EDITORIAL

Breast Cancer Screening with MRI — What Are the Data for Patients at High Risk?

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More than 275,000 women in the United States will receive a diagnosis of breast cancer this year, and 40,110 women will die of the disease.[1] Randomized trials have shown that the use of screening mammography in the general population reduces mortality associated with breast cancer by at least 24 percent.[2] Cancer is detected in 5 to 7 of every 1000 women on the first screening mammogram and in 2 or 3 of every 1000 women who undergo regular screening mammography. Although the average lifetime risk of breast cancer in an American woman is one in seven,[1] the risk increases in women who have a history of breast cancer, atypia or lobular carcinoma in situ, mantle irradiation for Hodgkin's disease, or a strong family history of breast cancer. Women with inherited mutations of the *BRCA1* or *BRCA2* gene have the highest risk of breast cancer. They make up 5 to 10 percent of women with breast cancer and are also at increased risk for ovarian cancer. The cumulative risk of breast cancer in women with *BRCA1* mutations is 3.2 percent by the age of 30 years, 19.1 percent by the age of 40, 50.8 percent by the age of 50, 54.2 percent by the age of 60, and 85.0 percent by the age of 70; the cumulative lifetime risk for carriers of *BRCA1* or *BRCA2* mutations is 50 to 85 percent.[3] Breast cancers in mutation carriers often occur at a young age, have "pushing margins" and a high nuclear grade, and lack estrogen receptors.[4]

How can we prevent breast cancer or make an early diagnosis of the disease in women with *BRCA* mutations? The strategies include bilateral prophylactic mastectomy, chemoprevention, and close surveillance, including yearly mammograms beginning at 25 to 35 years of age.[2,3,5] However, screening mammography detects less than half of the breast cancers in mutation carriers, perhaps owing to young age, dense breasts, or pathological features of the tumor.[5-8] Cancers in mutation carriers grow rapidly; half of them appear in the interval between annual mammograms. The median size of such "interval cancers" is 1.7 cm, and half have spread to axillary lymph nodes by the time they are detected.[5-8] It has been suggested that supplementing mammography with other imaging techniques, shorter screening intervals, or both may be valuable in mutation carriers.[2,5-8]

Magnetic resonance imaging (MRI) of the breast provides information about tissue vascularity that is not available from mammography. In many breast cancers there is neovascularity, which causes enhancement of the tumor after the injection of intravenous contrast material (gadolinium). The pattern (morphology) and time course (kinetics) of enhancement can determine the likelihood of malignancy.[9] Breast MRI is highly sensitive; its disadvantages include cost, variations in technique and interpretation, imperfect specificity, variation in parenchymal enhancement during the menstrual cycle (the midcycle is optimal), exclusion criteria (e.g., the presence of pacemakers or aneurysm clips or a patient's claustrophobia), and an unproved survival benefit.[10] Studies that have cumulatively evaluated breast MRI in more than 1000 high-risk patients found that the technique identified cancer that was not seen on mammography in 4 percent of cases (Table 1).[10-15]

In this issue of the *Journal*, Kriege et al.[16] report a prospective, nonrandomized study of clinical breast examination, mammography, and MRI in 1909 women who had a genetic or familial predisposition to breast cancer (lifetime risk, ≥15 percent) in the Netherlands. Of these women, 358 (19 percent) had *BRCA* mutations. This work makes im-

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Table 1. Results of Prior Nonrandomized Studies of the Screening of High-Risk Women with Breast MRI.*

