Screening Women at High Risk for Breast Cancer with Mammography and Magnetic Resonance Imaging

Constance D. Lehman, M.D., Ph.D.[1]
Jeffrey D. Blume, Ph.D.[2]
Paul Weatherall, M.D.[3]
David Thickman, M.D.[4]
Nola Hylton, Ph.D.[5]
Ellen Warner, M.D.[6]
Etta Pisano, M.D.[7]
Stuart J. Schnitt, M.D.[8]
Constantine Gatsonis, Ph.D.[2]
Mitchell Schnall, M.D., Ph.D.[9]
for the International Breast MRI
Consortium Working Group

[1] Department of Radiology, University of Washington, Seattle Cancer Care Alliance, Seattle, Washington.

[2] Center for Statistical Sciences, Brown University, Providence, Rhode Island.

[3] Department of Radiology, University of Texas—Southwestern Medical Center, Dallas, Texas.

[4] Radiology Imaging Associates, Porter Adventist Hospital, Denver, Colorado.

[5] Magnetic Resonance Science Center, Department of Radiology, University of California, San Francisco, California.

[6] Division of Oncology, Department of Medicine, Sunnybrook and Women's College Health Sciences Center and University of Toronto, Toronto, Ontario, Canada.

[7] Department of Radiology, University of North Carolina—Chapel Hill, Chapel Hill, North Carolina.

[8] Department of Pathology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts.

[9] Department of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania.

BACKGROUND. The authors compared the performance of screening mammography versus magnetic resonance imaging (MRI) in women at genetically high risk for breast cancer.

METHODS. The authors conducted an international prospective study of screening mammography and MRI in asymptomatic, genetically high-risk women age $\geq$ 25 years. Women with a history of breast cancer were eligible for a contralateral screening if they had been diagnosed within 5 years or a bilateral screening if they had been diagnosed > 5 years previously. All examinations (MRI, mammography, and clinical breast examination [CBE]) were performed within 90 days of each other.

RESULTS. In total, 390 eligible women were enrolled by 13 sites, and 367 women completed all study examinations. Imaging evaluations recommended 38 biopsies, and 27 biopsies were performed, resulting in 4 cancers diagnosed for an overall 1.1% cancer yield (95% confidence interval [95%CI], 0.3–2.8%). MRI detected all four cancers, whereas mammography detected one cancer. The diagnostic yield of mammography was 0.3% (95%CI, 0.01–1.5%). The yield of cancer by MRI alone was 0.8% (95%CI, − 0.3–2.0%). The biopsy recommendation rates for MRI and mammography were 8.5% (95%CI, 5.8–11.8%) and 2.2% (95%CI, 0.1–4.3%).

CONCLUSIONS. Screening MRI in high-risk women was capable of detecting mammographically and clinically occult breast cancer. Screening MRI resulted in 22 of 367 of women (6%) who had negative mammogram and negative CBE examinations undergoing biopsy, resulting in 3 additional cancers detected. MRI also resulted in 19 (5%) false-positive outcomes, which resulted in benign biopsies. *Cancer* 2005;103:1898–905. © 2005 American Cancer Society.

KEYWORDS: breast cancer, magnetic resonance imaging, screening, high risk.

Several risk factors for breast cancer have been identified, and testing for mutations in *BRCA1* and *BRCA2* is now available at multiple centers around the world. However, the impact of this information on patient management remains unclear. There are no studies that have demonstrated the risk reduction of prophylactic mastectomy in women who are at high risk for breast cancer, and the exact impact of chemoprevention in these patients is uncertain. Most experts suggest aggressive surveillance, consisting of a mammogram and physical examination every 6–12 months beginning between ages 25 years and 35 years. However, no data exist to indicate that such aggressive mammographic screening of this population has any effect on breast cancer mortality.

