

Breast MRI Screening for High-Risk Patients

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Although mammography can reduce breast cancer mortality rates in screened populations, its modest sensitivity, especially in younger women with strong family histories for breast cancer, has prompted the introduction of breast magnetic resonance imaging (MRI) for high-risk screening. Seven prospective screening trials for high-risk patients in which MRI has been added to mammography indicate the sensitivity of MRI to be twice that of mammography alone. The specificity of MRI is lower than mammography in most, but not all studies; however, the specificity of MRI improves to a level comparable to mammography in screenings subsequent to the initial prevalence screen. Although the target populations in breast MRI screening studies have been identified by genetic and familial risks, the superior sensitivity of MRI has been demonstrated at all levels of elevated risk, raising the possibility that MRI screening could benefit women with risk factors other than a positive family history. The published studies on breast MRI screening are reviewed herein, along with new screening guidelines that are currently shaping practice patterns. *Semin Breast Dis 11:67-75 © 2008 Elsevier Inc. All rights reserved.*

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After many years of controversy, it is now generally accepted that mammography reduces breast cancer mortality in screened populations,¹ and that this benefit is, partly or largely, responsible for the decline in breast cancer mortality seen outside the confines of clinical trials in countries where mammography is a standard screening practice.² Effective screening at specific intervals for any type of cancer is based on: (1) the natural history of the disease and its interruption, taking into account epidemiologic concerns, such as selection bias, overdiagnosis bias, lead-time bias, and length-time bias; and (2) the sensitivity of the screening tool. After an effective tool has been identified, there is the additional challenge of population compliance. Disease prevalence and incidence, along with specificity of the tool, are more pertinent to the socioeconomic realities of screening rather than effectiveness as defined by a reduction in mortality. Although great enthusiasm exists among health care professionals and the public for cancer screening,³ it is not always clear that screening strategies for earlier diagnosis alter outcomes, an issue that still surrounds lung cancer screening today.⁴ In the evolution of breast cancer screening, while the historic mam-

mography trials were underway, the Fisher theory of breast cancer biology was revolutionizing local management of the disease.⁵ The Fisher theory de-emphasized variations in local control since systemic disease dictated outcome early in the biologic life of the tumor. A corollary of this theory, unstated because its tenets were first proposed in the premammographic era,⁶ would have been that early diagnosis should have little or no impact on a cancer that has already established its tumor–host relationship, thus diminishing the importance of sojourn time. Yet, despite the widespread adoption of the Fisher theory, achieved primarily through the success of the NSABP B-04⁷ and B-06⁸ trials, the screening mammography trials (grounded more in Halstedian theory) were likewise successful,⁹ helping to merge theories of breast cancer biology into the “spectrum theory,”¹⁰ often called the “Hellman theory.” As currently conceptualized by the spectrum theory, the natural history of breast cancer allows a vulnerability to early detection in many, but not all, malignant tumors.

With natural history generating less controversy today, we are still left with potential epidemiologic biases; however, given the endpoint of mortality reduction achieved through the prospective, randomized trials with mammographic screening, these biases are minimized, if not negated.¹¹ Thus, the success of the mammography screening trials was much more than a victory for radiograph technology; instead, the trials were a victory for the early detection of breast cancer as a general

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principle, opening doors for further improvement. The remaining variables, then, are *compliance* at the population level and *sensitivity* of the screening tool at the individual level. Compliance with screening mammography has been heavily promoted in selected countries with efforts underway to expand access worldwide. As for improving sensitivity of the screening tool, in this case mammography, technologic developments to date have had limited impact.

Sensitivity of Screening Mammography Variouslly Defined

Although the landmark prospective trials in screening mammography have been scrutinized to an extraordinary degree with regard to mortality reduction, little attention has been paid to the sensitivity of mammography in the detection of cancer in these same clinical trials. Yet, in a review of sensitivity and estimations of sojourn times,¹² the sensitivity of mammography in these trials ranged from 39% in the Health Insurance Plan (HIP) study to 92% in the age 70 to 74 subset of the Swedish Two-County study. Most sensitivity determinations, though, were in the range of 60% to 66%, with Malmo at 61% overall, Edinburgh 63%, Canadian National Breast Cancer Screening Study (CNBSS-1, ages 40-49) 61%, and CNBSS-2 (ages 50-59) 66%.¹² Despite these relatively low values, a sensitivity level that often appears in the disclaimers of radiology reports, and is regularly reported by the mainstream media, is that mammography can find "90% of breast cancers in women who have no symptoms of the disease."¹³ Even the American Cancer Society offers the position statement that "mammography will detect about 80% to 90%" of asymptomatic cancers,¹⁴ although the origin of this sensitivity level is not referenced. Although 90% sensitivity may be the case for subsets of women based on age or low-density mammograms, the source of this number as erroneously applied to all screening mammograms is difficult to trace, perhaps reflecting omission of the word "palpable" from early studies of sensitivity. However, almost two decades ago, it was recognized that mammographic sensitivity was "approximately 50%" in the HIP study and "approximately 70%" in the Breast Cancer Detection Demonstration Project (BCDDP).¹⁵

