Utilization of magnetic resonance imaging in breast cancer screening

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Early detection of malignancy through breast cancer screening has contributed significantly to the decline in cancer-related mortality1. The U.S. Preventive Services Task Force recently reaffirmed its 2009 stance to begin mammography—the primary screening modality—starting from age 50 and continuing until age 742. However, that recommendation applies primarily to women at “average risk” for developing breast cancer during their lifetime. For women at “high risk,” the American Cancer Society has recommended magnetic resonance imaging (mri) of the breast as an adjunct to annual screening mammography3. How, then, is risk defined, and should these guidelines be strictly followed by clinicians?

Here, we focus first on describing the quality of mri as a screening tool. Then, we define risk categories and conclude with a discussion of the need for a more nuanced approach to the incorporation of mri into breast cancer screening.

In prospective nonrandomized studies across multiple centres throughout the world, contrast-enhanced mri achieves a high sensitivity of 70%–100% in the initial screening (prevalence) setting, compared with 40% or less for mammography in patients at high risk for developing breast cancer4-6. The specificity of mri in that setting has been hampered by its difficulty in distinguishing the often overlapping features of benign and malignant lesions, causing higher false-positive rates7. It is important to note, however, that these oft-cited statistics actually improve significantly in the setting of subsequent (incidence) screening rounds. As noted by Warner et al.8, the rate of benign biopsy is reduced by nearly one half from the initial screening round to the second screening round (11% vs. 6.6%). In a study of mri screening in BRCA mutation carriers and women with high familial risk, Riedl et al.9 highlighted the improvement in mri specificity from the first screening round to subsequent screening rounds. In addition, mri recall rates in their study declined dramatically from 26% on initial screening to 13% on second screening and 10% on third screening, emphasizing an improvement with successive rounds of screening. That finding was reinforced by Chiarelli and colleagues9 in their report of the Ontario Breast Screening Program evaluating mri and mammography in high-risk women. Those authors observed lower recall rates with subsequent rounds of screening (when images from a baseline mri are available for comparison) and with increased experience of mri use at testing centres. As noted by Chiarelli et al., mri screening might be criticized for achieving lower positive predictive values, but two thirds of the cancers would be otherwise missed. Therefore, acceptance of a lower positive predictive value of mri screening in return for the gain of a higher detection rate must be considered. In addition, mri can offer an important contribution to the detection of ductal carcinoma in situ (dcis). Kuhl et al.10 note that more than half of dcis lesions detected only by mri are histologically high grade (comprising more than half of all dcis) and tend to carry a worse prognosis and a higher probability of progressing to invasive disease if undetected.

In 2007, the American Cancer Society issued guidelines recommending that the risk of breast cancer be assessed by careful review of family history and clinical history and by genetic testing3. Women considered at high risk are those with known BRCA gene mutation, with first-degree relatives having known BRCA gene mutation, and with a lifetime risk exceeding 20% as measured by risk-assessment tools based primarily on family history of breast cancer.

Features of family history suggesting the presence of an autosomal-dominant high-penetrance gene include 2 or more first- or second-degree relatives with a history of breast or ovarian cancer, breast cancer in premenopausal women before the age of 50, and male relatives with breast cancer. Furthermore, genetic testing includes assessing for BRCA1 and BRCA2 mutations. Women with BRCA1 mutations have an estimated 65% risk of developing breast cancer by the time they are 70; those with BRCA2 mutations have an up to 45% risk11. In several studies, a significant increase in sensitivity is observed in women with known BRCA mutation12. Leach et al.13 found a sensitivity of 92% for mri and 23% for mammography in BRCA mutation carriers compared with 77% for mri and 40% for mammography in all patients. Kuhl et al.13 reported similar findings, with sensitivities of 100% for mri and 25% for mammography in BRCA mutation carriers compared with 91% for mri and 33% for mammography in all patients.

In addition to family history and genetic testing, clinical history associated with a significant risk for breast cancer includes women with a former history of Hodgkin disease—typically diagnosed at a young age (between 10 and 30 years)—and mantle field radiation. Although a history of lobular carcinoma in situ or atypical ductal hyperplasia increases the risk for breast cancer, no clear consensus has been reached about offering mri screening for this population. Although the time

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to initiate screening for women at high risk has been a matter of debate, testing is generally suggested to start 10 years before the age of earliest diagnosis of breast cancer in a first-degree relative and is recommended annually, in addition to mammography.

Although the use of breast MRI has risen significantly over the years, its use as a screening test has often been inconsistent with national guideline recommendations, which advise limiting MRI to “high-risk” groups, citing insufficient evidence for MRI use in “average-risk” or “intermediate-risk” groups. Nevertheless, are truly robust data available to sanction MRI screening only for high-risk women? Schrading, with various colleagues14,15, examined MRI screening in the average-risk population and found that the additional cancer detection rate achieved through breast MRI was sufficiently high (11 in 1000). More importantly, the incremental cancer detection rate was similar (about 5 in 1000) in high-risk women and in average-risk women with no family history of breast cancer, prior atypia, or other risk factors. As mentioned in an editorial by Berg16, sufficient data to support restriction of MRI based on high-risk factors such as family history appear to be lacking.