Screening film mammography and full-field digital mammography are the only imaging tools that explicitly have been approved for breast cancer screening by the United States Food and Drug Administration. However, both tools have difficulty detecting cancer in radiographically dense breast tissue. Women who are at high risk tend to develop cancer at a younger age, making mammographic screening more difficult due to the increased breast density in young women. Prior studies of magnetic resonance imaging (MRI) as a breast cancer screening technique in women who are at increased risk for breast cancer have reported higher sensitivity for breast MRI than for mammography and/or ultrasound.[1–6] However, the increased rate of biopsy and the additional cancer yield of MRI over mammography varied widely in prior studies.

The objective of this multicenter, international study was to determine the feasibility of using MRI to screen high-risk patients for breast cancer, including determining whether imaging and biopsy procedures are reliable and ensuring that the proposed interpretation criteria do not result in excessive false-positive examinations. In addition, the specific objective of this study was to estimate and compare the diagnostic yield and positive predictive value (PPV) of breast MRI versus mammography and clinical breast examination (CBE) in women who were at high risk for developing breast cancer.

MATERIALS AND METHODS
The International Breast MRI Consortium
This study was conducted by the International Breast MRI Consortium (IBMC), which was developed and supported by the National Cancer Institute and the Office of Women's Health to evaluate the role of MRI in breast cancer (Mitchell Schnall, principal investigator). Since its inception, the consortium has conducted two large, multicenter studies. Research insti-

tutions as well as community hospitals and clinics from the United States, Canada, and Europe participate.

Study Participants
Thirteen facilities located in the United States and Canada participated in this IBMC study. All facilities obtained approval to participate from their Institutional Review Boards, and written informed consent was obtained from all participants prior to entering into the study. Women were deemed eligible to participate in the study if they were age ≥ 25 years and had a lifetime risk of breast cancer $> 25\%$ based on family history or genetic test confirmation. Women without genetic testing confirmation had their risk assessed using the models published by Claus et al., Gail et al., Couch, or Berry et al.[7–10] Women who had a prior history of breast cancer diagnosis within 5 years of the entry date were eligible to participate by having their contralateral breast screened. Women who had received a breast cancer diagnosis that was > 5 years prior to study entry were eligible for bilateral screening provided that they had a probability of $> 50\%$ for breast cancer based on the study risk algorithm or that they had tested positive for a mutation in *BRCA1* or *BRCA2*.

Women who had contraindications to MRI examinations were excluded from the study. These contraindications included pregnancy, pacemaker, magnetic aneurysm clip or other implanted magnetic device, or severe claustrophobia. Because this was a screening trial, women who presented with palpable lesions or mammographic abnormalities prior to risk assessment were not eligible to participate.

Data Collection
All participating facilities collected data using study forms and submitted their data as web entries to the American College of Radiology (ACR). Quality-control procedures included review of each submission to identify critical missing forms or data. The ACR provided routine reports to each participating institution to identify patients with missing information and to clarify inconsistencies in information.

Clinical history.
Demographic information and a thorough medical history were collected, including hormonal medications, family and personal history of breast disease, family and personal history of other cancers, obstetric history, phase of menstrual cycle, and results of prior breast cancer screening.

Examinations.

All patients received a CBE, mammogram, and MRI examination as part of the study. Study protocol specified that both the mammogram and the CBE had to be performed within 90 days of the MRI examination.

The MRI scan protocol parameters included precontrast sagittal T2 (4000/80; 256 × 256) fast spin-echo images with fat suppression and both precontrast and postcontrast sagittal T1 (TR ≤ 50/TE ≤ 4.5; 256 × 128 × 32–60) three-dimensional, gradient-echo images with a 60-degree flip angle. The field of view was restricted to 16–18 cm, depending on patient size, and slices measured ≤ 3 mm in thickness. T1 images were acquired prior to and immediately after bolus injection of contrast.

The MRI and mammogram initially were interpreted without knowledge of the results of the other modality at the host institution. Separate MRI and mammogram readers were assigned for each institution to ensure blinded readings. All mammograms were coded according to the ACR Breast Imaging Reporting and Data Systems (BI-RADS™) lexicon, including breast composition, findings, and overall assessment. The overall assessment was performed according to a 5-point scale, as indicated in the ACR BI-RADS lexicon[11] (1, negative; 2, benign; 3, probably benign; 4, suspicious abnormality; and 5, highly suggestive of malignancy).