Although mammography outcome data are monitored more than any other radiologic study, with performance benchmarks well defined,¹⁶ the critical data reflective of mammographic sensitivity are not routinely monitored due to the inherent tracking challenges. Therefore, the sensitivity rate at one's own facility is usually unknown, and this has translated to a paucity of published data on the subject.

Because the historical screening trials employed what is now considered outmoded technology, the question arises as to the impact of technologic improvements in mammography. Although many advances are being studied, including contrast-enhanced mammography¹⁷ and tomosynthesis,¹⁸ the gradual improvement over the years in film screen mammography and the introduction of digital mammography has not yielded impressive gains in sensitivity. The Digital Mammo-

graphic Imaging Screening Trial (DMIST) coordinated by the American College of Radiology Imaging Network (ACRIN) was focused on a comparison of digital versus film screen; however, the overall sensitivity as defined by 12-month follow-up revealed 70% sensitivity with digital and 66% for film screen,¹⁹ comparable to the sensitivities in the historical trials. When the definition of sensitivity was extended to the unconventional duration of 15 months, there was no difference between the technologies, with both digital and film screen showing a remarkably low 41% sensitivity.

Trying to define false-negatives in a meaningful fashion is a difficult task with nonpalpable tumors. Traditionally, the method used to measure false-negative rates was through long-term follow-up, wherein the miss rate correlates with duration chosen, as noted in the DMIST study above. However, in studies using long-term follow-up, so-called false-negatives are actually a mix of: (1) true interval cancers that may not have been detectable on the prior screen by any means, (2) radiologic misinterpretations, (3) cancers with subtle mammographic changes not meeting biopsy threshold, and (4) mammographic failures due to dense breast tissue. From such a mix, it is difficult to sort out true mammographic failures.

Although overall density is implicated as the primary culprit in false-negativity, the more exact issue is the density level immediately adjacent to the tumor borders. A malignancy that develops within an island of patchy density will be equally occult on radiograph as a tumor developing in a mammographic "white out," at least until the former becomes large enough to interface with adipose tissue. When this anatomic limitation is added to the problem of diffuse histology as seen in lobular cancers, the implementation of a physiologic component to screening seems warranted.²⁰

Given these difficulties in accurately defining false-negatives through long-term follow-up, attention has focused recently on the more accurate approach of simultaneous adjunct imaging, primarily ultrasound and MRI. Although ultrasound has improved the sensitivity for cancer detection in women with dense breasts, defining tumors of similar size and stage as mammography,²¹ there has been some hesitation to endorse its routine use given its performance in the multimodality studies to be noted below in which all three common methods of breast imaging have been employed.

Breast MRI can be conceptualized as improving sensitivity through two means: (1) as with ultrasound, MRI helps to identify the cancers that are currently being missed through conventional mammography, and (2) MRI uniquely lowers the threshold of detection and thus re-defines sojourn times, the preclinical, but screen-detectable, phase of a tumor. In the first instance, that of more *reliable detection*, one should be able to predict improved survival (with either ultrasound or MRI) since many of these tumors are missed on mammography simply because of anatomic issues, not inherent biology. However, in the second instance, a hypothesized survival benefit of *earlier detection* is more tenuous given length-time bias, although there seems to be little reason to abandon spectrum theory, which so nicely explains the success of the mammography screening trials.

With this earlier detection, one should be cognizant of a rarely mentioned variable in defining false-negatives: when the threshold of detection is lowered by a new modality, then the sensitivity of the standard will drop significantly. If, for instance, an imaging modality were developed that could identify a cluster of 100 malignant cells, then the sensitivity of MRI would plummet. Using detailed analysis of mastectomy specimens as the reference to define false-negatives may seem an obvious choice as was done to define the 94% sensitivity in one of the early studies of high-spatial resolution MRI²²; however, routine pathologic processing with its random sectioning is of little value. Breast MRI, and sometimes conventional imaging, will define tumors that are missed with routine processing of a mastectomy specimen. Extensive serial sectioning and tissue analysis is required, a challenging task even in research settings if large numbers of specimens are to be studied.

