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ORIGINAL REPORT

Prospective Multicenter Cohort Study to Refine Management Recommendations for Women at Elevated Familial Risk of Breast Cancer: The EVA Trial

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ABSTRACT

Purpose
We investigated the respective contribution (in terms of cancer yield and stage at diagnosis) of clinical breast examination (CBE), mammography, ultrasound, and quality-assured breast magnetic resonance imaging (MRI), used alone or in different combination, for screening women at elevated risk for breast cancer.

Methods
Prospective multicenter observational cohort study. Six hundred eighty-seven asymptomatic women at elevated familial risk (≥ 20% lifetime) underwent 1,679 annual screening rounds consisting of CBE, mammography, ultrasound, and MRI, read independently and in different combinations. In a subgroup of 371 women, additional half-yearly ultrasound and CBE was performed more than 869 screening rounds. Mean and median follow-up was 29.18 and 29.09 months.

Results
Twenty-seven women were diagnosed with breast cancer: 11 ductal carcinoma in situ (41%) and 16 invasive cancers (59%). Three (11%) of 27 were node positive. All cancers were detected during annual screening; no interval cancer occurred; no cancer was identified during half-yearly ultrasound. The cancer yield of ultrasound (6.0 of 1,000) and mammography (5.4 of 1,000) was equivalent; it increased nonsignificantly (7.7 of 1,000) if both methods were combined. Cancer yield achieved by MRI alone (14.9 of 1,000) was significantly higher; it was not significantly improved by adding mammography (MRI plus mammography: 16.0 of 1,000) and did not change by adding ultrasound (MRI plus ultrasound: 14.9 of 1,000). Positive predictive value was 39% for mammography, 36% for ultrasound, and 48% for MRI.

Conclusion
In women at elevated familial risk, quality-assured MRI screening shifts the distribution of screen-detected breast cancers toward the preinvasive stage. In women undergoing quality-assured MRI annually, neither mammography, nor annual or half-yearly ultrasound or CBE will add to the cancer yield achieved by MRI alone.

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INTRODUCTION

Due to the earlier onset of familial as opposed to sporadic breast cancer, most guidelines for at-risk women recommend periodic screening from age 25 to 30 years onward.[1-7] However, the success of mammographic screening for familial breast cancer has been limited, with interval cancer rates (ie, the fraction of women in whom the screening diagnosis of breast cancer failed) of up to 55%.[8-23]

Nonmammographic screening methods, in particular magnetic resonance imaging (MRI) and—recently—breast ultrasound, have been used in addition to mammography to help compensate for the limitations of mammographic screening.[24-31] Annual MRI is now recommended in *BRCA* mutation carriers; in many countries, this recommendation has been extended to include all women with a lifetime risk of 20% or more.[1] Yet a number of issues remain.

First, establishing the respective importance of imaging methods for early diagnosis of breast cancer is a moving target. Quality assurance programs and reporting standards for breast MRI have

only recently been introduced.[32] Early reports on multicenter trials on MRI screening had demonstrated a relatively high false-negative rate of MRI, mainly due to a limited sensitivity for ductal carcinoma in situ (DCIS)—thus necessitating continued mammographic surveillance.[25,27] With the advent of standardized MR image interpretation criteria and quality assurance programs also for MRI,[32] it appears that the sensitivity for DCIS and the technique's overall specificity have been improved.[33-34]

Second, ultrasound has been suggested as an alternative to MRI.[24,31] However, it is unclear whether ultrasound can indeed replace MRI, and/or whether it is still useful— or redundant—in women who do undergo MRI screening.

Last, all current guidelines recommend annual screening. Further data to investigate the impact of shorter screening intervals would be desirable to corroborate or redefine current guidelines.

We report the results of a prospective screening study, designed to investigate the respective cancer yield and diagnostic accuracy of the different breast imaging methods (mammography, MRI, and ultrasound, used alone or in different combinations) for screening women at elevated familial risk. Secondary objective was to investigate the cancer yield of additional half-yearly screening with ultrasound and clinical breast examination (CBE).