Any suspicious MRI enhancing lesions were described based on lesion shape, borders, distribution, and internal architecture. The overall MRI assessment was classified on a 5-point scale (1, negative; 2, benign; 3, probably benign; 4, suspicious abnormality; and 5, highly suggestive of malignancy). A lesion was identified as malignant if there was a focal mass with irregular or spiculated margins, if enhancement was in a ductal distribution, if a solid lesion showed rim enhancement, or if there was intense regional enhancement in less than one quadrant. Benign lesions were identified as those that had smooth or lobulated margins with internal septations or if the mass was cystic.

All lesions that were given an assessment score of 4 or 5 on either mammography or MRI were recommended for biopsy. A retrospective review also was performed that included all images (MRIs and mammograms) from patients who had cancers that were diagnosed during the study.

Pathology

All core-needle and excisional breast biopsies were conducted and processed according to routine at the referent institution. Pathology reports and represen-tative slides from biopsies were sent to the study pathologist (S.J.S.) to verify the diagnosis. The study pathologist completed pathology result forms that were submitted to the ACR for inclusion in the study data base. For 8 of 27 biopsies (31%), slides were not available for central pathology review. For these patients, the information from the original pathology report was used.

Statistical Methods

Data were analyzed at the Center for Statistical Sciences at Brown University, which served as the biostatistics center for all IBMC trials. Data were monitored prospectively and were cleaned in a collaborative effort with IBMC data management located at the ACR. SAS software (version 8.0) and Stata software (version 7.0) were used to process data and to facilitate statistical analyses.

From these data, call-back rates, PPVs, and cancer yield by MRI and by mammography were estimated. For the purposes of estimating predictive value, MRI and mammography interpretations were dichotomized with scores of 1, 2, or 3 as negative for disease and scores of 4 or 5 as positive for disease. Exact confidence intervals were computed for dichotomized test performance. Invasive carcinoma or ductal carcinoma in situ (DCIS) were classified as malignant, and all others were classified as not malignant. When comparing these rates, the natural matching of the study design introduced correlation into that comparison and was accounted for by using a McNemar test and by inverting the test to produce appropriate confidence intervals. Because of this matching, modality comparisons did not require any adjustment for covariates.

RESULTS

Between July, 1999 and January, 2002, 390 eligible women were enrolled into the study. Twenty-three patients were excluded from the analyses for the following reasons: The mammogram was not performed, or the mammogram report or films were unavailable (*n* = 14 patients); the patient withdrew from study before imaging was complete (*n* = 2 patients); or the contrast-enhanced MRI not completed or results were not available (*n* = 7 patients). Thus, data from a total of 367 women were evaluated in this study. Table 1 presents the characteristics of eligible and analyzed women. The distribution of characteristics among the analyzable participants was almost identical to the distribution of characteristics among all eligible women, indicating a lack of bias by excluding participants with missing data.

Thirty-eight positive assessments for cancer oc-

TABLE 1
Patient Characteristics

| Characteristic | No. of patients (%) | |
	All eligible women (*n* = 390)	Women included in the analysis set (*n* = 367)
Age in yrs (mean ± SD)	45.0 ± 9.7	45.0 ± 9.7
Menopausal status		
Premenopausal	193 (49.5)	180 (49.1)
Surgical menopause	92 (23.6)	88 (24.0)
Postmenopause	68 (17.4)	65 (17.7)
Perimenopause	33 (8.5)	32 (8.7)
History of hormone use	231 (59.2)	215 (58.6)
Breast density		
Mostly fat (< 10% density)	25 (6.4)	24 (6.5)
Scattered fibroglandular tissue (11–50% density)	112 (28.7)	111 (30.3)
Heterogeneously dense (51–90% density)	177 (45.4)	174 (47.4)
Extremely dense (> 90% density)	57 (14.6)	56 (15.3)
Prior benign biopsy	147 (37.7)	142 (38.7)
Prior diagnosis of breast cancer	39 (10.0)	38 (10.4)

SD: standard deviation.

