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ORIGINAL REPORT

Multimodality Screening of High-Risk Women: A Prospective Cohort Study

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ABSTRACT

Purpose
Mammography has been established as the primary imaging screening method for breast cancer; however, the sensitivity of mammography is limited, especially in women with dense breast tissue. Given the limitations of mammography, interest has developed in alternative screening techniques. This interest has led to numerous studies reporting mammographically occult breast cancers detected on magnetic resonance imaging (MRI) or ultrasound. In addition, digital mammography was shown to be more sensitive than film mammography in selected populations. Our goal was to prospectively compare cancer detection of digital mammography (DM), whole-breast ultrasound (WBUS), and contrast-enhanced MRI in a high-risk screening population previously screened negative by film screen mammogram (FSM).

Methods
During a 2-year period, 609 asymptomatic high-risk women with nonactionable FSM examinations presented for a prospective multimodality screening consisting of DM, WBUS, and MRI. The FSM examinations were reinterpreted by study radiologists. Patients had benign or no suspicious findings on clinical examination. The cancer yield by modality was evaluated.

Results
Twenty cancers were diagnosed in 18 patients (nine ductal carcinomas in situ and 11 invasive breast cancers). The overall cancer yield on a per-patient basis was 3.0% (18 of 609 patients). The cancer yield by modality was 1.0% for FSM (six of 597 women), 1.2% for DM (seven of 569 women), 0.53% for WBUS (three of 567 women), and 2.1% for MRI (12 of 571 women). Of the 20 cancers detected, some were only detected on one imaging modality (FSM, n = 1; DM, n = 3; WBUS, n = 1; and MRI, n = 8).

Conclusion
The addition of MRI to mammography in the high-risk group has the greatest potential to detect additional mammographically occult cancers. The incremental cancer yield of WBUS and DM is much less.

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INTRODUCTION

Although the sensitivity of film screen mammography (FSM) has been typically quoted at approximately 85%,[1] more recent data from high-risk screening trials that include magnetic resonance imaging (MRI) suggest that FSM is less than 50% sensitive for the detection of breast cancer.[2] This has led to recommendations to augment screening mammography with contrast-enhanced MRI in selected women at high risk for developing breast cancer. Other modalities have also been demonstrated to detect cancers that are occult to FSM. Digital mammography (DM) has been demonstrated to have higher sensitivity for cancer relative to FSM in selected populations.[3] Whole-breast ultrasound (WBUS) has recently been shown to detect mammogram occult breast cancer in high-risk patients with radiographically dense breast.[4] There are no clear guidelines for the role of DM and WBUS in screening high-risk women. This is in part a result of the fact that there are few well-controlled studies that compare all three modalities (DM, WBUS, and MRI) with respect to their ability to detect breast cancer in high-risk patients who have negative film mammograms. We report here on a prospective, parallel-design study comparing DM, WBUS, and MRI with respect to their ability to detect incremental breast cancer in high-risk women with nonactionable FSM and clinical screens.

METHODS

Participants

The study was approved by the institutional review board and was Health Insurance Portability and Accountability Act compliant. All participants signed an informed consent. Women between the ages of 25 and 80 years who were considered at high risk for breast cancer based on any of the following were considered eligible: positive test for a mutation in *BRCA1* or *BRCA2*, $\geq$ 25% lifetime risk based on the Claus or Gail models, previous diagnosis of lobular carcinoma in situ or atypical hyperplasia (atypical ductal hyperplasia or atypical lobular hyperplasia), history of chest wall radiation before puberty, and a recent diagnosis of breast cancer in the contralateral breast. In participants with recent diagnosis of breast cancer, only the data from the cancer-free breast were included in the study. In addition, as part of entry criteria, all women had a nonactionable mammogram within 180 days of enrollment as well as no suspicious findings on clinical examination. For purposes of enrollment, a nonactionable mammogram was defined as a Breast Imaging Reporting and Data System (BIRADS) score of 1 or 2, a resolved BIRADS score of 0 or 3, or a BIRADS score of 4 associated with a biopsy negative for cancer based on interpretations performed as part of routine clinical care.