PATIENTS AND METHODS

Study Design

A prospective multi-institutional observational cohort trial Evaluation of Imaging Methods for Secondary Prevention of Familial Breast Cancer (EVA) was performed in four German academic breast centers. Screening examinations started on October 1, 2002, and continued until December 31, 2005, followed by a follow-up period of 1 year. The database was closed on July 1, 2007. The study design had been reviewed and approved by the institutional review boards of the participating institutions. All study participants provided written informed consent.

All participating women underwent the same annual screening protocol consisting of CBE, mammography, ultrasound, and MRI. All imaging studies had to be completed within a period of 6 weeks. Additional half-yearly screening was conducted with CBE and ultrasound in a subgroup of women (Table 1). Details of the reader studies are given in Appendix (online only).[35]

Screening Cohort

The inclusion criteria followed those laid down by the German Cancer Aid Consortium published previously (Table 2).[36] In women without personal history of breast cancer, the individual risk was quantified using the BRCAPRO model (CancerGene software version 3.4).[37-38]

Seven hundred twenty-five women met the inclusion criteria and were recruited. Of those, 38 were lost to follow-up after the first screening round (that had been rated as negative or benign); these data sets were not included because of lack of validation. The analysis cohort consisted of 687 women who underwent a total of 1,741 annual screening rounds. Of those, 62 were incomplete because not all three imaging methods had been done; these screening rounds were not considered for analysis of diagnostic accuracy and cancer yield, but results were recorded and included in the calculation of cancer prevalence and incidence. Therefore, 1,679 annual screening rounds are available for analysis of diagnostic accuracy and cancer yield. Of the 687 women of the analysis cohort, 370 opted for additional half-yearly screening and underwent 869 additional half-yearly rounds.

Women who underwent additional half-yearly screening were statistically significantly younger ($P < .0001$) and carried a significantly higher lifetime risk ($P < .0001$) compared to the subgroup that underwent annual screening only.

Table 1. Description of the EVA Cohort

Parameter	Total Cohort		Subcohort With Additional Half-Yearly Screening		Subcohort With Only Annual Screening	
	No.	%	No.	%	No.	%
Total No.	687	100.0	370	100.0	317	100.0
Age distribution						
Mean	44.6		41.9		47.8	
SD	6.3		6.8		5.9	
Median	44		43		47	
Range	25-71		25-69		30-71	
Menopausal status						
Premenopausal	495/687	72.2	257/370	69.5	239/317	75.4
Postmenopausal	192/687	27.8	113/370	30.5	78/317	24.6
Type of risk						
Women with familial history of breast cancer, no documented mutation, by LTR	436/687	63.5	206/370	55.7	230/317	72.6
20%	69/687	10.0	19/370	5.1	50/317	15.8
21%-30%	196/687	28.5	74/370	20.0	122/317	38.5
> 30%	171/687	24.9	113/370	30.5	58/317	18.3
Women with familial and personal history of breast cancer, no documented mutation	186/687	27.0	111/370	30.0	75/317	23.7
Women with documented *BRCA* mutation*	65/687	9.5	53/370	14.3	12/317	3.8
BRCA1	53/687	7.7	41/370	11.1	12/317	3.8
BRCA2	12/687	1.7	12/370	3.2	0/317	0

NOTE. LTR is calculated by the BRCAPRO model.
Abbreviations: EVA, Evaluation of Imaging Methods for Secondary Prevention of Familial Breast Cancer; SD, standard deviation; LTR, lifetime risk.
*Twenty-six of the mutation carriers also had a personal history of breast cancer at the time of study inclusion. They are included here.

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Table 2. Inclusion Criteria

Two or more first-degree relatives with breast and/or ovarian cancer, at least one of whom received a diagnosis before age 50 years
A single first-degree relative with breast cancer diagnosed before age 35 years
A single first-degree relative with ovarian cancer diagnosed before age 40 years
A single male first-degree relative with breast cancer
A single first-degree relative with bilateral primary breast cancer diagnosed before age 50 years
A single first-degree relative with both, breast and ovarian cancer
Two or more first-degree relatives with breast cancer diagnosed before age 50 years
Three or more first- or second-degree relatives with breast cancer at any age
Documented mutation in a breast cancer–relevant gene
Women with a personal history of breast cancer were included as long as they had not undergone bilateral mastectomy, had not received chemotherapy during the last 12 months, and had not been diagnosed with distant metastases

NOTE. A woman needed to meet one of the criteria to be eligible for inclusion in the Evaluation of Imaging Methods for Secondary Prevention of Familial Breast Cancer trial.