TABLE 2
Findings from 27 Biopsies Conducted as a Result of Positive Examinations[a]

Biopsy findings	Positive on mammography only[b]	Positive on MRI only[b]	Positive on both mammography and MRI
Benign	2	19	0
ADH or LCIS	1	1	0
Malignant lesions			
DCIS	0	1	0
Invasive	0	2	1

MRI: magnetic resonance imaging; ADH: atypical ductal hyperplasia; LCIS: lobular carcinoma in situ; DCIS: ductal carcinoma in situ.

[a] Eleven women who had positive examinations on either mammogram or MRI did not undergo biopsies.

[b] Examinations that resulted in a Breast Imaging Reporting and Data Systems assessment of 4 or 5 were considered positive.

curred on either MRI or mammography among the 367 women who comprised the analysis data set. Of these, 30 women had assessments that were positive only on MRI, 7 women had assessments that were positive only on mammography, and 1 woman had assessments that were positive both on MRI and on mammography. Although the study protocol called for a biopsy in all patients who had a positive examination, fine-needle aspiration revealed that two lesions were cysts, so those two women did not undergo tissue sampling. An additional 9 women did not undergo biopsy after positive findings, including 6 women who had BI-RADS 4 assessments on MRI (with negative, benign, or probably benign mammograms) and 3 women who had BI-RADS 4 assessments on mammography (with negative, benign, or probably benign assessments on MRI). For one of the six women who had positive MRI assessments, the lesion did not persist on subsequent MRI examination, and the biopsy was cancelled. For the other five women, the biopsy was declined by the patient and/or her physician based on benign mammography or ultrasound findings or based on patient preference to follow rather than biopsy the suspicious region. For the three women who had positive mammograms who did not undergo biopsy, one woman declined biopsy based on a benign ultrasound evaluation of the area, and two women declined based on a probably benign MRI assessment.

Table 2 presents the findings from the 27 biopsies that were conducted as a result of a positive examination. Eleven of 27 biopsies were performed under MRI guidance (7 wire localizations and 4 core-needle biopsies), 9 biopsies were performed under ultrasound guidance (1 wire localization and 8 core-needle biopsies), and 3 biopsies were performed under mammographic guidance (2 wire localizations and 1 core-needle biopsy). The specific imaging technique used to guide the biopsy was not reported in four patients. Four of the 27 lesions biopsied were diagnosed as malignant, and 23 lesions were diagnosed as either benign, atypical ductal hyperplasia (by exicisonal biopsy), or lobular carcinoma in situ.

All four women with malignant lesions had positive MRI examinations, whereas only one of those four lesions was detected by mammography. MRI also resulted in 20 false-positive findings, compared with 3 false-positive mammograms that resulted in the recommendation and receipt of a biopsy.

Table 3 presents the characteristics of the patients who had lesions that were identified as malignant in this study. Two of the lesions were found in women with scattered fibroglandular density, and two were identified in women with heterogeneously dense breast tissue (Fig. 1). Three of the 4 lesions were identified as infiltrating ductal carcinomas, ranging in size from 5 mm to 13 mm, and 1 lesion was DCIS. All women were lymph node negative, and none had metastases.

MRI and mammography provided concordant results in 330 of the 367 (90%) women (Table 4). Most discrepant assessments resulted from a positive MRI and a negative mammogram (30 assessments; 8.2%).

