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ORIGINAL REPORT

Triple-Modality Screening Trial for Familial Breast Cancer Underlines the Importance of Magnetic Resonance Imaging and Questions the Role of Mammography and Ultrasound Regardless of Patient Mutation Status, Age, and Breast Density

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
To evaluate the breast cancer screening efficacy of mammography, ultrasound, and magnetic resonance imaging (MRI) in a high-risk population and in various population subgroups.

Patients and Methods
In a single-center, prospective, nonrandomized comparison study, *BRCA* mutation carriers and women with a high familial risk (> 20% lifetime risk) for breast cancer were offered screening with mammography, ultrasound, and MRI every 12 months. Diagnostic performance was compared between individual modalities and their combinations. Further comparisons were based on subpopulations dichotomized by screening rounds, mutation status, age, and breast density.

Results
There were 559 women with 1,365 complete imaging rounds included in this study. The sensitivity of MRI (90.0%) was significantly higher ($P < .001$) than that of mammography (37.5%) and ultrasound (37.5%). Of 40 cancers, 18 (45.0%) were detected by MRI alone. Two cancers were found by mammography alone (a ductal carcinoma in situ [DCIS] with microinvasion and a DCIS with < 10-mm invasive areas). This did not lead to a significant increase of sensitivity compared with using MRI alone ($P = .15$). No cancers were detected by ultrasound alone. Similarly, of 14 DCISs, all were detected by MRI, whereas mammography and ultrasound each detected five DCISs (35.7%). Age, mutation status, and breast density had no influence on the sensitivity of MRI and did not affect the superiority of MRI over mammography and ultrasound.

Conclusion
MRI allows early detection of familial breast cancer regardless of patient age, breast density, or risk status. The added value of mammography is limited, and there is no added value of ultrasound in women undergoing MRI for screening.

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INTRODUCTION

Women with an inherited predisposition for breast cancer face a lifetime risk of 56% to 84% for developing the disease.[1,2] The management of women at such a risk presents a challenge to physicians. Despite the significant risk reduction that can be achieved by prophylactic bilateral mastectomy, the majority of women opt for intensified radiologic surveillance.[3] Currently, intensified breast cancer screening for women at high risk for the disease is being offered in the majority of developed countries. However, the regimens of the various screening programs differ widely.[4-13]

The triple-modality approach, which includes mammography, ultrasound, and magnetic resonance imaging, yields the highest detection rates but also has higher false-positive rates and costs.[6,8,9,11-14] Thus, the risks and benefits of each modality have to be carefully investigated and compared. The following systematic intraindividual comparative cohort study was designed to evaluate the various modalities alone and in combination. Preliminary results have been published previously.[11] Here, we publish

the final results. In addition to risk stratification, other characteristics, such as age and breast density, have been proposed to determine eligibility for MRI screening.[15] We analyzed various subpopulations of our cohort to search for patient characteristics and risk factors that may influence the accuracy and, therefore, the value of the various imaging modalities.

PATIENTS AND METHODS

This single-center, prospective, nonrandomized comparison study was reviewed and approved by the ethics committee of our institution.

Recruitment

Starting in 1999, women with a *BRCA1* or *BRCA2* mutation were recruited for this study.[11] From January 2002 until the end of the study in May 2011, we also included patients whose lifetime risk of developing breast cancer exceeded 20%, based on family history criteria[7] (summarized together with the exclusion criteria in the Appendix and Appendix Table A1, online only). All participating women gave written informed consent before entering the study.

Study Protocol

Screening rounds consisting of mammography, ultrasound, and MRI of the breast were performed every 12 months, with a maximum interval of 1 month between various modalities. Incomplete annual imaging rounds (ie, one or more of the three imaging modalities was not done) were not included for analysis. In addition to the annual triple-modality screening rounds, ultrasound examinations were offered every 6 months to *BRCA* mutation carriers. All imaging studies were interpreted by one of two radiologists with at least 6 years of reading experience, who were unaware of the results of the other screening modalities.