Procedures

The women underwent screening with the following modalities: bilateral full-field DM, bilateral WBUS, and bilateral contrast-enhanced MRI scheduled on the same day. Images were initially interpreted by different radiologists in the expected clinical context, with access to relevant clinical history. All readers were subspecialty-trained radiologists with extensive experience interpreting the modalities they were assigned. WBUS and MRI were assumed to be adjunctive to mammography, and DM would be a stand-alone modality. Therefore, WBUS and MRI were interpreted with access to FSM images and reports but otherwise blinded to each other and the DM. The DM was interpreted with clinical history but blinded to all other imaging information including FSM and the FSM report. The radiologist who performed the screening ultrasound examination also reinterpreted the entry FSM for study purposes. This initial set of interpretations is referred to as the blinded modality interpretations.

Immediately after the examinations and blinded interpretations, a conference of the three study radiologists was held to review the findings of all modalities in an unblinded (to the other modalities) fashion. All imaging findings detected by each imaging modality were discussed, and consistent indexing of findings was developed across all modalities. The reader of each modality then individually reinterpreted his or her assigned modality representing the unblinded modality interpretation. On review of all the imaging modalities, by consensus, all lesions were assigned a final consensus (considering the combined information from all modalities) BIRADS[5] rating and a percent likelihood of malignancy. Findings that were assigned BIRADS 0 on the blinded interpretations were either resolved by correlation with other modalities during the consensus conference or with additional projections performed on another day or were classified based on percent likelihood of malignancy using the BIRADS scale. All lesions receiving a consensus BIRADS rating of 4 or higher were recommended for biopsy. Following through on the biopsy recommendation was at the discretion of the patients' primary referring clinician.

Imaging Protocols

Breast MRI. Breast MRI examinations were performed with the patient prone in either a 1.5-T scanner (GE LX echo speed, GE Health, Nutley, NJ, or Siemens Sonata, Siemens Medical Solutions, Malvern, PA) or a 3-T scanner (Siemens Trio) with use of a dedicated surface breast coil array. The imaging protocol evolved over the course of the study; however, in all cases, it included bilateral fat-suppressed, T2-weighted images in the sagittal plane (4,000/85 [repetition time msec/echo time msec], 512 $\times$ 256) and a slab interleaved (13) three-dimensional, fat-suppressed spoiled gradient echo before and after the injection of contrast. The spoiled gradient echo sequence had a minimum spatial resolution of 20 cm over a 512*256 matrix and a minimum time resolution of 90 seconds (however, typically $<$ 1 minute) in the sagittal plane and slice thickness of 2 to 3.5 mm. Sequential postcontrast acquisitions were acquired for approximately 6 minutes after contrast injection. A rapid bolus injection of gadopentetate dimeglumine 0.1 mmol/kg (Omniscan; GE Health) followed by a 10-mL saline flush was administered in all participants. Subtraction images and dynamic signal intensity curves created for regions of interest selected by the interpreting radiologist were routinely available.

DM. Two DM views (craniocaudal and mediolateral oblique) were obtained from both breasts. Full-field DM was performed on a US Food and Drug Administration–approved GE DMAM machine. The images were reviewed as soft copy.

WBUS. Gray scale and Doppler (color flow and power) imaging was performed by using a state of the art ATL3000 (ATL, Bothell, WA) ultrasound scanner currently installed and in use in our facilities. The breast was first scanned in the radial and antiradial planes so that the entire volume of breast tissue was imaged. Sonographic evaluation of the entire breast was performed. Images from each significant finding were recorded. In the color Doppler mode of the scanner, the flow velocity was recorded on a videotape without aliasing at the lowest possible wall filter. Representative images were obtained of each of the four quadrants of each breast.

End Points

Pathology reports were reviewed for all biopsies performed on patients studied on protocol. All pathology diagnoses were coded as benign, atypical (included lobular carcinoma in situ), ductal carcinoma in situ (DCIS), or invasive cancer based on an extraction of information from the pathology report. Excisional biopsy reports were used to establish pathologic diagnosis for patients who underwent core needle biopsy and subsequent excision. All patients underwent 2-year clinical follow-up to establish cancer and vital status. Patients were considered negative only after 2 years of negative follow-up.