Although the biopsy recommendation rate for

TABLE 3
Characteristics of the Tumors Detected

Patient	Characteristics			Examination results[a]		MRI findings		Pathology results				
	Age (yrs)	Menopausal status	Breast density	Mamm	MRI	Enhancement	Margin	Shape	Rim	Histology	Size (mm)	TNM status
1	58	Surgical	Scattered	1	4	Focal	Irregular	Round	−	IDC	5.0	T1N0M0
2	37	Pre	Heterog.	1	5	Focal	Spiculated	Irregular	+	IDC	13.0	T1N0M0
3	66	Post	Scattered	5	5	Focal	Irregular	Irregular	+	IDC	10.0	T1N0M0
4	50	Surgical	Heterog.	1	4	Focal	Spiculated	Stellate	−	DCIS	NA	TisN0M0

MRI: magnetic resonance imaging; Mamm: mammography; TNM: tumor, lymph node, metastasis classification; −: negative; IDC: infiltrating ductal carcinoma; Pre: premenopausal; Heterog: heterogeneous; +: positive; Post: postmenopausal; DCIS: ductal carcinoma in situ; NA: not available.
[a] Examination results are reported according to Breast Imaging Reporting and Data Systems assessment.

MRI was higher compared with the rate for mammography (MRI: 8.5%; 95% confidence interval [95%CI], 5.8–11.8%; mammography: 2.2%; 95%CI, 0.1–4.3%), both examinations had similar PPVs (MRI: 12.9%; 95%CI, 3.6–30%; mammography: 12.5%; 95%CI, 0.3–52.7%).

Results from the biopsies performed and the cancer yield based on MRI and mammography are summarized in Table 5. Twenty-four of 367 women underwent biopsy based on a positive MRI, whereas 4 of 367 women (1.1%) underwent biopsy based on a positive mammogram. MRI had a total cancer yield of 1.1% (95%CI, 0.3–2.8%), whereas mammography had a total cancer yield of 0.3% (95%CI, 0.01–.5%). The additional cancer yield of MRI was 0.8% (95%CI, from − 0.3% to 2.0%) and was not statistically significant due to the small number of observed cancers. Mammography did not detect any cancers that were not found on MRI. A review of the mammograms from the three women who had MRI-only detected cancer demonstrated that the mammograms were of high quality and that the cancers were not visible on the mammograms in retrospect.

DISCUSSION

To our knowledge, this is the first multicenter, international study of screening MRI in women at high risk for breast cancer. By screening 367 women with mammography and MRI, we detected 4 breast cancers. All four cancers were identified by MRI, and only one cancer was identified by mammography. Our results are similar to findings from prior studies that demonstrated an improved cancer yield for MRI compared with mammography in women at high risk for breast cancer (Table 6). Twenty-three of 367 women (6.3%) in the current study were recommended for biopsy based on MRI, and the PPV of biopsies performed was

17%. The percentage of women recommended for biopsy (6.3%) was similar to that in prior studies, although the range in prior studies was wide (from 2.9% to 15.8%) as was the range of the PPV of biopsies (from 24% to 89%). Like prior studies, the benefit of added cancer yield in the current study was associated with a higher false-positive rate for MRI compared with mammography.

Because mammography is the current standard for screening in this patient population, it is important to determine the added cancer yield of MRI. In the current study, 3 of 367 women (0.8%) had cancer diagnosed by MRI after they had a negative screening mammogram. This added cancer yield from MRI alone is similar to the 2004 study by Kriege et al. of 1909 women at high risk which identified cancer by MRI alone in 1.2% of women screened.[6] Both yields are somewhat lower than those reported by prior single-site studies. However, prior pilot studies were small, and the estimated yields from most studies were contained within intervals of other studies, indicating no statistical differences in the reported yields. Overall, current studies report an average added cancer yield of 3.3%, with confidence intervals ranging across studies from 0.3% to 4.4% and up to 2.7–13.3%.

