undergone genetic testing themselves; those who are determined to have a lifetime risk greater than 20% based on models that are highly dependent on family history; and those with a history of lobular carcinoma in situ. MRI is also recommended for patients who underwent radiation treatment to the chest between 10 and 30 years of age, and in those who carry or have a first-degree relative who carries a genetic mutation in the TP53 or PTEN genes (Li-Fraumeni, Cowden, and Bannahyan-Ruvalcaba syndromes). MRI is specifically not recommended for screening women at average risk for breast cancer. This article describes the peer-reviewed, published clinical research trials evaluating breast MRI in high-risk patients, on which the NCCN guidelines were based, and provides suggestions for future research. (JNCCN 2009;7:1109–1115)

In the mid-1990s, specific genetic mutations associated with lifetime breast cancer rates as high as 85% were discovered, leading to heightened interest in how to identify women at inherited risk for breast cancer and provide preventive and surveillance protocols appropriate to this elevated risk. However, clinicians were then faced with having to counsel women regarding options if a genetic mutation was identified, when few options were available at that time. Bilateral prophylactic mastectomies were associated with a 90% reduction in risk for mortality from breast cancer, but few women, particularly those of younger ages, chose that option. Risk reduction strategies were suggested and, even though based on sparse data, recommendations for intensive mammographic surveillance were supported. Several organizations recommended annual mammography starting at 25 years of age for women identified at high risk. Eventually, it became clear that mammography was a poor method of screening for breast cancer in young, high-risk women with dense breast tissue. Sensitivity consistently less than 50% was observed in mammography screening trials. Furthermore, even in routinely screened high-risk patients, half of screen-detected breast cancers had already spread to the lymph nodes. Thus, not only was overall sensitivity poor, but sensitivity in detecting localized cancers was even worse, raising questions as to whether in fact more harm than benefit was provided to these young women at high risk.

Questions regarding risks associated with radiation from mammography in young women at high risk for breast cancer also were raised, and this has been an ongoing concern in terms of benefit and potential harm. In a recent study, a model was developed to estimate the lifetime risk for death from radiation-induced breast cancer caused by 5 annual mammograms among BRCA mutation carriers aged 40 years and younger. These estimates were used to determine in which age group mammography screening would be beneficial, assuming a 25% or less reduction in mortality from mammography in this age group. The authors found that, although screening mammography in high-risk women aged 35 to 39 years would have a net benefit, the estimated reduction in breast cancer mortality from screening women with BRCA mutations before 35 years of age was not substantially greater than the risk for radiation-induced breast cancer mortality.

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Given the limitations of mammography and concerns about the balance of benefits and harms, other methods for early detection of breast cancer in high-risk women were actively pursued. Several single and multicenter studies of screening MRI in high-risk women detected invasive breast cancers that were neither palpable nor visible on mammography (Figure 1). Based on published scientific evidence, in 2007 the American Cancer Society (ACS) recommended MRI be performed to improve early cancer detection in high-risk women. These recommendations, which are now supported by the NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Screening and Diagnosis (in this issue; to view the most recent version of the guidelines, visit the NCCN Web site at www.nccn.org), were intended to identify women at high risk and then provide more intensive and successful screening through MRI in addition to mammography.

**MRI Screening Trials**

Results from MRI screening trials have been reviewed extensively in prior publications. Overall, single and multisite trials comparing effectiveness of mammography, MRI, and often ultrasound confirmed MRI as the superior imaging tool for detecting breast cancer in asymptomatic, high-risk women (Table 1). In these studies, the sensitivity of MRI ranged from 71% to 100% compared with mammography (13%–59%) and ultrasound (13%–65%). Cancer yield from MRI alone averaged 22 cancers for every 1000 women screened, a rate of cancer detection roughly 10 times that achieved with screening mammography in average-risk women, and roughly twice the yield achieved with screening mammography in high-risk women. Across the studies, MRI approximately doubled the cancer yield compared with mammography screening alone. Combination mammography and MRI provided the highest sensitivity; the addition of ultrasound did not improve cancer detection.

