EDITORIALS

The Evolving Role of MRI in the Detection and Evaluation of Breast Cancer

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The age-adjusted rate of death from breast cancer in the United States was 24% lower in 2003 than it was in 1989,[1] a decline that has been attributed principally to both the role of mammography in detecting early-stage tumors and improvements in therapy. Indeed, early diagnosis and therapy have been the cornerstone of efforts to control breast cancer, since a readily accessible preventive strategy for women with an average risk has been elusive. Prevention is clearly the preferable strategy for controlling cancer, but for the foreseeable future, the control of breast cancer will depend mostly on early detection, careful diagnostic evaluation, and therapy.

The introduction and widespread use of mammography for the early detection of breast cancer is one of the most important recent achievements in the control of cancer. The prognostic value of detecting breast cancer while it is still localized to the breast exceeds what can be achieved with therapy when breast cancer is advanced, and over the past decade the trend toward a more favorable stage at diagnosis has played a major role in the reduction of the rate of death due to breast cancer.[2,3] Although the association is difficult to measure, it is likely that ultrasonography,[4] magnetic resonance imaging (MRI),[5,6] and digital mammography also improve the outcome when they are used as a substitute for or adjunct to conventional film mammography for women in whom conventional mammographic screening has not been useful. For example, digital mammography has recently been shown to be a more effective imaging tool in younger women and in women with heterogeneously or extremely dense breasts.[7] It is well established that conventional film mammography does not identify all breast cancers, and these other imaging methods can detect tumors that are occult on mammography or can provide more information about findings that were inconclusive with conventional imaging.

Once breast cancer has been detected, the importance of thorough and accurate breast imaging is paramount, because multicentric breast cancer may preclude breast-conserving strategies, and the detection of a synchronous, contralateral primary tumor may affect choices regarding surgery and reconstruction. The risk of local recurrence is a dark cloud that hangs over patients with newly diagnosed breast cancer and longer-term survivors, despite reassurances that multicentric or multifocal disease that may be present, but not visible, can be effectively treated by whole-breast irradiation and adjuvant therapy. Even with this reassurance, it is likely that most women would prefer the detection of such mammographically invisible lesions so that they could be factored into decision making with regard to treatment. For this reason, a growing proportion of patients with newly diagnosed breast cancer are undergoing further evaluation with MRI.

In this issue of the *Journal*, Lehman and colleagues report the results of their study of the effectiveness of MRI in the detection of cancer in the contralateral breast after negative clinical and mammographic findings in women with newly diagnosed breast cancer.[8] The follow-up period was long enough to permit an estimate of conventional measures of test performance, including the sensitivity, specificity, area under the receiver-operating-characteristic curve, and positive and negative predictive values. Among 969 study participants, MRI of the contralateral breast was performed within 60 days after the diagnosis of unilateral breast cancer and within 90 days after clinical and mammographic breast examination showed normal findings.

Among 33 patients in whom breast tumors were diagnosed in the contralateral breast during the 12-month follow-up period, 30 tumors (invasive tumors in 18 women and ductal carcinoma in situ in 12) were detected by means of MRI. Thus, the additional diagnostic yield of MRI was 3.1% after negative findings on mammographic and clinical breast examination, with 91% sensitivity and 88% specificity. Although this specificity is lower than that which would generally be acceptable in a screening program, it is likely to be acceptable to women with unilateral breast cancer, since they will place a high priority on a thorough evaluation for the presence of other primary lesions. As Lehman and colleagues note, the very high negative predictive value of MRI can be reassuring to women whose concern about the presence of undetected disease leads them to seek prophylactic mastectomy of the contralateral breast. The authors also note the advantage of treating synchronous cancers simultaneously, thus avoiding another round of therapy at a later time when the tumor in the contralateral breast would be detected by means of conventional imaging or on the basis of symptoms. There may be arguments that the added sensitivity of MRI of the contralateral breast comes at high cost in terms of false positive results and overdiagnosis due to the high rate of detection of ductal carcinoma in situ. Nevertheless, the false positive rate and the predictive value of a positive test are in an acceptable range, and there is little persuasive evidence that most cases of ductal carcinoma in situ are not progressive. Therefore, there is value in detecting and treating malignant tumors in the contralateral breast that were not identified by means of mammography and clinical breast examination.