There are other possible explanations for the lower average cancer yield found in the current study compared with prior studies. Biopsies were not performed in 11 patients who were recommended for tissue sampling in the current study. It is possible that some of these patients have as yet undiagnosed cancers. Eight patients did not undergo biopsy, because the patient or referring clinician felt that the biopsy was not necessary after other imaging results were benign. For example, in two patients, although the MRI results were suspicious, subsequent negative ultrasound studies led to a decision by the patients and
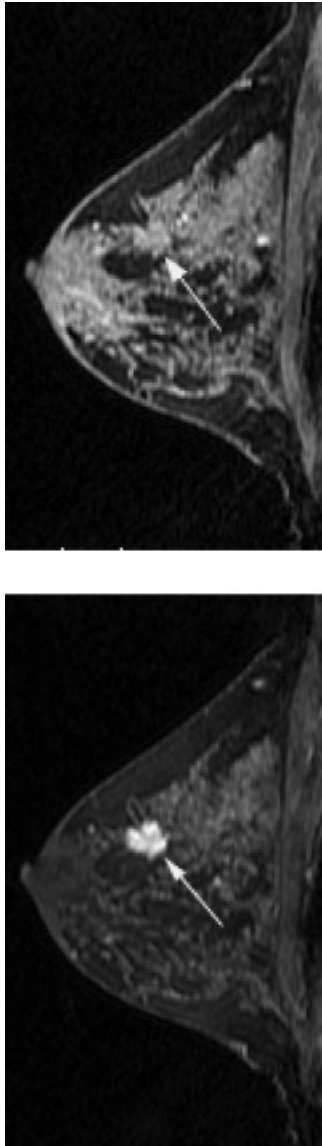
FIGURE 1. Sagittal pre-T2 (Top) and postcontrast T1 (Bottom) images from a patient with a negative, heterogeneously dense mammogram that demonstrated a 1.3-cm, irregular, enhancing mass with spiculated margins (arrows). Targeted ultrasound to this region of the breast demonstrated a solid mass that was biopsied and proven to be infiltrating ductal carcinoma.

TABLE 4
Comparison of Magnetic Resonance Imaging and Mammographic Assessments

MRI impression	No. (%): Mammographic impression		
	Negative	Positive	Total
Negative	329 (89.7)	7 (1.9)	336 (91.6)
Positive	30 (8.2)	1 (0.3)	31 (8.5)
Total	359 (97.8)	8 (2.2)	367 (100.0)

MRI: magnetic resonance imaging.

TABLE 5
Biopsies Performed Based on Mammography and Magnetic Resonance Imaging

Examination	No. (%)			
	Biopsies performed	PPV of biopsies performed	Total cancer yield	Additional cancer yield[a]
MRI	24/367 (6.5)	4/24 (17)	4/367 (1.1)	3/367 (0.8)
Mammography	4/367 (1.1)	1/4 (25.0)	1/367 (0.3)	0/367 (0.0)

PPV: positive predictive value; MRI: magnetic resonance imaging.

[a] Additional yield was defined as all cancers that were detected by the examination that were not detected by the other examination.

referring clinicians to decline the recommended biopsy. It is possible that there were fewer cancers in our patient population; in addition, it is possible that the patients who were included in our study were at lower risk compared with the patients in prior studies. In the 2004 study by Kriege et al., the group of women who were at highest risk (those who were known mutation carriers) had significantly higher rates of cancer detected compared with women who were at high risk or moderate risk who were not known mutation carriers.[6]

There are limitations to our study. This was a pilot study with no long-term follow-up of patients to identify potential false-negative MRI results or delayed diagnoses when biopsies were declined. In addition, only a single round of screening with mammography and MRI was performed in the study. Thus, we do not have data to guide appropriate intervals if MRI is used to complement mammography in screening women at high risk. We do not have detailed information on prior screening with MRI or mammography. It is possible that our lower cancer yield was secondary to our patients' screening history.

Although no cancers were missed by MRI in our study, prior reports have identified cancers through mammography that were not identified by MRI. Thus, we do not recommend MRI as a replacement for mammography but as a complement. A negative MRI should not overrule a recommendation for biopsy based on a suspicious mammogram. There are few studies to provide guidelines for screening intervals in high-risk populations. At this time, most centers that perform high-risk screening with MRI and mammography perform both examinations annually. At some centers, the annual mammogram and the MRI are separated by 6 months. There also is sparse information regarding the optimal age at which to begin high-

TABLE 6
Comparative Sensitivity of Screening Mammography, Ultrasound, and Magnetic Resonance Imaging in Women at Increased Risk for Breast Cancer