Importantly, the sensitivity of MRI has varied across studies that included both mammography and MRI, and usually is not 100%. False-negative MR examinations are more commonly associated with ductal carcinoma in situ (DCIS) rather than invasive lesions. In a study of 1909 women at increased risk for breast cancer, Kriege et al. found that 5 of 8 cancers detected with mammography but missed on MRI were DCIS lesions. However, these earlier studies showing decreased sensitivity of MRI for DCIS relied on acquisition techniques with relatively low spatial resolution. More recent trials using high spatial resolution techniques indicate MRI has a higher sensitivity for detecting DCIS than mammography.

Although MRI has considerably higher sensitivity than mammography, its lower specificity has been a concern expressed in several prior reports. Along with significantly increased cancer detection with

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**Figure 1** A 30-year-old female with history of prior Hodgkin lymphoma treated with chest irradiation. Screening right craniocaudal (A) and mediolateral oblique (B) mammograms show no suspicious findings. Axial image (C) from immediate-post contrast T1-weighted fat-suppressed MR sequence shows an irregular mass measuring 10 mm at 5 o’clock (arrow). Biopsy confirmed invasive ductal carcinoma.
MRI, more women will have positive MR examinations than mammograms. However, this difference in the rate of positive examinations in a population with a much higher prior probability of breast cancer is balanced by a high (45%) cancer yield after MRI-indicated biopsy. Furthermore, in trials reporting specificity over multiple rounds of screening, false-positive results decrease significantly after the first screening. For example, in a study by Warner et al., the percentage of MR examinations interpreted as suspicious decreased from 26% in baseline screening to 10% in subsequent screening, and in a study by Kuhl et al. callback rates decreased from 15% on first screening examination to 9% on subsequent rounds of screening. Over subsequent rounds of screening, recommendations for biopsy based on suspicious MRI findings continue to decrease. In the 2004 Canadian study by Warner et al. biopsy was recommended at baseline MRI for 10% of high-risk women and for fewer than 5% in subsequent rounds of screening.

In addition, all studies comparing MRI with ultrasound in the same patient population have shown the specificity of MRI to be significantly higher. Thus, MRI is similar to mammography, with a higher false-positive rate expected on the initial screening examination and false-positive rates declining over subsequent examinations.

### Impact of Screening MRI on Stage at Diagnosis

No randomized clinical trials have assessed the impact of breast screening MRI on mortality rates. Surrogate markers of mortality, specifically size of tumor and nodal status, have reported significantly smaller cancers diagnosed in women screened with

<table>
<thead>
<tr>
<th>Author (Study)</th>
<th>Study Design</th>
<th># Cancers Detected/ Total # Screened</th>
<th>Mam Sensitivity</th>
<th>US Sensitivity</th>
<th>MRI Sensitivity</th>
<th>Cancer Yield from MRI Alone</th>
<th>Biopsies Recommended Based on MRI</th>
<th>Biopsies Performed Based on MRI</th>
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<tr>
<td>Tilanus-Linthorst et al.</td>
<td>P</td>
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<td>Podo et al.</td>
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<td>Morris et al.</td>
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<td>3.8% (14/367)</td>
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Abbreviations: Mam, mammography; P, prospective; PPV, positive predictive value; R, retrospective; US, ultrasound.

*To be included in these studies, subjects had to have a negative mammogram.

†The results are shown for 45 of the 50 cancers diagnosed. Five cases were omitted that did not have all imaging performed.

‡One patient who had an MRI-only detected cancer in this study did not undergo ultrasound.

§Two cancers in the study were identified as ‘interval’ and not detected by either screening examination.
MRI compared with those screened with mammography, and have also noted significantly lower rates of positive nodal disease at diagnosis in MRI-screened populations than in controls screened with mammography alone.

In a study by Krieger et al.,17 2 external age-matched control groups had more than double the incidence of nodal disease than those screened with MRI (P < .001). In a study by the International Breast MRI Consortium of high-risk screening MRI,20 all MR-detected cancers were node-negative, and another study by Tilanus-Lintinghorst et al.14 showed that patients who underwent MR screening had less than half the incidence of positive nodes compared with controls (19% vs. 42%).