Mammography

Two-view mammograms (mediolateral oblique and craniocaudal) were performed using various mammography systems. Suspicion of malignancy was scored according to the American College of Radiology (ACR) Breast Imaging and Reporting Data System (BI-RADS) categories.[16] Breast density was evaluated according to the ACR breast composition classification, with densities ranging from ACR grade 1 (< 25% glandular tissue) to ACR grade 4 (> 75% glandular tissue).[16,17]

Ultrasound

Ultrasound of the breast was performed using various ultrasound systems. Until 2004, imaging reports were assessed according to a five-category scale modeled on the mammographic ACR BI-RADS categories. After 2004, reports were assessed according to the ultrasound edition of the ACR BI-RADS atlas.[18,17]

MRI

Until September 2008, MRI of the breast was performed on a 1.0-T scanner with a dedicated breast coil (Gyroscan T10-NT; Philips, Amsterdam, the Netherlands). Thereafter, a 1.5-T MRI scanner MAGNETOM Avanto (Siemens, Berlin, Germany) was used. Details concerning the MRI sequence protocol are summarized in the Appendix. To minimize hormone-related background breast tissue enhancement, premenopausal women were scheduled on the seventh to fourteenth day of their menstrual cycle.[19] Morphology and enhancement kinetics criteria were used to distinguish between benign and malignant lesions.[17,20] Until 2004, results were categorized according to the mammographic BI-RADS system, and thereafter, they were categorized according to the ACR BI-RADS atlas.[17]

Final Diagnosis and Follow-Up

Patients with benign imaging findings in all modalities (ie, BI-RADS category 1 or 2) were confirmed if no interval cancer occurred before the next imaging follow-up. For patients without imaging follow-up, the database was reviewed for patient history (eg, mastectomy or death). When no history was available, patients or their relatives were contacted through a telephone survey to determine their health status. If no follow-up was available, benign imaging was confirmed if no cancer was detected by the other imaging modalities. In case of a probably benign finding (BI-RADS category 3), 6-month follow-up screens were ordered until the lesion was categorized as either benign or suspicious.[21] If one or more of the three imaging modalities resulted in a suspicious finding (ie, BI-RADS category 4 or 5), biopsy was performed.[22,23]

Data Analysis

Pathology results were grouped into malignant (in situ, invasive, and metastatic cancer) and benign lesions (all other histopathologic findings). Benign lesions representing atypical ductal hyperplasia (ADH), and the modalities with which they were detected, were recorded. The cancer yield was calculated as the ratio between the number of cancers and the number of screening rounds.[6] Interval cancers were defined as cancers detected within 12 months after a screening round that was negative for malignancy.[24] The interval cancer rate was calculated as the ratio between the number of interval cancers and the number of complete screening rounds with follow-up of at least 1 year. The diagnostic performance parameters of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the three surveillance modalities and their combinations.

To explore additional patient characteristics, in addition to the hereditary risk factor, for the selection of women for screening with MRI, the data set was divided into pairs of complementary subgroups using the following criteria: number of screening rounds: first screening round versus subsequent screening rounds; mutation status: *BRCA1/2* mutation carriers versus non–mutation carriers (wild types and unclassified variants in *BRCA1* or *BRCA2*); age: women ≤ versus > 50 years old; and breast density: women with low breast density (ACR breast composition grades 1 and 2) versus high breast density (ACR grades 3 and 4). The diagnostic performance parameters (sensitivity, specificity, PPV, and NPV) were calculated for each screening modality in all complementary subgroups.

The diagnostic performance parameters of MRI were compared with those of mammography and ultrasound, as well as with the various combinations of modalities. Further, diagnostic performance parameters were compared between the three modalities within each subgroup. Finally, diagnostic performance parameters of each modality were compared between complementary subgroups. For details on the statistical analysis, see the Appendix.

RESULTS

Patient Population

There were 559 women, 22 to 83 years of age (median age, 44 years), who met the inclusion criteria. Of these, 156 patients (28%) were *BRCA1/2* mutation carriers (Table 1). Of a total of 1,506 annual surveillance rounds, 141 (10%) were incomplete, either for technical problems or because of a lack of patient compliance. Thus, the 559 women underwent 1,365 complete imaging rounds, with an average of 2.45 rounds per woman (for details on screening attendance, see the Appendix).

Table 1. Mutation Characteristics of 559 Women Under Surveillance Because of a High Risk for Breast Cancer

Mutation Status	Patients		Age (years)		
	No.	%	Range	Median	Mean
Total	559		22-83	42	50
BRCA1/2 positive	156	28	22-80	39	41
BRCA1	115	21	22-80	38	41
BRCA2	41	7	23-76	40	42
No *BRCA* mutation	297	53	23-83	42	43
Unclassified variant	184	33	23-67	42	43
Wild type	113	20	23-83	43	44
Incomplete genetic records	106	19	23-74	42	42

Of the 559 women, 239 (43%) were followed up at our hospital after the trial. One breast cancer that developed within the first year of this follow-up was considered an interval cancer (patient 40 in Table 2). Of the further 146 patients (26%) reached in a telephone survey, none developed breast cancer within the screening period. Of the remaining 174 patients (31%) without follow-up, 53 patients (9.5%) had bilateral mastectomies and ceased their study participation, 14 patients (2.5%) died during the study, and 107 patients (19%) were lost to follow-up.