Imaging Methods and Quality Assurance

All participating institutions run accredited multidisciplinary breast units that are continuously performance monitored[39-40]; this includes the technological and clinical performance of mammography and breast ultrasound, but not of MRI services. Therefore, additional criteria were implemented to ensure quality of MRI. Participating institutions were required to document experience with at least 200 breast MRI studies per year and offer verifiable experience with MR-guided biopsy (wire localization and/or MR-guided vacuum biopsy). A preliminary version of the MR–Breast Imaging Reporting and Data System (BIRADS) lexicon was used to organize interpretation and reporting. Readers underwent a training session to ensure adequate and unambiguous clinical application of the MR-BIRADS terminology, and were trained in use of MRI criteria for diagnosing DCIS. Details of the imaging methods and standard of reference are given in the Appendix. The follow-up period ranged from 12.8 to 40.0 months, mean 29.18 months, median 29 months.

Statistical Considerations

BIRADS diagnoses of all recorded lesions were dichotomized in that categories 1, 2, and 3 were taken as test negative, and 4 and 5 were taken as test positive result. Histopathologic diagnoses were dichotomized in that a diagnosis of invasive or DCIS cancer was accepted as a malignant diagnosis or disease positive; all other histologic results including lobular carcinoma in situ were categorized as benign or disease negative. In addition, an uneventful follow-up at 12 months was accepted as disease negative. Sensitivities, specificities, positive and negative predictive values were calculated on a per-patient (not per-breast or per-lesion) basis for all screening rounds. McNemar's test was used to detect statistically significant differences in the outcomes of the diagnostic methods. In addition, an receiver operating characteristic analysis was performed on a per-lesion basis (ROCKIT, version 1.1B2; University of Chicago, Chicago, IL). A P value of less than .05 was used as threshold to indicate statistical significance. Cancer yield was calculated as a true-positive imaging diagnosis per 1,000 screening rounds (women years).

RESULTS

Twenty-seven women (27 of 687; 3.9%) were diagnosed with breast cancer during the study period, four of whom had multifocal or multicentric disease, none had bilateral cancer. Mean age at diagnosis was 43.1 years (standard deviation, 0.9 years; median, 43 years; range, 28 to 64 years). Annual breast cancer incidence was 15.5‰ (27 of 1,741), with 13.9‰ (10 of 718) in the first, 16.2‰ (10 of 617) in the second, and 17.2‰ (seven of 406) in the third year (Appendix Fig A1, online only). Nine breast cancers occurred in women with personal history, of whom seven were contralateral or second primary cancers, two were local recurrences. Seven hundred twenty-eight individual lesions were recorded (382 participants with 695 benign and 27 participants with 33 malignant lesions).

Overall, 21 women (21 of 27; 77%) were diagnosed with minimal cancer (ie, Tis or invasive cancers $\leq$ 10 mm, N0, M0); during incidence screening, the rate was 82% (14 of 17; Tables 3 and 4).

All cancers were diagnosed during the annual screening rounds. None was identified during the regular half-yearly clinical visits or became clinically obvious in between annual screening rounds. No cancer was identified during one of the 62 incomplete screening rounds.

The cancer yield (per 1,000 women years) of the different imaging methods is given in Figure 1 and Table 4. Results of the different imaging methods, stratified by type of risk, are given in Appendix Table A1. The sensitivity achieved by ultrasound alone (37%) and mammography alone (33%) was comparable ($P = .72$); the combined use of mammography and ultrasound yielded a slightly, but statistically not significantly higher sensitivity (48%; $P < .12$). MRI alone was significantly more sensitive (93%) than mammography or ultrasound alone ($P < .0001$) or combined ($P < .005$). Adding mammography to MRI did not allow a statistically significant increase of sensitivity ($P = .5$).