**Technique and Interpretation Considerations**

In response to the growing use of MRI in breast imaging and questions raised regarding the variation in performance of breast MRI across a diversity of practices, the American College of Radiology (ACR) supported a task force to develop a breast MRI accreditation program. This program is scheduled to open for applications by early 2010. The intention is to provide guidance and oversight for the performance of high-quality breast MRI. Specifications regarding technical parameters for quality images, use of breast MRI-guided biopsy, and initial and continuing qualifications of technologists and interpreting physicians will be specified and assessed.

Sites accredited by the ACR will be required to perform audits to track the consistency and accuracy of physician interpretations of breast MR scans. As the field evolves, it is expected that guidelines for practice performance will be established similar to those that have been created for mammography audit programs. These performance benchmarks will support quality improvement of breast MRI programs for acceptable callback rates, biopsy rates, and cancer yield from biopsies performed based on positive MR examinations.

Both the ACR and European Society of Breast Imaging (EUSOBI) have published guidelines for technical components of high-quality breast MRI. The ACR Breast Imaging Reporting and Data System (BI-RADS) now includes a section dedicated to breast MRI,26 and the ACR Imaging Network has published acquisition methods required for participation in breast MRI ACRIN trials, such as ACRIN 6667, the study of occult cancers in the contralateral breast of women with a recent breast cancer diagnosis.22 The minimum requirements for contrast-enhanced breast MRI include use of a dedicated breast coil and imaging with 1.5T or greater magnetic field strength. A minimum of 2 postcontrast T1-weighted series are required, with initial postcontrast images within 4 minutes and delayed postcontrast images within 8 minutes after contrast administration, with a maximum image slice thickness of 3 mm. The EUSOBI supports these requirements, including imaging with a dedicated breast coil at 1.5T field strength or greater, obtaining a minimum of 2 postcontrast T1-weighted series with initial images within 2 minutes of contrast administration, and slice thickness less than 3 mm (2.5 mm).27 Sites performing breast MRI must be able to perform MRI-guided tissue sampling. Suspicious lesions initially identified on breast MRI can be clinically, mammographically, and sonographically occult. These lesions require tissue sampling using MRI guidance for needle biopsy or wire localization and excision.

The NCCN Clinical Practice Guidelines in Oncology: Breast Cancer (to view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org) emphasize the importance of the quality of the personnel, facility, and equipment supporting any breast MRI program:

- Breast MRI examinations should be performed and interpreted by an expert breast imaging team working in concert with the multidisciplinary treatment team...
- Breast MRI examinations require a dedicated breast coil and breast imaging radiologists familiar with the optimal timing sequences and other technical details for image interpretation. The imaging center should have the ability to perform MRI-guided needle sampling and/or wire localization of MRI-detected findings.28

**Financial Costs Associated With Screening MRI Programs**

Two studies have found breast MRI screening to be cost-effective in select high-risk patient populations, and particularly in patients with known BRCA
Also, several software programs can assess lifetime risk and probability of carrying a mutation, providing an opportunity to determine whether a patient is at sufficient risk to justify beginning screening earlier with MRI and mammography, according to ACS or NCCN guidelines.

Importantly, as the diagnostic accuracy of MRI continues to improve and as more experience with MRI screening in high-risk patients accumulates, adjustments to model inputs will be needed. For example, in the model by Plevritis et al., probability of additional diagnostic evaluation was 32% after a baseline screening MRI, reducing to 20% after a subsequent MRI. These recall rates are significantly higher than many more recent reports. It is expected that callbacks of less than 10% at first screening and less than 5% in subsequent screenings can be achieved in practices adept at interpreting screening MR examinations. Adjusting model inputs to reflect this higher rate of performance would significantly change the cost-effectiveness estimates associated with high-risk screening MRI programs.