Defining false-negatives is thus open to many variables. Complicating the picture for mammography is the fact that the degree of breast density dictates a wide range of sensitivities at the individual level, rendering generalizations meaningless for a woman trying to make a decision about adjunct imaging for her screening regimen. Overall, though, the 70% sensitivity figure for mammography as defined in the DMIST study with 12-month follow-up seems to be a reasonably accurate number as applicable to the patient population that presents for routine screening in the U.S. For those younger women who participated in the high-risk screening studies using MRI, though, this 70% sensitivity for mammography turns out to be remarkably optimistic.

Prospective Trials of MRI Screening in High-Risk Patients

A comparative analysis of the seven prospective trials²³⁻²⁹ where MRI has been used to augment mammography in screening high-risk patients is presented in Table 1. Each trial has unique features with regard to patient entry criteria, the inclusion of women with prior cancer, technique of MRI, data presentation, single site versus multi-site, whether or not

radiologists were blinded, and other features that make direct comparisons difficult.

Despite these differences, a consistent feature is noted wherein MRI sensitivity is twice that of mammography alone. In a recent analysis combining the five largest studies,³⁰ the sensitivity of mammography was 40%, whereas the sensitivity of MRI was 81%. Although this substantial improvement in sensitivity has been ascribed to the fact that these trials are skewed toward younger high-risk women with, perhaps, denser breasts, subset analyses are suggesting the vastly improved sensitivity with MRI has broader application.

In the Toronto study²⁴ where all participants were positive for one of the two breast cancer susceptibility genes—either BRCA-1 or BRCA-2—subset analysis has revealed that the difference in sensitivity between MRI and mammography was no greater for women under 50 than for women ages 50 and older.³¹ And, although it is assumed that breast density in this younger high-risk population is greater, thus selectively lowering mammographic sensitivity, another subset analysis of the Toronto study revealed that, even in the low-density group, the sensitivity of mammography was less than 50%.³² Although these findings cannot readily be extrapolated to the BRCA-negative population (primarily because of the unique features of BRCA-1-related tumors), these subset analyses had results that were contrary to the expectations of the investigators.³³

In the German trial, subset analysis is available according to levels of risk.²⁶ In this study, only 8% of the participants were BRCA-positive ($n = 43$), and for this group, mammographic sensitivity was 25% (2/8) and MRI sensitivity was 100% (8/8). However, comparable differences were seen in the lower levels of risk. Patients at a 21% to 40% lifetime risk ($n = 241$), defined primarily through the Claus model, had a mammographic sensitivity of 25% (5/20) and a MRI sensitivity of 100% (20/20). Then, in the lowest risk group, where women had only a 20% lifetime risk ($n = 110$), mammographic sensitivity was 50% (3/6) and MRI sensitivity was again 100% (6/6). These results support the notion that the doubling of sensitivity in cancer detection through breast MRI is not so much a function of risk levels as it is a function of the inherent attributes of the screening tool.

Table 1 Prospective Non-Randomized Studies Using Multi-Modality Breast Imaging for High-Risk Screening

Reference	Site	Total No.	Mean Age, Years	% BRCA+	Sensitivity as a Single Modality			Cancer Yield with MRI Alone (%)
					Mammo	Ultrasound	MRI	
Kriege, et al. ²³ 2004	The Netherlands (MRISC)	1909	40 (19 to 72)	18.8%	40% (18/45)	N/A	71% (32/45)	2.2
Warner, et al. ²⁴ 2004	Canada	236	47 (26 to 65)	100%	36% (8/22)	33% (7/21)	77% (17/22)	3.0
Leach, et al. ²⁵ 2005	U.K. (MARIBS)	649	40 (35 to 49)	18.5%	40% (14/35)	N/A	77% (27/35)	2.9
Kuhl, et al. ²⁶ 2005	Germany	529	42 (27 to 59)	8.1%	33% (14/43)	40% (17/43)	91% (39/43)	3.6
Sardanelli, et al. ²⁷ 2007	Italy (HIBCRIT)	278	46 (25 to 79)	60%	59%* (10/17)	65%* (11/17)	94%* (15/16)	2.2
Lehman, et al. ²⁸ 2007	United States (IBMC)	171	46 (25 to 72)	43%	33% (2/6)	17% (1/6)	100% (6/6)	2.3
Riedl, et al. ²⁹ 2007	Austria	327	41 (22 to 80)	27.5%	50% (14/28)	43% (12/28)	86% (24/28)	3.7

Abbreviation: N/A, study did not include screening ultrasound.