Breast Cancers

There were 204 (15%) suspicious imaging findings (BI-RADS category 4 and 5) reported in 1,365 complete screening rounds. Of these, 38 (19%) proved to be malignant. Two additional cancers were found during the study period, one BI-RADS 3 lesion at MRI that was biopsied at the patient's request and one interval cancer. Thus, the interval cancer rate was 0.1% (one in 1,191 surveillance rounds with follow-up). Detailed data on all the 40 carcinomas are listed in Table 2. The overall cancer yield decreased from 3.4% (19 cancers in 558 screenings) at the first screening rounds to 2.6% (20 cancers in 807 screenings) at the subsequent screening rounds ($P = .39$).

Diagnostic Imaging Performance

The sensitivity of MRI was 90% (36 of 40 cancers detected), which was significantly higher than the sensitivities of mammography and ultrasound, both with sensitivities of 38% (15 of 40 cancers detected), and the combination of both, with a sensitivity of 50% (20

Table 2. Summary of Surveillance Round, Imaging Results, and Tumor Stage of Detected Cancers

				BI-RADS Category				TNM Stage			
Patient No.	Age (years)	Mutation Status	Surveillance Round (No.)	US	MG	MRI	Histology	T	N	M	Tumor Grade
1	45	*BRCA2*	1	1	4	3	IDC	mic	0	0	3
2	34	UV	1	1	1	4	DCIS	is	0	0	2
3	55	UV	1	3	3	4	DCIS	is	0	0	2
4	38	*BRCA1*	1	4	4	4	DCIS	is	0	0	2
5	55	Unknown	1	4	4	5	DCIS	is	0	0	1
6	55	Unknown	1	4	4	5	DCIS	is	0	0	1
7	52	UV	1	4	1	4	DCIS	is	0	0	3
8	31	Unknown	1	1	1	4	DCIS	is	0	0	2
9	48	Wild type	1	1	4	4	DCIS	is	0	0	1
10	35	*BRCA1*	1	5	5	5	IDC	2	1b	0	3
11	42	*BRCA1*	1	1	1	4	IDC	1b	0	0	3
12	62	Unknown	1	1	1	4	IDC	1b	0	0	2
13	48	UV	1	1	1	5	IDC	2	0	0	3
14	41	Unknown	1	5	1	5	IDC	2	1a	0	2
15	66	Wild type	1	5	1	5	IDC	1c	0	0	2
16	43	Unknown	1	1	1	4	IDC	1b	0	0	1
17	63	Wild type	1	5	5	4	IDC	1c	0	0	2
18	53	*BRCA1*	1	1	1	3	IDC	1a	0	0	1
19	27	Unknown	1	5	5	5	Metastasis from ovarian cancer	NA	NA	NA	NA
20	49	UV	2	2	2	4	DCIS	is	0	0	1
21	41	*BRCA2*	2	1	1	4	IDC	mic	0	0	3
22	53	Wild type	2	1	1	4	DCIS	is	0	0	2
23	50	Wild type	2	1	1	4	DCIS	is	0	0	3
24	46	*BRCA2*	2	1	4	4	DCIS	is	0	0	2
25	36	*BRCA1*	2	4	4	5	IDC	1b	0	0	3
26	64	UV	2	2	1	4	IDC	1a	0	0	1
27	36	UV	3	1	1	4	IDC	mic	0	0	3
28	42	*BRCA2*	3	2	2	4	DCIS	is	0	0	2
29	43	UV	3	1	4	4	IDC	mic	0	0	3
30	42	*BRCA2*	3	2	2	4	IDC	1a	0	0	2
31	62	UV	3	4	4	4	IDC	1c	0	0	3
32	47	UV	3	4	1	4	IDC	1c	1a	0	2
33	32	*BRCA1*	3	1	1	4	IDC	1c	0	0	2
34	62	Wild type	3	1	4	3	Mucinous IDC recurrence	n/a	0	0	2
35	41	UV	4	2	2	4	IDC	1b	0	0	2
36	80	*BRCA2*	4	5	5	4	IDC	1c	0	0	3
37	43	*BRCA1*	4	5	5	5	Medullary carcinoma	2	0	0	3
38	48	*BRCA1*	5	2	2	4	IDC	1b	0	0	3
39	55	*BRCA1*	7	4	1	4	DCIS	is	0	0	3
40	38	*BRCA1*	5(interval)	2	2	1	Medullary carcinoma	1c	0	0	3

Abbreviations: BI-RADS, Breast Imaging and Reporting Data System; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; is, in situ; M, metastasis; MG, mammography; mic, microinvasion; MRI, magnetic resonance imaging; N, node status; NA, not applicable; T, tumor; US, ultrasound; UV, unclassified variant.