Study	Country	No. of Patients	No. with *BRCA+* (%)	No. with Prior BC (%)	Mean Age (Range)	Imaging Method	Study Design	No.with Biopsy (%)†	No. with Cancer/ No. with Biopsy (%)‡	No. with BC on MRI/ No. of Women (%)§	No. with DCIS/No. with BC (%)¶
					yr						
Kuhl et al.[11]	Germany	192	35 (18)	58 (30)	39 (18–65)	M, US, MRI	Prospective	14 (7)	9/14 (64)	6/192 (3)	1/6 (17)
Tilanus-Linthorst et al.[12]	The Netherlands	109	12 (11)	NA	43 (20–74)	M, MRI	Prospective	9 (8)	3/9 (33)	3/109 (3)	0/3 (0)
Warner et al.[13]	Canada	196	96 (49)	55 (28)	43 (26–59)	M, US, MRI	Prospective	23 (12)	6/23 (26)	4/196 (2)	0/4 (0)
Podo et al.[14]	Italy	105	NA	40 (38)	46 (25–77)	M, US, MRI	Prospective	9 (9)	8/9 (89)	7/105 (7)	3/7 (43)
Stoutjesdijk et al.[15]	The Netherlands	75‖	15 (20)	NA	NA	M, MRI	Retrospective	14 (19)	11/14 (79)	6/75 (8)	0/6 (0)
Morris et al.[10]	United States	367	19 (5)	245 (67)	50 (23–82)	M, MRI	Retrospective	64 (17)	14/59 (24)	14/367 (4)	8/14 (57)
Total	—	1044	177 (17)	398 (38)	45 (18–82)	Variable	—	133 (13)	51/128 (40)	40/1044 (4)	12/40 (30)

* *BRCA+* denotes a *BRCA* mutation, BC breast cancer, DCIS ductal carcinoma in situ, M mammography, US ultrasonography, and NA not available.

† The number refers to biopsies recommended for lesions detected on MRI that were or were not seen by mammography; the percentage refers to the frequency of these biopsies among all patients in the study.

‡ The number refers to cancers evident on MRI that were or were not seen by mammography.

§ The number refers to mammographically occult cancers evident on MRI; the percentage refers to the frequency of mammographically occult, MRI-evident cancers in all patients who underwent MRI screening for breast cancer.

¶ The number refers to the proportion of mammographically occult, MRI-evident cancers that were ductal carcinoma in situ.

‖ The lifetime risk of breast cancer was ≥15 percent. Data include one lymphoma identified by MRI only in a mutation carrier among the invasive cancers. Of 179 women in the study, 75 women had mammography and MRI within four months and are included in this table.

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portant contributions. Kriege et al. provide data on almost twice as many patients and twice as many mutation carriers as were included in all previously published evaluations of MRI in high-risk patients combined. Those who interpreted the MRIs and mammograms were unaware of the results of the other technique. The investigators analyzed their data in subgroups according to quantified levels of risk. Their study confirms the high sensitivity of MRI in identifying invasive breast cancer in high-risk patients.

Kriege et al. found that the breast-cancer detection rate was 9.5 per 1000 woman-years of follow-up overall: 7.8 per 1000 for women with a 15 to 29 percent lifetime risk, 5.4 per 1000 for those with a 30 to 49 percent lifetime risk, and 26.5 per 1000 for carriers of *BRCA1* or *BRCA2* mutations. Among 45 cancers, 22 (49 percent) were identified by MRI but not mammography, 10 (22 percent) were identified by both MRI and mammography, and 8 (18 percent) were identified by mammography but not MRI. Of these 45 tumors, 4 were interval cancers, and 1 was identified by clinical examination only. Certain features appeared in more than half of cancers in mutation carriers: they were diagnosed in women between the ages of 30 and 39 years; they were invasive cancers; and the tumors were of high nuclear grade, estrogen receptor–negative, and node-negative. Only 17 percent of cancers in mutation carriers were interval cancers. In their analyses, MRI, as compared with mammography, had higher sensitivity (71 percent vs. 40 percent) but lower specificity (90 percent vs. 95 percent).

Kriege et al. report that short-term follow-up MRI was recommended in 7 percent of examinations, as compared with 10 to 25 percent in prior reports.[11,17] MRI had limited sensitivity (17 percent) in detecting ductal carcinoma in situ; in prior studies, the sensitivity of MRI for this type of lesion ranged from 0 percent[13] to 100 percent.[11,14] Kriege et al. also report that MRI had lower specificity than mammography, but Kuhl et al.[11] found that MRI had higher sensitivity and specificity than mammography. Refinement and standardization of MRI technique and interpretation may improve specificity while retaining high sensitivity. Not addressed by Kriege et al. is the potential role of ultrasonography in screening high-risk women. In studies that supplemented mammography with both MRI and ultrasonography, MRI had higher sensitivity and specificity than ultrasonography and was superior in detecting ductal carcinoma in situ (Table 2).[11,13,14]