Screening by MRI in BRCA mutation carriers also should not be limited by age. Phi et al.17 investigated age-related screening accuracy in women with BRCA1/2 mutations and found screening sensitivity to be similar in women 50 or more years of age and women less than 50 years of age—with higher specificity. The authors thus concluded that it would be reasonable to offer MRI screening to BRCA mutation carriers beyond the age of 50 years. Those recommendations have since been incorporated into the European Society of Breast Imaging breast MRI recommendations18.

The ability of MRI to play a broader role in the screening realm is in good part limited by significant costs and the time-intensiveness of testing. Not surprisingly, interest in how to best exploit the known sensitivity of MRI for cancer detection has been growing, keeping in mind considerations of economics, logistics, and patient comfort. It is well recognized that invasive carcinomas and high-grade DCIS tend to demonstrate fast initial uptake of contrast (within the first 90 seconds after contrast administration)19. An abbreviated MRI (ABMRI) screening protocol could therefore preferentially detect cancers that enhance rapidly and that might be biologically significant, while requiring decreased scan time20–22. To that end, a small but growing body of literature evaluating the efficacy of an ABMRI protocol is demonstrating consistently high sensitivity of ABMRI for malignancy23–25. Kuhl et al.26 reported a prospective study assessing the utility of an abbreviated protocol in more than 600 women, with the first post-contrast T1-weighted images and maximum intensity projections being used for interpretation. The authors detected all 11 cancers with a reported sensitivity of 100%. Mango et al.25 evaluated a similar abridged protocol with first post-contrast T1-weighted images and maximum intensity projections in 100 women with 100 known malignancies. All 100 cancers were detected by at least 1 reader, with 92 of the 100 being detected by all readers. Mann and colleagues27 used T2-weighted imaging in addition to first post-contrast imaging in an evaluation of 48 women with 12 breast malignancies. Their shortest protocol achieved a sensitivity of 86%, which was lower but not significantly different from their full protocol sensitivity of 95%. Abbreviated MRI therefore appears to be highly sensitive for cancer detection, with markedly reduced acquisition times compared with traditional full MRI breast protocols. An ABMRI protocol could allow for wider utilization of breast MRI in screening.

Furthermore, Veltman et al.28 evaluated first-pass high temporal resolution and high spatial resolution protocol imaging in both malignant and benign lesions. Although the authors found that combined analyses resulted in the best performance, high temporal resolution analysis alone demonstrated good performance, similar to that with slow high spatial resolution analysis alone. The authors quantitatively evaluated the pharmacokinetic parameters K trans (a vascular transfer constant dependent on blood flow and vascular permeability), V c (an estimate of extravascular extracellular volume fraction), and K ep (a rate constant between the interstitial space and blood plasma), finding that those parameters were significantly higher for malignant lesions than for benign lesions.

Mann and colleagues27 used ultrafast MRI (high temporal resolution dynamic MRI) with stochastic trajectory acquisitions (0.9×1×2.5 mm with a temporal resolution of 4.3 seconds) and compared that technique with standard dynamic MRI. Maximum slope of the relative enhancement for evaluated lesions (95 benign and 104 malignant) was compared with standard dynamic kinetic curves. The authors found higher accuracy for lesion detection with the ultrafast method compared with standard kinetic analysis (area under the curve: 0.812 vs. 0.692; p = 0.0061).

Although the discussion of breast MRI in screening often includes mention of a lack of overall survival benefit, the lack of benefit improvement is likely a result of smaller sample sizes in previous studies and thus inadequate power to detect small but significant gains in survival. Although the Dutch MRI screening study by Saadatmand et al.29 showed a trend toward overall survival benefit, the multicentre U.K. high-risk Magnetic Resonance Imaging for Breast Screening trial demonstrated that early detection by screening did result in improved survival30.

Overall survival should also be weighed against other significant findings gained through testing. Saadatmand et al.28 reported an improvement in breast cancer–specific metastasis-free survival in women with BRCA mutation or familial risk. The clinical relevance of metastasis-free survival or progression-free survival should not be ignored, because it may affect quality of life maintained during the “journey,” with fewer invasive and toxic interventions during that period. Moreover, clinicians and the women being screened hold different perspectives on the harms of overdiagnosis and false positives. Despite the anxiety caused by false-positive results, women still appear to prefer minimal regret, favouring overtreatment31.

Although recommendations from national and society organizations such as the U.S. Preventive Services Task Force and the American Cancer Society help to guide clinicians in making decisions about breast cancer screening, the ultimate approach has to be more nuanced.
and complex. Given the growing information about the utility of MRI in non-high-risk populations, which are not reflected in the guidelines, the clinician must, in the end, take into account all the available information when treating each individual patient. Further studies to better comprehend biologic, molecular, and demographic patient subtypes are recommended to develop more evidence-based data for determining risk and guiding screening recommendations in the future.

CONFLICT OF INTEREST DISCLOSURES
We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare that we have none.

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REFERENCES