Table 3. Diagnostic Performance of the Three Screening Modalities Used Alone and in Combination

Screening Modality	Sensitivity*	P†	Specificity‡	P†	PPV	P†	NPV	P†
US								
No./total No.	15/40	< .001	1,284/1,325	< .001	15/56	.145	1,284/1,309	< .001
Rate, %	37.5		96.9		26.8		98.1	
95% CI	24.2 to 53.0		95.8 to 97.7		1.70 to 3.96		97.2 to 98.7	
MG								
No./total No.	15/40	< .001	1,287/1,325	< .001	15/53	.105	1,287/1,312	< .001
Rate, %	37.5		97.1		28.3		98.1	
95% CI	24.2 to 53.0		96.1 to 97.9		18.0 to 41.6		97.2 to 98.7	
MRI								
No./total No.	36/40	NA	1,178/1,325	NA	36/183	NA	1,178/1,182	NA
Rate, %	90.0		88.9		19.7		99.7	
95% CI	76.9 to 96.0		87.1 to 90.5		14.6 to 26.0		99.1 to 99.9	
US + MG								
No./total No.	20/40	< .001	1,268/1,325	< .001	20/77	.111	1,268/1,288	
Rate, %	50.0		95.7		26.0		98.4	< .001
95% CI	35.2 to 64.8		94.5 to 96.7		17.5 to 36.7		97.6 to 99.0	
US + MRI								
No./total No.	36/40	1.000	1,163/1,325	< .001	36/198	< .001	1,163/1,167	.075
Rate, %	90.0		87.8		18.2		99.7	
95% CI	76.9 to 96.0		85.9 to 89.4		13.4 to 24.1		99.1 to 99.9	
MG + MRI								
No./total No.	38/40	.148	1,168/1,325	< .001	38/195	.788	1,168/1,170	.161
Rate, %	95.0		88.2		19.5		99.8	
95% CI	83.5 to 98.6		86.3 to 89.8		14.5 to 25.6		99.4 to 100.0	
US + MG + MRI								
No./total No.	38/40	.148	1,159/1,325	< .001	38/204	.168	1,159/1,161	.165
Rate, %	95.0		87.5		18.6		99.8	
95% CI	83.5 to 98.6		85.6 to 89.1		13.9 to 24.5		99.4 to 100.0	

Abbreviations: MG, mammography; MRI, magnetic resonance imaging; NA, not applicable; NPV, negative predictive value; PPV, positive predictive value; US, ultrasound.
*Cancers detected.
†*P* values were calculated using the generalized estimating equation model and are presented for comparison of the diagnostic performance of each modality or combination of modalities with the diagnostic performance of MRI alone.
‡Cancer correctly not detected.

of 40 cancers detected; all $P < .001$). No cancer was detected by ultrasound alone. Two cancers (5%) were detected with mammography only, and 18 cancers (45%) were detected with MRI only. The sensitivity achieved by MRI in combination with mammography was not significantly higher than that achieved by MRI alone (Table 3). Four (10%) of 40 cancers were missed with MRI. Of these, two patients showed microcalcifications, which were detected on both views of the mammogram. One of these was a grade 3 ductal carcinoma in situ (DCIS) with microinvasion, which showed no correlate at MRI, even at retrospective analysis. The other was a recurrence of a grade 2 mucinous carcinoma with a large intraductal component and multiple invasive components less than 1 cm. It was not described on MRI, possibly because of strong background enhancement, which led to a BI-RADS 3 classification. The third cancer, detected only by MRI but classified as BI-RADS 3 and biopsied at the patient's request, was a 5-mm grade 1 invasive ductal carcinoma. The fourth cancer was the interval cancer, which became palpable 3 months after a negative screening round and which was negative also in retrospect. Pathology revealed a 15-mm grade 3 invasive medullary carcinoma.

The advantage of MRI over conventional imaging techniques was similar for the 14 DCISs (35%) in this study. Although MRI detected all 14 DCISs (100%), mammography and ultrasound each detected five DCISs (36%), and together, they detected seven DCISs (50%). The other seven DCISs were detected by MRI only.