*9/18 cancers were palpable in this study, and not all patients had all 3 forms of imaging. For the 9 non-palpable cancers, mammographic sensitivity was 33%, ultrasound sensitivity 25%, and MRI sensitivity 89%.

Table 2 Specificity of Three Modalities Used in Prospective High-Risk Screening Studies

	Mammography	Ultrasound	MRI
Kriege, et al. ²³ 2004 The Netherlands	95.0%	N/A	89.8%
Warner, et al. ²⁴ 2004 Canada	99.8%	96%	95.4%
Leach, et al. ²⁵ 2005 United Kingdom	93.0%	N/A	81.0%
Kuhl, et al. ²⁶ 2005 Germany	96.8%	90.5%	97.2%
Sardanelli, et al. ²⁷ 2007 Italy	(77% PPV)*	(65% PPV)*	(63% PPV)*
Lehman, et al. ²⁸ 2007 United States	(50% PPV)*	(25% PPV)*	(43% PPV)*
Riedl, et al. ²⁹ 2007 Austria	98%	98%	92%

Abbreviation: N/A, study did not include ultrasound.

*Did not report specificities.

Specificities (or alternatively, positive predictive values [PPVs]) in the seven prospective trials are presented in Table 2. With the exception of the German trial, specificity for MRI is lower than mammography. However, these differences in specificity are not particularly large; and, in the aforementioned combined analysis,³⁰ the PPV of mammography was 47%, whereas the PPV of MRI was 53%. Although it is generally conceded that MRI prompts more recalls and more biopsies, with attendant costs and patient anxiety, it has also been noted that the false-positive MRI studies tend to decline as the radiology learning curve progresses,³⁴ and that specificity improves substantially on the second and subsequent rounds of screening compared with the first round.³⁵

Features of screen-detected tumors discovered in the prospective trials are presented in Table 3. The percentage of interval cancers is much lower than seen in high-risk screening studies using mammography alone, where interval cancers have occurred at rates as high as 46% in BRCA-positive patients.³⁶ Mean diameters of invasive cancers, percentage of in situ cases, and percentage of node-negative cancers are comparable to what is seen in general population screening; however, it must be considered that these studies are skewed toward the initial prevalence screen. Thus, the initial cancers are not appreciably different in stage than what would be found on mammography screening; however, due to the higher sensitivity, one is actually evaluating roughly twice the

number of cancers discovered by mammography alone. This lends support to the premise that the primary benefit of MRI screening is not necessarily finding cancer "earlier" than mammography, but simply finding the cancers missed by mammography. Then, this increased sensitivity up front is later reflected by fewer interval cancers.

That said, support for MRI identifying cancers earlier than mammography is found in the characteristics of those tumors discovered by MRI alone compared with other modalities. Such a comparison is made in the study from Germany²⁶ as reflected in Table 4. After breakdown into method of discovery, subsets are rather small in number; however, it is noteworthy that downstaging through MRI seems apparent. And although this can be attributed to length-time bias, we know from the mammography screening trials that such downstaging proved to be a predictive surrogate for mortality reduction. Also, whereas a tumor measurement of 1.2 cm may not seem much different than 0.75 cm, diameter is merely a convenient alternative to actual tumor volume. Using the geometric formula $V = 4/3\pi r^3$, the volume of sphere with a 1.2-cm diameter (0.90 mL) is more than four-fold the volume of sphere with a 0.75 diameter (0.22 mL). Thus, "two doubling times earlier" is an alternative way to describe the lead time that MRI discovery provided the cancer patients in the German trial.

Table 3 Tumor Features in Prospective Multi-Modality Surveillance Studies

	Size (Diameter) of Invasive Lesions	Percentage of Stage 0 (in situ)	Percentage of Node-Negative Invasive Cancers	Percentage of Interval Cancers
Kriege, et al. ²³ 2004 The Netherlands	43.2% <1.0 cm	11.8%	78.6%	9.8%
Warner, et al. ²⁴ 2004 Canada	1.1 cm mean (1st screen); 1.3 cm mean (2 nd screen)	27.3%	86.7%	4.5%
Leach, et al. ²⁵ 2005 United Kingdom	1.5 cm mean	17.1%	80.8%	5.7%
Kuhl, et al. ²⁶ 2005 Germany	29%* <1.0 cm	23%*	84%*	2.3%
Sardanelli, et al. ²⁷ 2007 Italy	1.4 cm mean	22.2%	77%	0
Lehman, et al. ²⁸ 2007 United States	Not reported: of 4 invasive tumors classified, 3 were T-1 and 1 was T-2	20%	75%	single screen
Riedl, et al. ²⁹ 2007 Austria	Not reported: of 17 invasive tumors classified, 10 were T1b or smaller.	37%	88.2%	3.5%

*Study included women with prior history of breast cancer where there were three local recurrences; values are based on those women without prior cancer.

