Breast MRI for Women With Hereditary Cancer Risk

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Approximately a decade ago, germline mutations in BRCA1 and BRCA2 were identified as the most common detectable causes of a hereditary predisposition to breast (and ovarian) cancer.1,2 A recent meta-analysis of 22 studies indicated that the average risk of breast cancer by 70 years is 65% for women with BRCA1 mutations and 45% for BRCA2 mutations,3 although the risk may be substantially higher in some families. Women with BRCA1 mutations in their fourth and fifth decade of life have on average approximately a 30-fold higher risk of breast cancer than women without mutations, and BRCA2 mutation carriers are at 10-fold to 16-fold higher risk.3

Confronted by breast cancer risks of this magnitude, it is not surprising that a significant fraction of mutation carriers elect to undergo prophylactic mastectomy, a procedure that has been shown to reduce breast cancer risk by 90% or more.4,6 However, for many women, the physical and psychological morbidity of risk-reducing surgery is unacceptable. Although adjuvant therapy with tamoxifen appears to reduce contralateral breast cancer risk in affected mutation carriers,7,8 its value as primary prevention in unaffected women remains uncertain.9 While our group and other researchers have described a significant reduction in breast cancer risk among women with mutations who enter premature menopause as the result of a risk-reducing oophorectomy,10,11 protection is clearly incomplete.

Women at hereditary risk who choose not to undergo preventive mastectomy have been advised to undergo breast self-examination, clinical breast examination (CBE), and annual mammography beginning at an early age (25-30 years).12,13 However, in large cohorts of BRCA mutation carriers undergoing such surveillance in New York and the Netherlands, nearly 50% of breast cancers identified were diagnosed in the interval between screening studies and nearly half of the invasive breast cancers had metastasized to axillary nodes at the time of diagnosis.14,15 The relative insensitivity of mammography among women at hereditary risk results from several factors, including the underlying breast density of these young women, the benign mammographic appearance of some BRCA-associated breast cancers, and the rapid growth rate of these frequently high-grade tumors.16

Magnetic resonance imaging (MRI) has emerged as an extremely powerful tool in breast cancer management.17-23 The use of the contrast agent gadolinium, in combination with sophisticated imaging protocols, allows the identification of tumor neovascularity, which cannot be detected by conventional mammography.17 In this issue of JAMA, the article by Warner and colleagues24 from a large single-institution study using this new technology provides important new information for women at hereditary risk regarding their surveillance options.

In the study by Warner et al, 236 women with germline BRCA1 or BRCA2 mutations underwent annual multimodality screening with CBE, mammography, screening ultrason, and breast MRI, all performed on the same day. An interval CBE was performed 6 months later. Systematic imaging and follow-up protocols were followed to minimize unnecessary biopsies generated by nonmalignant enhancement on MRI. Consistent with previous surveillance studies in women at hereditary risk,14,15 only 45% of the identified cancers would have been detected by “conventional” screening (mammography and CBE). However, of the 22 cancers diagnosed, 77% were detected by MRI, and 32% were identified by MRI alone. MRI identified a significantly greater proportion of breast cancers than either mammography (36%) or ultrasound (33%).

These results are similar to those of a recently reported, multi-institutional study performed in the Netherlands by Kriege et al,25 in which 1909 women at a 15% or more lifetime breast cancer risk (including 358 BRCA mutation carriers) were screened annually with concurrent mammography and MRI. Of the 45 cancers diagnosed in the Netherlands cohort,25 22 (49%) were detected by MRI alone, with an overall sensitivity of 71% for MRI vs 40% for mammography. Comparison of the positive predictive value (PPV) of an abnormal MRI in these and other studies is hampered by differences in the definitions used, but 17 (46%) of 37 “positive screens” in the study by Warner et al24 were assigned.
associated with a diagnosis of cancer, as were 21 (32%) of 65 MRIs interpreted as suspicious or highly suggestive of malignancy (Breast Imaging Reporting and Data System [BI-RADS] 4 or 5) in the study by Kriege et al. The differences in predictive value, as well as sensitivity and specificity in these and prior studies (Table), may also reflect different levels of experience and consistency in radiological interpretations in single-institution vs multi-institution settings. In the studies by Kriege et al and Warner et al, however, receiver operating characteristic curves, a function of both sensitivity and specificity, confirm a greater diagnostic accuracy for MRI as compared with mammography.

Although these results clearly affirm that MRI is significantly more sensitive than mammography in detecting breast cancer in women at hereditary risk, a number of fundamental questions remain. First, it is not yet clear whether the enhanced sensitivity of MRI will translate into a reduction in breast cancer–related mortality. The observation of an apparent decrease in sensitivity of MRI after the initial screen in both studies (Warner et al and Kriege et al) sounds a cautionary note. A randomized controlled trial with mortality as a primary end point would be desirable to prove the benefit of MRI screening in mutation carriers but accrual to such a study is likely to prove difficult. Indirect evidence suggests that MRI screening leads to downstaging of detected cancers, which may translate into a survival benefit. Although 21% of cancers detected were associated with axillary nodal metastases in the Netherlands study, this rate was significantly lower than in 2 control groups not receiving MRI screening. Tumor size was also significantly smaller in the MRI group. In the study by Warner et al, only 2 cancers (9% of the total) were associated with axillary nodal metastases, and each of these cases was identified at the initial (prevalent) cancer screen. All incident cancers were in situ or stage I lesions. These findings are the most encouraging yet reported for MRI screening.