One hundred sixty-six suspicious imaging findings were false positive, either by biopsy (n = 158) or as a result of the lack of their presence at biopsy and follow-up (n = 8). Of these, 147 (88.6%) were called suspicious at MRI, 38 (22.9%) at mammography, and 41 (24.7%) at ultrasound, resulting in a significantly lower specificity and PPV for MRI than for mammography or ultrasound. Of 158 histopathologically verified false-positive results, 49 (31.0%) were ADH. Of these lesions, MRI detected 46 (93.9%), mammography detected 12 (24.5%), and ultrasound detected eight (16.3%; $P < .001$; Table 4). Thus, 46 (31%) of 147 false-positive MRI findings represented ADH at histology.

Table 4. False-Positive Lesions Detected by the Various Modalities and the Portion of These Lesions Representing Atypical Ductal Hyperplasia

	False-Positive Lesions		Atypical Ductal Hyperplasia	
Screening Modality	No.	%	No.	%
Total	166	100	49	100
Ultrasound	41	34.7	8	16.3
Mammography	38	22.9	12	24.5
Magnetic resonance imaging	147*	88.6	46*	93.9

*$P < .001$ for comparison of magnetic resonance imaging with other modalities.

Subgroup Analyses

In all subgroups dichotomized by screening round, mutation status, age, and breast density, MRI achieved significantly higher sensitivities than mammography or ultrasound (largest $P = .017$ [P values not shown in tables]). Similarly, in all subgroups dichotomized by screening round, mutation status, and age, MRI achieved significantly lower specificities than mammography or ultrasound ($P < .001$ in all subgroups [P values not shown in tables]).

In a second analysis, we investigated whether screening rounds, mutation status, age, or breast density influenced the diagnostic performance parameters for each individual modality. No statistically significant differences in sensitivity and NPV could be shown between complementary subgroups for any single imaging modality (Table 5).

DISCUSSION

The results of this prospective cohort study confirm that, in women with a high familial risk for breast cancer, MRI has a significantly higher sensitivity for invasive and preinvasive cancers than mammography and ultrasound. Almost half of all cancers (45%) were found by MRI only. Mammography led to the detection of two additional cancers (a DCIS with microinvasion and a DCIS with multiple invasive areas of < 10 mm). This did not lead to a significant increase in sensitivity (sensitivity of MRI *v* MRI plus mammography, 90% [95% CI, 76.9% to 96.0%] *v* 95% [95% CI, 83.5% to 98.6%], respectively; $P = .15$). The use of ultrasound did not lead to the detection of additional cancers but increased

Table 5. Diagnostic Performance of Ultrasound, Mammography, and MRI, Depending on the Number of Screening Round, Mutation Status, Age, and Breast Density

Screening Modality	Screening Round			Mutation Status			Age			ACR Breast Composition		
	First	Subsequent	*P*	Wild Type	*BRCA*	*P*	≤ 50 Years	> 50 Years	*P*	Grade 1/2	Grade 3/4	*P*
Ultrasound												
Sensitivity												
Rate	47.4	28.6	.234	29.4	37.5	.783	26.9	57.1	.089	38.5	35.7	1.000
No./total No.	9/19	6/21		5/17	6/16		7/26	8/14		10/26	5/14	
Specificity												
Rate	95.7	97.7	.038*	96.1	99.1	.022*	95.9	99.2	.005*	97.6	96.1	.114
No./total No.	517/540	767/785		660/687	449/453		898/936	386/389		662/678	622/647	
PPV												
Rate	28.1	25.0	1.000	15.6	60.0	.011*	15.6	72.7	.000*	38.5	16.7	.079
No./total No.	9/32	6/24		5/32	6/10		7/45	8/11		10/26	5/30	
NPV												
Rate	98.1	98.1	.978	98.2	97.8	.661	97.9	98.5	.520	97.6	98.6	.258
No./total No.	517/527	767/782		660/672	449/459		898/917	386/392		662/678	622/631	
Mammography												
Sensitivity												
Rate	42.1	33.3	.592	29.4	43.8	.798	34.6	42.9	.736	34.6	42.9	.736
No./total No.	8/19	7/21		5/17	7/16		9/26	6/14		9/26	6/14	
Specificity												
Rate	96.5	97.6	.272	96.4	98.9	.013*	96.8	97.9	.336	98.2	96.0	.024*
No./total No.	521/540	766/785		662/687	448/453		906/936	381/389		666/678	621/647	
PPV												
Rate	29.6	26.9	1.000	16.7	58.3	.019*	23.1	42.9	.182	42.9	18.8	.070
No./total No.	8/27	7/26		5/30	7/12		9/39	6/14		9/21	6/32	
NPV												
Rate	97.9	98.2	.729	98.2	98.0	.824	98.2	97.9	.796	97.5	98.7	.116
No./total No.	521/532	766/780		662/674	448/457		906/923	381/389		666/683	621/629	
MRI												
Sensitivity												
Rate	89.5	90.5	.916	94.1	81.3	.191	92.3	85.7	.602	92.3	85.7	.602
No./total No.	17/19	19/21		16/17	13/16		24/26	12/14		24/26	12/14	
Specificity												
Rate	84.6	91.8	< .001*	86.6	94.3	< .001*	87.9	91.3	.091	90.6	87.2	.065
No./total No.	457/540	721/785		595/687	427/453		823/936	355/389		614/678	564/647	
PPV												
Rate	17.0	22.9	.354	14.8	33.3	.018*	17.5	26.1	.283	27.3	12.6	.016*
No./total No.	17/100	19/83		1 6/108	13/39		24/137	12/46		24/88	12/95	
NPV												
Rate	99.6	99.7	.649	99.8	99.3	.217	99.8	99.4	.402	99.7	99.6	.932
No./total No.	457/459	721/723		595/596	427/430		823/825	355/357		614/616	564/566	