Table 4 Impact of Individual and Combined Modalities on Tumor Downstaging Reported by Kuhl, et al.²⁶

	Median Size of Invasive Lesions	Node-Positivity	DCIS
Detected by: Mammography (Mammo)	1.2 cm	4/10	3/9
Detected by: Ultrasound (US)	1.3 cm	5/12	0/9
Detected by: Mammo & US	1.3 cm	5/16	3/9
Detected by: MRI (overall)	1.1 cm	5/31	8/9
Detected by: MRI (alone)	0.75 cm	0/14	5/9

Screening Recommendations for MRI As a Result of the Prospective Trials

The National Comprehensive Cancer Network (NCCN) has recommended that BRCA-positive patients begin annual mammography and annual breast MRI (in addition to clinical exams and self-exams) starting at age 25.³⁷ However, the NCCN provides no MRI guidelines for the vast majority of women who fall outside this category.

In 2007, the American Cancer Society (ACS) issued new guidelines for screening high-risk patients,³⁸ with recommendations based primarily on the published literature from the clinical trials noted above. Annual breast MRI is recommended along with annual mammography for high-risk women starting at age 30. The definition of high risk is clearly defined by several parameters: BRCA-positive patients, untested first-degree relatives of BRCA-positive patients, as well as women who harbor any one of several rare genetic syndromes predisposing to breast cancer. Not based on the published literature with regard to MRI efficacy, but through expert opinion, annual MRI is also recommended for those women at very high risk due to a history of radiation to the chest wall between the ages of 10 and 30.

But it is the following category of “high risk” in identifying patients for MRI screening according to ACS guidelines that has caused the most debate and deliberation among practicing radiologists and clinicians: “Lifetime risk of approxi-

mately 20% to 25% or greater, as defined by BRCAPRO or other models that are largely dependent on family history.” Emphasis is placed on familial and genetic risk for breast cancer since this risk category alone was used for entry into all of the prospective MRI screening trials. A summary of inclusion criteria for these trials is presented in Table 5.

Although The Netherlands study²³ included patients at a lifetime risk of 15% minimum, the subset analysis was performed for women with risk between 15% and 29%. The only group to include women at a minimum 20% risk, and to study this modestly elevated risk group as a subset, was the German trial,²⁶ where 110 women were so designated (6 cancers discovered; 3/6 by mammography, 6/6 by MRI). Some studies used descriptive criteria for entry rather than an absolute minimum risk based on a mathematical model. Drawing from these entry criteria, the ACS guidelines have emphasized the need to focus on lifetime risk based on family history and genetic mutation probabilities.

The “approximately 20% to 25%” recommendation has raised questions as to its ambiguity. However, this phrase was intentional because of the differences in calculations with the various mathematical models and the fact that each of the models is imperfect and likely to be refined over time. It should be pointed out that the rather common family history of a single first-degree relative with postmenopausal breast cancer is usually not enough to reach the recommended threshold. Ideally, patients interested in MRI screening should undergo a formal risk assessment using multiple mathematical

Table 5 Entry Requirements and Models Used to Select Patients for High-Risk Surveillance in Prospective Studies

	Minimum Risk for Study Entry	Models Used for Study Entry
Kriege, et al. ²³ 2004 The Netherlands	15% lifetime	Claus
Warner, et al. ²⁴ 2004 Canada	BRCA-positivity	N/A; all study patients were confirmed BRCA-1 & BRCA-2 mutation carriers
Leach, et al. ²⁵ 2005 United Kingdom	Annual risk of 0.9%	Not stated (women whose affected 1st-degree had a 60% chance of harboring a BRCA mutation)
Kuhl, et al. ²⁶ 2005 Germany	20% lifetime	Claus & descriptive criteria*
Sardanelli, et al. ²⁷ 2007 Italy	No absolute minimum	Descriptive criteria based on family history†
Lehman, et al. ²⁸ 2007 United States	No absolute minimum	–BRCA-positive –Likelihood of BRCA-positivity greater than 20% –Descriptive criteria‡
Riedl, et al. ²⁹ 2007 Austria	No absolute minimum	–BRCA-positivity –modified Claus

*As outlined by the Consortium on Familial Breast and Ovarian Cancer of the German Cancer Aid.