The report by Kriege et al. highlights an important issue: How do we evaluate the efficacy of a screening test, and what is the desirable balance between sensitivity and specificity? Any method of breast-cancer screening has the potential for benefit (lifesaving cancer detection) and for harm (cost, anxiety, follow-up imaging, or benign biopsy). The prognosis is better for small, early cancers, but detecting small cancers at an early stage does not guar-

Table 2. Sensitivity and Specificity of Mammography, MRI, and Ultrasonography for Detecting Tumors in High-Risk Women.*

Study	Country	Mammography		Ultrasonography		MRI	
		Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Kuhl et al.[11]	Germany†	3/9 (33)	89/96 (93)	3/9 (33)	77/96 (80)	9/9 (100)	91/96 (95)
Warner et al.[13]	Canada‡	3/7 (43)	188/189 (99)	3/6 (50)	167/180 (93)	6/7 (86)	172/189 (91)
Podo et al.[14]	Italy§	1/8 (13)	97/97 (100)	1/8 (13)	97/97 (100)	8/8 (100)	96/97 (99)
Total	—	7/24 (29)	374/382 (98)	7/23 (30)	341/373 (91)	23/24 (96)	359/382 (94)

* Numbers in parentheses are percentages.

† The sensitivity of mammography was 29 percent (2 of 7) for invasive cancer and 50 percent (1 of 2) for ductal carcinoma in situ (DCIS); the sensitivity of ultrasonography was 29 percent (2 of 7) for invasive cancer and 0 percent (0 of 2) for DCIS; and the sensitivity of MRI was 100 percent (7 of 7) for invasive cancer and 100 percent (2 of 2) for DCIS.

‡ The sensitivity of mammography was 33 percent (2 of 6) for invasive cancer and 100 percent (1 of 1) for DCIS; the sensitivity of ultrasonography was 60 percent (3 of 5) for invasive cancer and 0 percent (0 of 1) for DCIS; and the sensitivity of MRI was 100 percent (6 of 6) for invasive cancer and 0 percent (0 of 1) for DCIS.

§ The sensitivity of mammography was 20 percent (1 of 5) for invasive cancer and 0 percent (0 of 3) for DCIS; the sensitivity of ultrasonography was 20 percent (1 of 5) for invasive cancer and 0 percent (0 of 3) for DCIS; and the sensitivity of MRI was 100 percent (5 of 5) for invasive cancer and 100 percent (3 of 3) for DCIS.

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antee improved survival rates; detecting nonlethal cancers or cancers that have already metastasized will not decrease mortality. Only a randomized, controlled trial with death as the end point can definitively prove that any screening intervention improves survival.[18]

Without information provided by randomized, controlled trials, the management of breast cancer may be guided by other reports, such as observational studies, data extrapolation, and expert opinion.[19] Whereas breast cancer develops in only a minority of women in the general population, the disease develops in most women who are *BRCA* mutation carriers (50 to 85 percent). For mutation carriers, the benefit of high sensitivity may outweigh the effects of imperfect specificity. The Blue Cross–Blue Shield Association's Technology Evaluation Center has adopted criteria for technology assessment, including that the technology improve the net health outcome; a recent report concluded that using MRI to screen women at high genetic risk for breast cancer meets this criterion.[20] The new data reported by Kriege et al. provide further evidence of a benefit.

MRI can detect otherwise occult breast cancer in high-risk patients and is probably most beneficial to those at highest risk. Data are accumulating in support of supplementing mammography with MRI to detect cancer in carriers of *BRCA* mutations. MRI may also be valuable in screening women with an increased risk due to nongenetic factors (e.g., prior breast cancer), but more work is needed to substantiate this possibility, including analysis of the contribution of MRI in subgroups with defined risk factors and quantified levels of risk. No data support the use of MRI in screening women at normal risk. Ideally, breast MRI should be performed at facilities that follow technical and interpretive guidelines[9] and that can perform biopsies of lesions detected by MRI alone.[21] Whether the excellent results reported in the literature can be achieved in practice remains to be determined. Further outcomes research is essential to develop evidence-based recommendations for methods of breast-cancer screening that are tailored to the specific needs of women at various levels of risk.

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