Abbreviations: ACR, American College of Radiology; MRI, magnetic resonance imaging; NPV, negative predictive value; PPV, positive predictive value.
*Significant differences = $P < .05$; P values are presented for the comparison of subgroups for each modality separately. (P values for the comparison of different modalities within a subgroup are described in the text.)

false-positive findings. MRI was also more sensitive and less specific in all analyzed subgroups dichotomized by screening round, *BRCA* status, age, and breast density.

Similar to prior reports on the screening of high-risk patients with MRI, the number of interval cancers in our study was low and cancers were detected at a favorable stage.[8,25] One (2.5%) of our 40 cancers was an interval cancer, 35% were DCIS, and 7.5% were node positive. A study on mammography and ultrasound screening of women at elevated risk, in which MRI was not included, detected 22% interval cancers, 15% DCIS, and 20% node-positive cancers.[26] This difference in the detection of interval cancers, as well as lower stage cancers, is, at least in part, attributable to the use of MRI. A low recurrence rate of these early-stage cancers detected with MRI has been reported.[25,27]

In our study, 14 (35%) of 40 cancers were DCIS, all of which were detected by MRI and seven (50%) of which were detected only by MRI. This confirms more recent reports on the superiority of MRI over mammography in detecting DCIS in both high-risk and general patient populations.[8,28,29]

One of the main concerns about MRI as a modality for breast cancer screening is its low PPV.[10,12,13,30-32] In our hands, the PPV of MRI was 19.7%, significantly lower than that of mammography (28.3%) and ultrasound (26.8%). But, as reported in other studies, we observed a significant increase in the specificity of MRI from 85% in the first screening round to 91% in subsequent screening rounds.[33] Only the latter should be compared with the specificities of mammography and ultrasound, because, in many cases, MRI was the only newly added modality, and specificities are usually lower during the first screening round for any given modality.

In addition, 46 (31%) of the 147 false-positive findings at MRI in our study contained ADHs at pathology. ADH is an advanced precancerous lesion and, similar to DCIS, a nonobligate direct precursor lesion of invasive ductal cancer.[34-37] Thus, surgical resection without chemotherapy or radiotherapy in these high-risk patients may be considered a means of primary prevention. In addition, the diagnosis of ADH may aid in further individual risk assessment.[38]

Considering the inevitability of increasing costs and false-positive rates with every additional screening modality and considering the high sensitivity of MRI alone, the question arises whether any modalities can be omitted at high-risk screening. In our study, two cancers (5%) were found only with mammography. This is in agreement with recent studies that reported even fewer[9,32] or no additional cancers found with mammography.[39] Earlier studies have reported higher percentages of up to 18%.[8,10,30,33] The improvement in sensitivity of MRI in more recent reports might be explained by technical advances in breast MRI, improved diagnostic criteria, and an improved familiarity of radiologists with reading breast MRI, which includes an improved ability to diagnose DCIS with MRI.[29]

To maximize the yield of screening with MRI while reducing costs and unnecessary false-positive findings, additional selection criteria other than risk could be beneficial. High breast density in young patients is known to influence the sensitivity of mammography but has no effect on the sensitivity of MRI, which leads to the assumption that the observed beneficial effect of MRI decreases with age. Therefore, in some countries, additional MRI is offered only until age 50 or 60 years.[5,18] Dichotomizing our cohort into complementary subgroups by age and breast density showed that these factors had no relevant effect on the sensitivities of the various modalities, because any differences were outweighed by the markedly higher sensitivity of MRI compared with mammography and ultrasound in all subgroups. Therefore, offering breast MRI screening in addition to mammography to women with a high familial risk of breast cancer beyond the age of 50 years seems reasonable.