A second question is the relative value and timing of MRI screening vis-à-vis mammograms and, possibly, screening ultrasound. MRI and conventional mammography appear to be complementary; in the study by Warner et al, both modalities diagnosed cases of ductal carcinoma in situ missed by the other screening tool. Ultrasound also detected a small number of cancers not identified by MRI, and “triple screening,” not used in the study by Kriege et al, improved sensitivity to 95%. Although interval cancer was not a major issue in the current study, 20% of cancers detected in mutation carriers in the Netherlands study presented within 12 months of imaging. If these interval cancers resulted from “kinetic failures” of detection due to the higher proliferative rate of tumors in BRCA mutation carriers, the optimal screening strategy may be to alternate mammography and MRI (with or without ultrasound) at 6-month intervals.

Questions also remain regarding the specificity of MRI screening. In the study by Warner et al, the specificity of MRI improved from 93% to 99% during the 3 screening rounds. However, Warner et al only considered examinations as false-positive if a biopsy was performed with a benign result, and the calculated specificity would likely be significantly lower if examinations resulting in additional studies (“diagnostic” MRI or 6-month follow-up studies) were also considered positive. Despite suboptimal specificity, the PPV of a persistently abnormal MRI was high (46% overall),

Table. Comparison of Magnetic Resonance Imaging and Other Modalities in Women at Hereditary Risk for Breast Cancer

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients (BRCA Mutation Carriers)</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive Predictive Value, %</th>
<th>MRI-Detected Breast Cancers With Axillary Metastases, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tilanus-Linthorst et al, 2000</td>
<td>109</td>
<td>100</td>
<td>94.0</td>
<td>33.0</td>
<td>0</td>
</tr>
<tr>
<td>MRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stoutjesdijk et al, 2001</td>
<td>139</td>
<td>100</td>
<td>93.0</td>
<td>43.0</td>
<td>50</td>
</tr>
<tr>
<td>MRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mammography</td>
<td></td>
<td>42.0</td>
<td>96.0</td>
<td>33.0</td>
<td></td>
</tr>
<tr>
<td>Warner et al, 2004†</td>
<td>236 (236)</td>
<td>77.0</td>
<td>95.0</td>
<td>46.0</td>
<td>9</td>
</tr>
<tr>
<td>MRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mammography</td>
<td></td>
<td>36.0</td>
<td>99.8</td>
<td>88.9</td>
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<tr>
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<td>33.0</td>
<td>96.0</td>
<td>29.0</td>
<td></td>
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<tr>
<td>Kriege et al, 2004†</td>
<td>1909 (358)</td>
<td>71.1</td>
<td>90.0</td>
<td>32.3</td>
<td>21</td>
</tr>
<tr>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Mammography</td>
<td></td>
<td>40.0</td>
<td>95.0</td>
<td>47.8</td>
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<tr>
<td>Kuhl et al, 2003</td>
<td>462</td>
<td>96.1</td>
<td>95.1</td>
<td>56.9</td>
<td>35†</td>
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<tr>
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<tr>
<td>Mammography</td>
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<td>43.0</td>
<td>94.3</td>
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<tr>
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<td></td>
<td>47.0</td>
<td>88.4</td>
<td>17.5</td>
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</tbody>
</table>

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; MRI, magnetic resonance imaging.

*Aggregate sensitivity values were derived from data provided in Table 3 of Warner et al; calculation of specificity was based on biopsy rates.
†Sensitivity and specificity values were based on BI-RADS score of at least 3; positive predictive values were based on BI-RADS score of 4 or 5.
‡Overall, 18 of 51 tumors detected were MRI-detected breast cancers with axillary metastases; however, only 49 of 51 tumors were observed on MRI.
largely because of the remarkably high incidence of breast cancer in BRCA mutation carriers (5.5% of initial screens and 4.1% of subsequent screens). MRI screening in groups of women with lower disease prevalence will certainly result in substantially lower PPVs and a less favorable risk-to-benefit ratio.

Warner et al have clearly documented the risks and benefits of breast MRI screening in women at the highest levels of hereditary risk. Their findings, in combination with those of Kriege et al, strongly suggest that women with BRCA mutations should be offered such screening. Women and their physicians must, however, be aware that both sensitivity and specificity of screening MRI may be substantially less than described if different imaging protocols are followed or if experienced radiologists and suitable technology, including the capability to perform magnetic resonance–guided biopsies, are not available.26 A technology assessment by 1 large insurance carrier has already supported the rationale for MRI screening of BRCA mutation carriers and other women at high hereditary risk for breast cancer, even in the absence of a randomized controlled trial demonstrating a mortality benefit.27 Remaining questions, largely centered on specificity, recall rate, and PPV, argue against routine application of MRI screening for women at lesser degrees of risk without carefully designed studies, preferably randomized controlled trials, delineating test performance in those specific populations.

REFERENCES