The responsible use of MRI for the evaluation of the breast is focused primarily on patients with a high probability of breast cancer, and it includes screening in women who are known or likely carriers of a *BRCA1* or *BRCA2* mutation. The American College of Radiology's practice guideline for the performance of breast MRI outlines 12 clinical applications of MRI in the evaluation of breast disease.[9] Coincident with this issue of the *Journal*, the American Cancer Society is publishing new recommendations for breast-cancer screening in women at high risk for breast cancer.[10] In the 2003 update to its guideline for breast-cancer screening, the American Cancer Society stated that women at increased risk for breast cancer might benefit from the earlier initiation of screening, shorter screening intervals, or the addition of screening methods such as breast ultrasound or MRI.[11] On the basis of newer evidence, as well as requests from clinicians for greater guidance in the use of breast MRI, the guideline now recommends annual breast-cancer screening by means of MRI for women with approximately 20% or greater lifetime risk of breast cancer, according to risk models that are largely dependent on a strong family history of breast or ovarian cancer. Annual MRI screening is also recommended for women who have undergone radiotherapy to the chest for Hodgkin's disease.[10] The updated guideline also states that there is insufficient evidence to make a recommendation for or against MRI screening in women with a personal history of breast cancer, carcinoma in situ, or atypical hyperplasia or in women with extremely dense breasts.

Although breast MRI is not available in every clinical setting, its availability is increasing. In a recent national survey of 575 U.S. breast-imaging practices from the membership database of the Society of Breast Imaging, 12% of practices reported that they offer breast-cancer screening with MRI, and 51% reported offering diagnostic evaluation with MRI.[12] However, there have been concerns about the increasing use of breast MRI and the wide-ranging quality of the examinations. It is unclear whether the results reported by Lehman and colleagues could be reproduced in all centers offering MRI today. Of particular concern are facilities that perform breast MRI but lack the ability to perform biopsies. Patients at such facilities who require follow-up evaluation at a center with the capacity to perform a biopsy in effect have to undergo a repeat of the entire imaging procedure. The new American Cancer Society guidelines strongly recommend that breast MRI not be performed in the absence of the capacity to perform biopsies.

This year, the American College of Radiology is likely to initiate a voluntary accreditation program for breast MRI that is similar to its current programs for mammography and breast ultrasonography. Participation in the new program will probably be greater than that for mammography before the passage in 1992 of the Mammography Quality Standards Act (MQSA), which mandates accreditation, because some health plans will require participation as a criterion for reimbursement. However, if the experience with accreditation for mammography and stereotactic breast biopsy is a guide, many facilities will not participate in this program. For this reason, the Institute of Medicine's Committee on Improving Mammography Quality Standards has recommended that the reauthorization of the MQSA not only remove the exemption on interventional mammographic procedures but also include breast ultrasound and MRI in the requirement for compulsory accreditation.[13] The original goal of the MQSA was to provide women in every community with the assurance of high-quality mammographic evaluation, and that level of assurance should be achieved for any imaging procedure that is used in the detection and diagnosis of breast disease.

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CETP Inhibitors to Increase HDL Cholesterol Levels

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Plasma levels of high-density lipoprotein (HDL) cholesterol are inversely related to the incidence of coronary heart disease and stroke. The lowering of low-density lipoprotein (LDL) cholesterol with statin therapy reduces the risk of atherosclerotic cardiovascular disease but only by about one third. These findings have led to the idea that raising HDL cholesterol might be a treatment for atherosclerosis. On the basis of the high-HDL phenotype of a human genetic deficiency of cholesteryl ester transfer protein (CETP),[1] a new class of drugs that inhibit CETP was developed.[2] Although the CETP inhibitor torcetrapib is effective at raising HDL cholesterol levels, it recently failed in a large clinical trial. As reported by Pfizer to the Food and Drug Administration, the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) study involving 15,000 patients at high risk for coronary heart disease was stopped prematurely, after a little more than a year, because of an excess of deaths, myocardial infarction, angina, revascularization procedures, and heart failure in patients receiving torcetrapib plus atorvastatin, as compared with those receiving atorvastatin alone.[3] In this issue of the *Journal*, Nissen et al. report on an independent, parallel study, called the Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE) trial (ClinicalTrials.gov number, NCT00134173),[4] which evaluated the effect of torcetrapib–atorvastatin therapy versus atorvastatin alone on atherosclerotic burden in coronary arteries, using intravascular ultrasonography to image plaque.