Statistical Analysis

To estimate the relative yields of each modality as if it were applied as a clinical screening test, the blinded modality assessments were considered the primary data source. The blinded assessment were divided into actionable (BIRADS rating of 0, 3, 4, or 5) and nonactionable (BIRADS rating of 1 or 2) on the assumption that the actionable assessments at screening would lead to further diagnostic evaluation and cancer discovery. Actionable assessments were considered positive screens, and nonactionable assessments were considered negative screens. Descriptive statistics were developed on a per-patient basis by modality. A person was not counted in an analysis for a particular modality if no images were obtained using that modality. This situation occurred, for example, when a woman was unable to be screened using MRI because of contraindications, scheduling difficulties, or her unwillingness to submit to MRI for screening. If a modality identified a lesion as actionable (positive) but another lesion was eventually found to be malignant, then at the patient level, this modality was scored as having missed a cancer. The cancer yield of each modality was calculated as the number of patients with a positive screen for that modality corresponding to a cancer diagnosis divided by the total patients imaged by that modality. Sensitivity and specificity for each modality were compared. To assess the statistical significance of intermodality differences, we made paired comparisons across modalities of sensitivity and specificity using McNemar's test. Data management and statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary NC) and Stata version 10.1 (Stata, College Station, TX).

RESULTS

Six hundred twelve high-risk women were enrolled onto this study from May 2002 through July 2007. Three women withdrew before undergoing any imaging, leaving an analysis cohort of 609 women. The ages ranged from 27 to 81 years, with a median age of 49 years at study entry. Eighteen women were ultimately diagnosed with cancer on study. The breast density distribution in all eligible women

Table 1. Risk Factors and Eligibility Criteria for Study of Cancer in High-Risk Patients (N = 609)

Risk Factor	All Participants*		Participants With Cancer*	
	No.	%	No.	%
Diagnostic information				
Cancer in contralateral breast	251	41.2	7	39
Atypia, ALH, ADH	70	11.5	4	22
Diagnosis of LCIS	49	8.1	3	17
Patient history				
Prior cancer in one or both breasts	62	10.2	0	0
BRCA1	27	4.4	2	11
BRCA2	17	2.8	2	11
BRCA1 or *BRCA2*	44	7.2	4	22
Radiation before puberty	1	0.2	0	0
Lifetime risk				
Gail model > 25%	152	25	5	28
Claus model > 25%	142	23.3	4	22

Abbreviations: ALH, atypical lobular hyperplasia; ADH, atypical ductal hyperplasia; LCIS, lobular carcinoma in situ.
*Numbers can total more than 609 participants and 18 participants with cancer and percentages can total more than 100 because each participant could have more than one risk factor.

(women diagnosed with cancer) based on the radiologists' interpretation was 2.0% extremely dense, 57.6% heterogeneously dense, 37.1% scattered fibroglandular tissue, and 3.3% fatty. The distribution of risk factors for all eligible women and those ultimately diagnosed with cancer is included in Table 1.

In total, 79 (13.0%) of 609 women underwent biopsy. This resulted in the diagnosis of 20 cancers in 18 women. The overall per-patient biopsy yield was 23%, and the overall cancer yield was 3%. To estimate the cancer yields and biopsy yields for each modality as if it were deployed as part of the screening regimen, patients with actionable findings on the blinded read were observed through the interpretation process to determine how many women biopsied or diagnosed with cancer had the biopsied lesion identified as an actionable finding on the initial blinded read. The final consensus assessments for each patient that were associated with an actionable blinded assessment (BIRADS of 0, 3, 4, or 5) by modality, the number of those women who underwent biopsy, and the corresponding number of women with a resultant cancer diagnosis are listed in Table 2. Table 3 lists the estimated sensitivity, specificity, biopsy yields, and cancer yields by modality if each modality were used independent of each other.

Table 4 lists the characteristics of the 20 cancer lesions found in 18 women. In total, there were 11 invasive cancers detected in 11 patients and nine DCIS lesions detected in seven patients. A single patient had three DCIS lesions diagnosed. The histology, lesion size, and nodal status of the 20 cancers are listed in Table 4. Note that several cancers were only detected on one imaging modality (FSM, n = 2; DM, n = 3; WBUS, n = 1; and MRI, n = 8).