Significant differences in specificity and PPV could be demonstrated for specific modalities between some complementary subgroups. Specificities and PPVs were lower for all three modalities in the younger patient group and in the higher breast density group. This can be explained by denser and more biologically active breast tissue in younger patients, where, for example, growing or contrast-enhancing fibroadenomas or hormone-induced changes of healthy or fibrocystic breast tissue can raise suspicion for malignancy. As reported by others and discussed earlier, specificities were significantly lower for all three modalities in the first screening rounds compared with subsequent screening rounds.[33] Finally, specificities and PPVs were significantly lower for all three modalities in non–*BRCA* mutation carriers compared with *BRCA* mutation carriers. The lower PPVs in non–*BRCA* mutation carriers can be explained by the lower pretest likelihood for the disease in this group. The lower specificity may be a result of an overestimation of the breast cancer risk in the non–*BRCA* mutation carriers and may have resulted in an unwarranted low threshold to call lesions suspicious. It is important for women to be aware of these factors that influence specificity and to understand and accept the risk of false-positive findings before undergoing any screening.

A limitation of this study is that 31% of our patients had no follow-up after their final screening round. This was, in part, a result of a tendency of participants to continue their surveillance at centers closer to them once these centers started offering MRI screening. The interval cancer rate in patients who did have a follow-up was low, with a rate of 0.1%. The likelihood for interval cancers within the remaining patients without follow-up was, therefore, also low. Because the main aim of our study was to compare the value of the three screening modalities relative to each other, rather than absolutely, we chose not to exclude the studies without follow-up.[30]

The numbers of cancers in the dichotomized subgroups were small. Thus, it is possible that we could not observe a difference in sensitivities or PPV for any specific modality between correlating subgroups, when there actually was a difference. Nonetheless, any such difference would be outweighed by the superiority of MRI compared with mammography and ultrasound in all subgroups.

In conclusion, the use of MRI to screen women at an increased risk for breast cancer improved the detection of invasive cancers and DCIS, regardless of mutation status, age, or breast density. The high sensitivity of MRI comes with a low specificity, which seems to be most pronounced in the first screening round, in young patients, and in patients without a *BRCA* mutation. Mammography may not be indicated for all high-risk patients, and its use should be considered on a personalized basis. Ultrasound should be used only when MRI is not available or contraindicated.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERMS

***BRCA1*:** a tumor suppressor gene known to play a role in repairing DNA breaks. Mutations in this gene are associated with increased risks of developing breast or ovarian cancer.

***BRCA2*:** a tumor suppressor gene whose protein product is involved in repairing chromosomal damage. Although structurally different from *BRCA1*, *BRCA2* has cellular functions similar to *BRCA1*. *BRCA2* binds to RAD51 to fix DNA breaks caused by irradiation and other environmental agents. Also known as the breast cancer 2 early onset gene.

magnetic resonance imaging: a procedure in which radio waves and a powerful magnet linked to a computer are used to create detailed pictures of areas inside the body. These pictures can show the difference between normal and diseased tissue.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Triple-Modality Screening Trial for Familial Breast Cancer Underlines the Importance of Magnetic Resonance Imaging and Questions the Role of Mammography and Ultrasound Regardless of Patient Mutation Status, Age, and Breast Density

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Appendix

Exclusion Criteria

Exclusion criteria included the following: age less than 25 years (with the exception of women with relatives who were diagnosed with breast cancer before 30 years of age, who were included 5 years before that relative's age at diagnosis); women from families with a proven gene mutation who themselves had tested negative for that particular mutation because they do not bear a higher risk than the average female population; bilateral mastectomy; stage IV breast cancer; pacemaker not compatible with magnetic resonance imaging (MRI); pregnancy or lactation; and clinical symptoms of breast cancer at first presentation (eg, palpable mass; such women could enter the trial 1 year after their treatment).