MRI missed two cancers (two of 27; 7%) in two women. None had a documented mutation, but one had a history of breast cancer. This was a 39-year-old patient with a 3-mm microinvasive cancer who had calcifications categorized as BIRADS4 on mammography. The lesion had also been visible, but rated as BIRADS3 on MRI. The other patient was a 52-year-old with low-grade DCIS with mammographic calcifications; this was the only malignant lesion that was completely invisible on breast MRI.

In summary, two cancers were only diagnosed by mammography (two of 27, 7%), none was only diagnosed by ultrasound, and 14 cancers (14 of 27, 52%) were only diagnosed by MRI; these were eight (50%) of the total 16 invasive cancers and six (55%) of the 11 DCIS.

Thirty women (30 of 687; 4.4%) underwent biopsy for false positive diagnoses. A final BIRADS3 was assigned in 237 screening rounds of 130 women, necessitating a short-term follow-up (237 of 1,679; 14.1%). On a method-wise analysis, a mammographic short-term follow-up was recommended in 68 women; an ultrasound follow-up in 136 (only considering annual ultrasound studies), and an MRI follow-up in 118.

The positive predictive value was highest for MRI (48.0%), followed by mammography (39.1%) and ultrasound (35.7%).

Diagnostic accuracy (area under the ROC curve) of MRI was significantly higher than that of mammography or ultrasound or the combined use of both methods, and the accuracy did not change significantly with the added use of ultrasound or mammography or both to MRI (Fig 2 and Table 5).

Clinical examination was positive in 110 screening rounds. In one of these, the palpable abnormality corresponded to breast cancer. All other cancers were clinically occult at the time of diagnosis. In the remaining 109 palpable findings, a final diagnosis of benign changes was established either by biopsy or by an uneventful follow-up. This yields a sensitivity of 3% (one of 27) and a positive predictive value of 0.9% (one of 110) for CBE.

In none of the 869 half-yearly screening visits recorded in 370 participants, a new breast cancer was diagnosed; neither by clinical breast examination, nor by screening ultrasound, despite this

Table 3. Stage Distribution: Overall, First Versus Subsequent Screening Rounds, By Type of Risk

Parameter	Overall		First Screening Round		Incidence Screening Rounds		Women With Documented Mutation*		Women Without Mutation†		Women With Additional Personal History‡		Women Without Personal History and Without Mutation§	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Total No. of women diagnosed with breast cancer	27	100	10	100	17	100	5	100	22	100	9	100	14	100
T stage														
Tis	11/27	41	2/10	20	9/17	53	1/5	20	10/22	45	3/9	33	7/14	50
Invasive	16/27	59	8/10	80	8/17	47	4/5	80	12/22	55	6/9	67	7/14	50
N stage														
N0	24/27	89	8/10	80	16/17	94	4/5	80	20/22	91	8/9	89	13/14	93
N1	3/27	11	2/10	20	1/17	6	1/5	20	2/22	9	1/9	11	1/14	7
M stage														
M0	27/27	100	10/10	100	17/17	100	5/5	100	22/22	100	9/9	100	14/14	100
M1	0/27	0	0/10	0	0/17	0	0/5	0	0/22	0	0/9	0	0/14	0
Size distribution (T) of invasive cancers														
T1	15/16	94	7/8	88	8/8	100	4/4	100	11/12	92	6/6	100	6/7	86
T1a	1/16	6	0/8	0	1/8	12.5	0	0	1	8	1	17	0	0
T1b	8/16	50	4/8	50	4/8	50	2	50	6	50	4	67	3	43
T1c	6/16	38	3/8	38	3/8	37.5	2	50	4	33	1	17	3	43
T2	1/16	6	1/8	13	0/8	0	0/4	0	1/12	8	0/6	0	1/7	14
T3	0/16	0	0/8	0	0/8	0	0/4	0	0/12	0	0/6	0	0/7	0
T4	0/16	0	0/8	0	0/8	0	0/4	0	0/12	0	0/6	0	0/7	0
Nuclear grade														
Invasive cancers														
1	3/16	19	1/8	12.5	2/8	25	1/4	25	2/12	17	1/6	17	1/7	14
2	7/16	44	6/8	75	1/8	12.5	2/4	50	5/12	42	1/6	17	4/7	57
3	6/16	37.5	1/8	12.5	5/8	62.5	1/4	25	5/12	42	4/6	67	2/7	29
DCIS														
1	1/11	9	0/2	0	1/9	11	0/1	0	1/10	10	0/3	0	1/7	14
2	4/11	36	1/2	50	3/9	33	0/1	0	4/10	40	2/3	67	2/7	29
3	6/11	55	1/2	50	5/9	55.5	1/1	100	5/10	50	1/3	33	4/7	57