**Future Directions**

Currently, a growing number of guidelines endorse MRI screening for known or suspected carriers of high-penetrance mutations on breast cancer susceptibility genes. What is less clearly defined is a strategy to ensure that these women are identified early enough to benefit from participating in a program of tailored screening. Current evidence indicates that most women with inherited risk for breast cancer are not being identified. Identification of high familial risk requires a family history of both the maternal and paternal sides covering 3 generations. Breast imagers not practicing in settings specializing in meeting the needs of high-risk patients rightly question whether they have the capacity to conduct complex risk assessment. The situation is similar for primary care providers, most of whom have limited time and expertise to gather and scrutinize pedigrees. Nevertheless, until referring physicians are better able to assess family history, breast imagers should be prepared to collect a sufficient family history of cancer to identify whether a patient may benefit from further assessment by a qualified genetic counselor. Also, several software programs can assess lifetime risk and probability of carrying a mutation, providing an opportunity to determine whether a patient is at sufficient risk to justify beginning screening earlier with MRI and mammography, according to ACS or NCCN guidelines.

Although neither the NCCN nor ACS endorses an age cutoff for high-risk screening MRI programs, the United Kingdom’s National Health Service’s National Institute for Health and Clinical Excellence does not recommend MRI in high-risk women after 50 years of age, presumably based on the assumption that declining breast density diminishes the cost-effectiveness of MRI compared with mammography in high-risk women. However, the mean age of women who participated in the studies was in the mid 40s, with many women participating while in their 50s and 60s. Although the added advantage of MRI has been attributed to technical features that are superior in showing neovascularity in dense breast tissue, Bigenwald et al. recently showed superior performance of MRI over mammography regardless of breast density, a finding supported by multiple other prior reports, suggesting that not only the density but also the imaging characteristics of tumors may warrant lifetime MRI screening in high-risk women.

Additional research is needed to understand performance of screening MRI across the full spectrum of risk groups, such as women with dense breast tissue or those with prior biopsies documenting atypia. No published studies have evaluated MRI as a screening tool in populations that are also at increased risk based on familial or genetic patterns. Although prior biopsy of atypia and breast density are clearly independent predictors of breast cancer risk, insufficient evidence exists regarding the value of MRI in these populations. Port et al. examined the performance of MRI among women in the Memorial Sloan Kettering (MSK) Special Surveillance Breast Program who had biopsy confirmed atypia or lobular carcinoma in situ (LCIS), and concluded that MRI offered a small added benefit in patients with a prior diagnosis of LCIS but no added value over mammography for improved cancer screening in patients with atypia.

Continued research on the role of MRI in detecting and diagnosing DCIS is encouraged. Earlier reports of low sensitivity of MRI for DCIS are of less concern today because more recent reports show that MRI has high sensitivity for DCIS when performed with high spatial resolution techniques.
In the future, noncontrast methods of screening MRI may be possible. Diffusion imaging and MR spectroscopy provide information that can distinguish benign from malignant lesions, and these methods of breast MRI do not require contrast injection. These applications are not currently part of clinical care and require further study to clarify if either method will make significant contributions to enhanced breast cancer detection or diagnosis. Audit programs must be supported to not only assess and monitor the diagnostic performance of breast MRI in community practice but also provide feedback to individual programs on their performance. The suspected variation in performance across the diversity of community practices offering breast MRI is concerning, but data clarifying the extent of the variation are sparse. Educational programs are essential to improve radiologist performance in breast MRI interpretation, with emphasis on achieving both high sensitivity and specificity of interpretations.

Conclusions

NCCN recommendations for high-risk screening with MRI are consistent with those of the ACS and supported by published clinical research. Both organizations support the role of MRI in select high-risk women, including as an adjunct to annual mammography and clinical breast examination in women who are determined to have a lifetime risk greater than 20% based on models that are highly dependent on family history. NCCN also recommends considering MRI for women with a prior diagnosis of LCIS. For women with a personal history of breast cancer who have a less than 20% risk based on family history, neither organization currently recommends for or against screening MRI, and these decisions should be made between the provider and patient based on considerations of benefits and risks. Neither organization supports MRI screening in women at average risk.

Currently, early detection of breast cancer affords a woman the best hope for cure. Mammography alone in populations at high risk because of known or suspected inherited susceptibility is not sufficient, and studies have shown that it will miss more than half of the prevalent, detectable cancers. MRI detects a high number of cancers missed by mammography and detects most breast cancers at a significantly earlier stage. Efforts to educate women and their providers on the importance of assessing individual risk and understanding the contributions of MRI to screening programs for high-risk women are encouraged.

References

Role of MRI in Breast Cancer Screening