†Family history with a minimum of 3 breast or ovarian cancers in 1st or 2nd degree relatives on either the maternal or paternal side.

‡At least 2 instances of ovarian or breast cancer among the participant and 1st or 2nd degree relatives within the same lineage; or, Ashkenazi Jewish ethnicity with one 1st or two 2nd degree relatives with breast or ovarian cancer, or patient is Ashkenazi Jewish and had breast cancer. Where breast cancer was required to meet criteria, participant age of diagnosis was less than 50 or premenopausal.

models, as well as genetic counseling. This session is an ideal opportunity to provide informed consent about MRI as a screening modality.

The other feature of the ACS guidelines that has generated some confusion is the moderate risk category (15-20% lifetime risk) where there is "insufficient evidence" at this point to warrant a recommendation for or against MRI screening. In this group are the tissue risks (ADH, ALH, and LCIS), dense mammograms, and women with a past history of breast cancer. Some of the mathematical models include tissue risks, and it is not uncommon, for example, that a young patient with ADH as her only risk factor will exceed the 20% threshold for lifetime risk and thus qualify for MRI screening. Thus, the comment seems warranted that the ACS has rendered "guidelines" and that decisions to recommend MRI for screening in these "intermediate risk" patients should be made on a case-by-case basis with other clinical factors in mind.

Although there is evidence of some benefit to screening patients diagnosed with LCIS, but not yet for ADH,³⁹ as well as limited data supporting the use of MRI in the cancer patients included in the high-risk trials noted above, there are no published studies where breast density has been used as the sole criteria for trial entry. Thus, the overwhelming amount of available data to support MRI screening is based on results in women with genetic and familial risks. If positive results for these other risk categories emerge from clinical

trials, it can be anticipated that guidelines will change accordingly.

Mercy Health Center Experience

We were prompted to consider high-risk screening based on a retrospective study published in 2003 that evaluated 367 consecutive high-risk patients with normal findings on mammography and examination, where there was a 3.5% yield of breast cancer (13/367) through MRI.⁴⁰ Our in-house protocol was established as an extension of our risk assessment/genetic testing program before formal guidelines by any organization or society, so there was no precedent on which to build.

That said, we considered breast density to be an equal determinant of MRI benefit to that imparted by calculated risk, the former being a predictor of a mammographic "miss" and the latter being a predictor of MRI yield through disease prevalence and incidence. Thus, inclusion of mammographic density in our protocol was based not so much on its well-documented role as an independent risk factor,⁴¹ equal in at least one study to the predictive ability of the Gail model,⁴² but as the indicator of a weak modality in a dual-modality screening approach. This two-parameter concept has subsequently been supported by UK screening guidelines that include "women ages 40 to 49 with a 10-year risk greater than

Table 6 Asymptomatic Patients* (Negative Exam and Negative Mammograms) Diagnosed with Breast Cancer at Mercy Health Center on the Initial Prevalence Screen with MRI

	Age	Histology/Size	Final Stage	Indication for MRI Screening	Lifetime Risks for Breast Cancer and BRCA Probabilities, as Calculated Prior to the MRI			
					Gail	Claus	Tyrer-Cuzick†	BRCA‡ Risk
#1	53	Invasive ductal, Gr 1, 0.5 cm	Stage I	Moderate FH§ & tier 3 breast density¶	16%	7%	15%	<5%
#2	49	Invasive ductal, Gr 1, 0.6 cm	Stage I	Hx of ADH, opposite breast (tier 2)	16%	N/A	36%	(baseline)
#3	58	DCIS, Gr 1 (0.8 cm by MRI)	Stage 0	Moderate family hx & tier 3 breast density	15%	6%	12%	<5%
#4	75	Invasive ductal, Gr 2, 1.0 cm	Stage I	Weak FH; hx of ADH, opposite breast; tier 4 breast density	15%	N/A	21%	(baseline)
#5	51	Invasive ductal, Gr 2, 1.0 cm	Stage I	Hx of ADH, opposite breast & tier 3 breast density	13%	N/A	20%	(baseline)
#6	53	Invasive ductal, Gr 1, 1.8 cm	Stage I	Moderate FH & tier 4 breast density	16%	10%	14%	<5%
#7	50	DCIS, Gr 3 (1.1 cm by MRI)	Stage 0	Moderate FH & tier 4 breast density	19%	12%	19%	<5%

*Includes those women previously diagnosed with ADH (atypical ductal hyperplasia), while excluding patients who had upgrades to malignancy through surgical excisions at the ADH biopsy site.