Study site (reference)	Study design	Follow-up (mos)	Mean age in yrs (range)	Cancers detected (%) (no. detected/screened)	Sensitivity (%) Mammography	Sensitivity (%) MRI	Sensitivity (%) US	Cancer yield from MRI alone No. (%)	Cancer yield from MRI alone CI (%)[a]	No. of biopsies recommended as a result of MRI (%)	PPV of biopsies performed based on MRI (%)
Germany (Kuhl et al., 2000[1])	P	12	39 (18–65)	4.7 (9/192)	33 (3/9)	100 (9/9)	33 (3/9)	6/192 (3.0)	0.9–6.0	14/192 (7.3)	64
Canada (Warner et al., 2004[2])	P	36	47 (26–65)	9.3 (22/236)	36 (8/22)	77 (17/22)	33 (7/21)	7/236 (3.0)[b]	1.7–7.1	37/236 (15.7)	46
Italy (Podo et al., 2002[3])	P	24	46 (25–77)	7.6 (8/105)	13 (1/8)	100 (8/8)	13 (1/8)	7/105 (6.7)	2.7–13.3	9/105 (8.6)	89
The Netherlands (Tilanus-Linthorst et al., 2000[4])	P	12	42 (22–68)	2.8 (3/109)	0 (0/0)	100 (3/3)	—	3/109 (2.8)	0.6–7.8	5/109 (4.6)	60
United States (Morris et al., 2003[5])	R	None	50[c] (23–82)	3.8 (14/367)	0 (0/0)[d]	100 (14/14)	—	14/367 (3.8)	2.1–6.3	59/367 (15.8)	24
The Netherlands (Kriege et al., 2004[6])	P	33	40 (19–72)	2.4 (45/1909)	40 (18/45)	71 (32/45)	—	22/1909 (2.2)	1.1–2.4	56/1909 (2.9)	57
Current study	P	None	45 (26–86)	1.1 (4/367)	25 (1/4)	100 (4/4)	—	3/367 (0.8)	0.2–2.4	23/367 (6.3)	17

MRI: magnetic resonance imaging; US: ultrasound; CI: confidence interval; PPV: positive predictive value; P: prospective study design; R: retrospective study design.
[a] Exact binomial CI.
[b] One patient who had only an MRI-detected cancer in this study did not receive US.
[c] Reported median.
[d] To be included in this study, women had to have a negative mammogram.

risk screening. Currently, most programs initiate screening at age 25 years, because this group is at high risk for early breast cancers. In our study, the youngest patient was diagnosed with invasive carcinoma at age 37 years, and the oldest was diagnosed at age 66 years.

In this study, we demonstrated that a multisite international screening MRI study of this patient population was feasible. Over a period of 2.5 years, 13 sites performed MRIs and collected data from 390 women who were at high risk for breast cancer. Although the specificity of MRI has been challenged, in our study, we found that only 5% of women underwent benign biopsy, and the PPV of biopsies performed was 17%. The study results underscore the importance of long-term follow-up in future studies to address the potential of false-negative MRI results, false-negative biopsies, and delayed diagnoses when recommended biopsies are declined.

In conclusion, it is reasonable to consider MRI as a complement to mammography in screening patients who are at high risk for breast cancer. MRI can detect mammographically occult breast cancers in women at high risk, as reported in prior studies. Although 75% of the cancers detected in the current study were occult on mammography, the overall yield of breast cancer by MRI still was relatively low. However, the 3 patients who were diagnosed by MRI alone among 367 patients (0.8%) is approximately 10-fold the yield of cancers diagnosed in women at average risk who underwent screening mammography,[12] an accepted screening tool that has reduced breast cancer mortality in that patient population. The current findings support the recent suggestion by the American Cancer Society that women at high risk for breast cancer discuss with their health care provider the potential benefits and risks of MRI as a complement to screening mammography.[13] Our results support the benefit of MRI in detecting mammographically occult cancers and find that the risk of undergoing a benign biopsy is ≈ 5% in high-risk women.

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