DISCUSSION

Our prospective multimodality screening study of 609 high-risk patients consisting of FSM, DM, MRI, and WBUS resulted in detection of 20 cancers in 18 patients. The unique blinded, unblinded, and consensus reading paradigm simulated the clinical process of screening followed by diagnosis and thus provides strong insight into modality performance in clinical context. Although at the time of enrollment the patients in our study had no unresolved suspicious findings on clinical breast examination and had a negative or resolved screening mammogram within 6 months of study entry, reinterpretation of the FSM resulted in upgrading findings in three participants and findings not called on the outside study in three participants that ultimately led to a diagnosis of cancer. The modest reproducibility of mammography interpretations is well known.[6,7] Although compliance with biopsy recommendations was based on the discretion of the primary care clinician, most patients with final consensus assessments of 4 or higher underwent biopsy. The relatively large number of MRI lesions that seem to not have undergone biopsy are primary related to nonvisualization at the time of the biopsy scan. All of these patients were cancer free at 2 years of follow-up.

Our results confirm findings suggested in other previously published screening studies on high-risk populations.[8-18] The sensitivity of MRI was higher than that for mammography; however, this was not statistically significant in part because of the limited power to detect all but huge differences in sensitivity with modest numbers of cancers detected. However, even with our modest numbers of detected cancers, the sensitivity of MRI was significantly better than sonography ($P = .002$). The specificity for MRI was somewhat lower than for the other modalities, but this difference was in part mitigated by a reduction in the number of biopsies related to resolution of the finding at

Table 2. Modality and Pathology Findings (N = 609)

Modality	No. of Participants With Actionable Blinded Modality Assessment	No. of Actionable Consensus Scores in Participants With Final Modality Scores of 3, 4, or 5*			No. of Biopsies Performed on Participants With Consensus Scores of 3, 4, or 5*	No. of Participants With Cancer Found at Biopsy*	
		3	4	5		DCIS	CA
Film screen mammography	55	8	22	1	21	3	3
Digital mammography	72	20	21	1	20	4	3
MRI	129	41	57	4	48	3	9
Ultrasound	79	15	22	2	20	0	3

Abbreviations: DCIS, ductal carcinoma in situ; CA, cancer; MRI, magnetic resonance imaging.
*Actionable blinded mortality assessment = Breast Imaging Reporting and Data System rating of 3, 4, or 5.

Table 3. Sensitivity, Specificity, Biopsy Yield, and Cancer Yield by Modality

Modality	Sensitivity	Specificity	Biopsy Yield		Cancer Yield*	
			No. of Cancers/ No. of Biopsies	%	No. of Cancers/ No. of Participants Imaged	%
Film screen mammography	0.33	0.94	6/21	29	6/597	1.0
Digital mammography	0.39	0.91	7/20	35	7/569	1.2
MRI	0.71	0.79	12/48	25	12/571	2.1
Ultrasound	0.17	0.88	3/20	15	3/567	0.5

NOTE. This table assumes that a positive test is one with a Breast Imaging Reporting and Data System rating of 3, 4, or 5.
Abbreviation: MRI, magnetic resonance imaging.
*Some patients did not have all the tests as a result of contraindications, patient refusal, or logistical reasons.

the time of the biopsy scan. This supports the value of the biopsy scan as a short-term follow-up assessment.

Our data support the recommendations made by the American Cancer Society for MRI screening of women with greater than 20% to 25% lifetime risk for breast cancer.[19] Note that the overall cancer yield of FSM is underestimated in our study because women presented with nonactionable FSM. The FSM yield is reflective of rereading of the FSM. In addition, DM and FSM are expected to correlate, so that the overall DM yield would be higher than that which is estimated from this study if it were used in isolation. Therefore, our study reflects the incremental yield over a baseline FSM examination interpreted by a community radiologist.

On the basis of our results, the role of screening ultrasound is unclear. Although, the WBUS studies were performed by dedicated breast imagers in a university hospital, there was one cancer detected by ultrasound alone. Ultrasound had the lowest sensitivity and biopsy yield. Although American College of Radiology Imaging Network (ACRIN) 6666 clearly showed mammographically occult ultrasound-detected cancers, the positive predictive value was 8.9%.[4] In addition, the ACRIN trial did not have the benefit of MRI in the first round of screening. In addition, if screening WBUS studies are performed by radiologists, taking into consideration the time spent by the radiologist performing and interpreting the study, the cost of the ultrasound examination may be higher than for a contrast-enhanced MRI study.