†Tyrer-Cuzick calculations include ages of all unaffected family members, though this information was not always available.

‡BRCA risks determined through multiple models (Couch, Frank, BRCAPRO) to determine if any patients qualified for BRCA testing under any guidelines.

§FH, family history; "moderate" indicating a single 1st-degree relative or multiple 2nd-degree relatives; "weak" family history in patient #4 was breast cancer diagnosed in the patient's mother at age 91.

¶Density levels as described by American College of Radiology guidelines, with "tier 3" indicating heterogeneously dense tissue (50% to 75% density) and "tier 4" indicating extremely dense tissue (75% to 100% density).

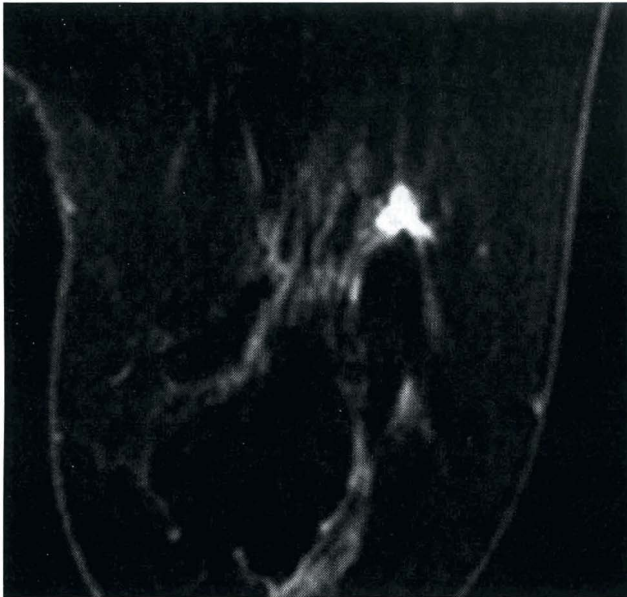


Figure 1 Breast MRI from a 53-year-old female whose sister was diagnosed with breast cancer at age 48. Although this was the only traditional risk factor for the patient, mammographic density was extreme, in and of itself an additional risk factor, as well as a predictor of low mammographic sensitivity. A 1.8-cm invasive ductal carcinoma, grade 1, node-negative, was identified on MRI screening.

20% or a 10-year risk greater than 12% and a dense breast

Using a point system with equal weighting for both risk and density, 1 to 3 points are assigned to three levels of risk as outlined by a risk assessment working group,⁴⁴ and 1 to 3 points are assigned to levels of density (0 = predominantly fatty breasts, 1 = patchy fibroglandular pattern, 2 = heterogeneously dense breasts, 3 = extremely dense breasts) according to American College of Radiology guidelines.⁴⁵ Point totals indicate, first, whether or not MRI is indicated, and if so, at what interval. Whereas studies to date have focused on annual MRI, it has to be considered that MRI is not being used as a sole screening modality, but as a complement to mammography. Therefore, it might make sense to expand MRI screening to include more women, but at longer intervals, rather than recommending screening as an annual-or-nothing concept. Not only has there been previous success with biennial screening, but there is also a biologic basis for considering longer intervals in older women where tumor doubling times are longer, even in those women with hereditary risk.⁴⁶

In our protocol, when patients have point totals of 3 to 4, biennial MRI screening is recommended, and with 5 to 6 points, annual MRI is recommended. With 1 to 2 points, MRI is not a formal recommendation, although we have a group of patients who would like to proceed anyway. We monitor these women for whom we agree to triennial MRI to see if any benefit can be demonstrated. However, for women at no increased risk and with fatty replacement or only patchy

densities on mammography, we discourage the use of screening MRI.

Of 241 initial screens to date, we have identified 7 cancers in asymptomatic women with normal mammograms and normal examination, for a yield of 2.9%. The details on these 7 patients are provided in Table 6. All patients with MRI-discovered cancer were node-negative with a mean tumor diameter of 1.0 cm, and with in situ cases identified in 2/7 (29%). Most notably, though, none of these patients would have qualified for MRI screening based on family history risk as outlined by the ACS, and none came close to reaching threshold for considering BRCA genetic testing. Four patients met our threshold for MRI screening by virtue of a moderate family history, but only when coupled to breast density (example in Fig. 1). Three patients might have qualified for MRI screening according to a liberal interpretation of the “20%” threshold in the ACS guidelines where ADH had been diagnosed (example in Figs. 2 and 3), and where the Tyrer-Cuzick model calculated risk levels of 20% or above.