MRI Sequence Protocol

Until September 2008, MRI of the breast was performed on a 1.0-T scanner with a dedicated breast coil (Gyroscan T10-NT; Philips, Amsterdam, the Netherlands). The MRI sequence protocol consisted of a sagittal T2-weighted sequence and axial T1-weighted three-dimensional gradient-echo dynamic sequences. Images were obtained once before intravenous contrast agent administration and six times at intervals of 70 seconds thereafter. After September 2008, a 1.5-T MRI scanner MAGNETOM Avanto (Siemens, Berlin, Germany) was used. Axial T1-weighted dynamic sequences were measured once before and four times after contrast agent injection at intervals of 90 seconds. This was followed by a sagittal T2-weighted sequence with fat suppression (turbo inversion recovery magnitude).

Statistical Analysis

Statistical computations were performed using IBM SPSS Statistics Version 21.0 (IBM, Armonk, NY) and CIA Version 2.2.0 (Trevor Bryant, University of Southampton, Southampton, United Kingdom). Diagnostic image performance parameters are presented using frequencies, percentages, and 95% CIs.

To compare different modalities regarding sensitivity, specificity, positive predictive value, and negative predictive value, logistic regression for repeated measures (using the generalized estimating equation model) was assessed. Comparing specificities and negative predictive values of different modalities, repeated measures were modeled for modalities as well as for different screening rounds. Because there were only two women with two malignant lesions (of a total of 40), malignant lesions were considered as independent. Thus, repeated measures were modeled for different modalities only. Correlations among measures from the same individual were modeled using an unstructured covariance matrix.

Subgroups were compared using Fisher-Freeman-Halton tests for differences in sensitivity and positive predictive value. Logistic regressions for repeated measures were used for differences in specificity and negative predictive values. Comparing the specificity and negative predictive values of independent subgroups (eg, wild type *v BRCA1*/*BRCA2*), repeated measures were modeled for screening rounds. In case of comparing subgroups, which at least partly consist of complementary data (eg, age group, because, as a result of longitudinal data, a woman may be part of the ≤ 50 and > 50 year age groups), repeated measures were modeled for subgroups as well as for different screening rounds. Again, correlations between measures from the same individual were modeled using an unstructured covariance matrix. $P \leq .05$ was considered to indicate a significant result.

Screening Attendance

Of a total of 1,506 annual surveillance rounds, 141 (10.3%) were incomplete, either for technical problems or because of lacking patient compliance. Ultrasound was not performed in 62, mammography in 96, and MRI in 33 rounds. Thus, the 559 women underwent 1,365 complete imaging rounds, with an average of 2.45 rounds per woman. Imaging surveillance of eligible women lasted for one to 11 complete imaging rounds. After the first surveillance round completed by all 559 participants, 287 women (51.4%) had a second imaging round, 203 women (36.4%) had a third round, 118 women (21.2%) had four rounds, 81 women (14.5%) had five rounds, 49 women (8.8%) had six rounds, 30 women (5.4%) had seven rounds, 19 women (3.4%) had eight rounds, 13 women (2.3%) had nine rounds, four women (0.7%) had 10 rounds, and two women (0.4%) had 11 complete imaging rounds.

The discrepancy between the long study period and the relatively low number of screening rounds can be explained by multiple factors. First, recruitment was contiguous throughout the entire study period and was rather slow, especially in the beginning. Second, 53 (9.5%) of the 559 women underwent prophylactic bilateral mastectomy over the course of the trial and were excluded from the study population at the time of their operation. Third, 14 women (2.5%) died during the course of the study. Fourth, time intervals were sometimes longer than 1 year, even though patients were invited by mail, and again by telephone, in cases of nonattendance. Finally, 253 women (45%) dropped out before completion of the study or did not show up for imaging follow-up. The relatively high drop-out rate is at least partially based on the fact that, at the initiation of this study, the University Hospital of Vienna was the only center providing MRI breast cancer screening for high-risk patients. Over time, additional centers started providing a similar service, and many patients who lived further away from Vienna switched to such centers to avoid cumbersome travel.

Table A1. Family History Inclusion Criteria for High-Risk Screening in Austria[7]

Criterion (applies to affected first-degree relatives on the same side of the family)*
3 breast cancers at age ≤ 60 years
2 breast cancers at age ≤ 50 years
1 breast cancer at age ≤ 35 years
1 breast cancer at age ≤ 50 years and one ovarian cancer at any age
2 ovarian cancers at any age
1 male and 1 female cancer at any age

NOTE. Women who fulfilled these family history criteria were advised to undergo genetic testing at our institution, but remained within the study, even if they decided not to be tested or if they tested negative for a predisposing mutation.
*A woman's personal cancer history can contribute to the criteria.