Table 4. Characteristics of 20 Cancers in 18 Women

Participant No.	Histology	Grade	Size (mm)	Nodal Status	Modalities That Detected Malignancy	Final BIRADS Rating	Likelihood*	Breast Density†	Age (years)	Risk‡
1	Invasive ductal	NA	4	0	FSM	4	5	3	44	*BRCA1*
2	Invasive ductal	Low	5	0	DM, MRI	3	1	3	40	Gail
3	Invasive ductal	Low	NA	NA	MRI	5	90	2	63	Contralateral
4	Invasive ductal	Low	8	0	MRI	4	5	2	57	Gail
5	Invasive lobular	Moderate	5	0	MRI	4	10	2	50	Gail
6	Invasive ductal	Moderate	1.5	0	DM, MRI	4	50	2	36	*BRCA1*
7	Invasive ductal	Low	4	0	FSM, DM, MRI, US	5	95	3	43	Claus
8	Invasive ductal	Low	4	0	MRI	4	25	2	55	Contralateral
9	Invasive ductal	Moderate	25	0	US§	4	5	3	52	Contralateral
10	Invasive ductal	Moderate	22	0	MRI	4	5	2	61	Contralateral
11	Invasive lobular	NA	1	0	FSM, US, MRI	4	50	3	50	Gail
12	DCIS	Low	NA		MRI	4	10	3	49	LCIS
13	DCIS	Low	NA		FSM, DM	4	5	3	49	LCIS
14	DCIS	Low	NA		DM	4	5	3	49	LCIS
15	DCIS	High	NA		MRI	4	3	3	53	Contralateral
16	DCIS	Low	NA		FSM	4	20	3	28	Contralateral
17	DCIS	Moderate	NA		DM	4	5	3	28	*BRCA2*
18	DCIS	Moderate	NA		FSM, DM	4	10	3	62	LCIS
19	DCIS	High	NA		MRI	4	15	2	48	Contralateral
20	DCIS	Moderate	NA		DM	4	10	3	41	*BRCA2*

Abbreviations: BIRADS, Breast Imaging Reporting and Data System; NA, not available; FSM, film screen mammography; DM, digital mammography; MRI, magnetic resonance imaging; US, ultrasound; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ.
*Likelihood of malignancy based on consensus opinion expressed on a scale of 0% to 100%.
†Density was graded as follows: 1 = fatty, 2 = scattered fibroglandular densities, 3 = heterogeneously dense, and 4 = extremely dense.
‡Claus and Gail refer to whether lifetime risk percentages exceed 25%. Contralateral refers to patients with contralateral cancer. The patient's highest risk factor is listed.
§Patient 9 did not undergo MRI because of a contraindication.

The Digital Mammographic Imaging Screening Trial (DMIST), which compared the sensitivity of FSM with that of DM, found that DM was more sensitive in cancer detection in pre- or perimenopausal women, women with dense or extremely dense breasts, and women less than 50 years old.[3] In our group of women with screening-detected cancers, 39% of the women (seven of 18 women) had scattered fibroglandular density, and the remaining 61% (11 of 18 women) had dense breast tissue. Of the 20 individual cancers detected in our study, DM detected seven cancers, and FSM detected six cancers (Table 2). These results would be consistent with the DMIST findings; however, the increased cancer yield falls well below the yield provided by MRI. With the rapid growth in the number of centers offering DM, high-risk patients might be best served by having their mammogram performed using a digital system.

At this time, there are no randomized studies demonstrating that MRI improves survival by earlier detection; such a study would be expensive to undertake and would take years to complete if mortality was the end point. The study also would need to enroll a large number of patients to achieve statistical significance. The various screening MRI trials[8-18] have consistently showed high sensitivity of MRI in the detection of occult breast cancer. It is also noted that MRI was particularly effective in detecting invasive cancer, detecting cancer in nine of 10 patients with invasive cancer who were imaged with MRI and being the only modality to detect five invasive cancers.

In conclusion, our results, as well as the results of previously reported studies, support the use of MRI as a complement to mammography in high-risk populations. DM does not seem to be an alternative to MRI in this regard but may represent an alternative to FSM in these patients. The role of sonography in this population seems limited to patients with a contraindication to MRI.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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