Our yield to date through breast MRI screening, at least on prevalence scans, is comparable to those studies that have relied on risk alone for entry, yet none of our cancer patients would have met minimum risk levels for entry to those prospective trials. The groups defined by ACS as requiring further research—tissue risks, breast density, prior cancer—appear to be fertile ground for future study.

Future Considerations

Many in the breast MRI field look forward to new developments in spectroscopy that could help significantly through



Figure 2 Although this 49-year-old female had reasonable mammographic sensitivity (patchy, fibroglandular tissue, tier 2 according to ACR guidelines), she had a solitary identifiable risk factor—atypical ductal hyperplasia (ADH)—that had been previously diagnosed in the opposite breast. Breast MRI screening revealed a 0.6-cm invasive ductal carcinoma, grade 1, node-negative.

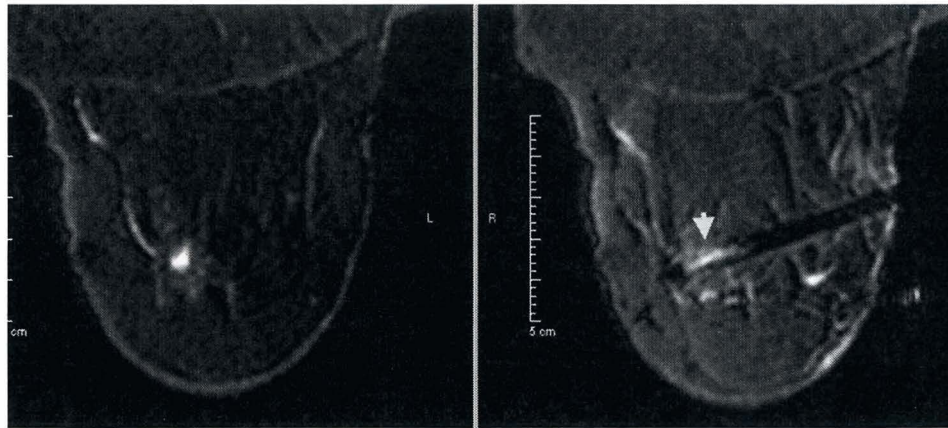


Figure 3 The patient in Fig. 2 was called back for second-look ultrasound and repeat mammography, but no lesion could be identified for targeted biopsy, prompting an MRI-directed biopsy. In the image on the right, the area of MRI enhancement (arrow) has dropped into the slot of the advancing needle in preparation for vacuum-assisted biopsy.

improving specificity.⁴⁷ Yet, even with better specificity, the fact remains that the annual yield on incident screens is going to be low, even for most patients considered at high risk. With the exception of gene-positive patients, the majority of so-called high-risk patients follow the general life incidence curves wherein screening will be most productive in later years. Thus, much can be said for the UK screening guidelines, which, outside of gene-positive patients, are based on 10-year calculations.

Screening trials with breast MRI to date have been predicated on the notion that higher risk will generate higher yields, thus translating to better cost-effectiveness. Interestingly, in one of the few studies that has addressed cost-effectiveness when adding MRI to mammographic screening in BRCA-positive patients,⁴⁸ cost-effectiveness was increased when the sensitivity of the mammogram was lower, ie, extremely dense breasts, lending support to the inclusion of breast density in patient selection for MRI.

However, a more attractive concept than levels of risk, or density, or both, when it comes to guiding efficient breast MRI use would be to determine the actual presence or absence of occult breast cancer missed by mammography through biomarkers circulating in the blood. Whereas many consider this an improbable feat due to the heterogeneity of breast cancer, others have called for such a goal to be recognized,⁴⁹ and increasing attention is being paid to developing a screening blood test for the detection of breast cancer with breast MRI as an integral feature of such a strategy.⁵⁰⁻⁵² Such a test would also provide an offering for those women too young to qualify for imaging under current screening guidelines, women who refuse mammography for whatever reason, and for women in parts of the world without access to mammography.

At our institution, we have tried to facilitate this goal through an IRB-approved protocol to collect serum samples on patients undergoing breast MRI, both benign controls and women with malignant findings, so that correlations can be made to results from multi-modality imaging, rather than mammography alone. Over 1000 women in Oklahoma have

contributed to this research agenda, providing more than 5000 aliquots for study. At first, any viable blood test would have to serve in a complementary role to screening mammography, efficiently selecting patients for MRI. But a further reach into the future might find low-cost blood screening as a prelude to cancer localization through high-cost imaging, not only for breast cancer, but eventually all types of cancer.

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