Abbreviation: DCIS, ductal carcinoma in situ.
*Includes one woman with personal history of breast cancer.
†Includes eight women with personal history of breast cancer.
‡Includes one woman with a mutation (*BRCA1*).
§These 14 women are a subset of the 22 women without mutation (column 5 of Table 3).

subgroup exhibited a significantly higher average risk compared with the cohort that underwent annual screening only.

DISCUSSION

In this prospective multicenter screening trial on women at elevated familial risk, with measures for quality assurance established not only for mammography and ultrasound, but also for MRI, screening was successful in that the stage of breast cancers at the time of diagnosis was low, and the rate of interval cancers was 0%. Although stage distribution is only a surrogate end point, and although a downward shift of stage does not prove a survival benefit, the detection of high-grade DCIS or of small, node-negative breast cancers is closely correlated with a reduction in breast cancer mortality.[41-42]

In good agreement with previous trials,[13-14,24-30] MRI proved to be the most important contributor to this success. The cancer yield achieved with MRI alone was significantly higher than that achieved with mammography or ultrasound or both, and it did not increase significantly if MRI was read in conjunction with mammography or ultrasound. This means that the outcome of this multimodality screening program was solely determined by the use of MRI, whereas the use of other imaging methods, including mammography, had no significant influence on cancer yield.

Systematic annual screening mammography is currently recommended for all women at increased familial risk—despite the superior diagnostic performance of MRI compared to mammography that was consistently found across all, including the very early, published screening trials.[7,13,15,21,24,25,27-30] If further studies confirm the high sensitivity of MRI for invasive cancers and for DCIS that was found in the EVA trial, then it is conceivable to discontinue mammographic screening in young women who have access to quality assured screening breast MRI. Even existing evidence suggests that this may be an option for (or may even be advisable to) young women younger under 40, especially if they carry a *BRCA1* mutation or a high risk of heterozygosity. In these women, mammographic sensitivity is known to be exceedingly low. This is not only caused by the very early onset of

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Table 4. Diagnostic Indices of Imaging Methods Used Alone or in Different Combination

	Parameter																				
	Mx			US			Mx + US			MRI			MRI + US			MRI + Mx			MRI + Mx + US		
Index	%	95% CI	No.	%	95% CI	No.	%	95% CI	No.	%	95% CI	No.	%	95% CI	No.	%	95% CI	No.	%	95% CI	No.
Sensitivity	33.3	17.2 to 53.9	9/27	37.0	20.0 to 57.5	10/27	48.1	29.1 to 67.6	13/27	92.6	84.2 to 98.7	25/27	92.6	84.2 to 98.7	25/27	100.0	85.8 to 100.0	27/27	100.0	85.8 to 100.0	27/27
Specificity	99.1	98.5 to 99.5	1,638/1,652	98.0	98.2 to 99.3	1,634/1,652	98.3	97.5 to 98.8	1,625/1,652	98.4	95.9 to 98.9	1,625/1,652	98.5	97.7 to 99.0	1,627/1,652	97.6	96.7 to 98.2	1,612/1,652	97.6	96.7 to 98.2	1,612/1,652
PPV	39.1	20.4 to 61.2	9/23	35.7	19.3 to 55.8	10/28	32.5	19.1 to 49.2	13/40	48.0	34.2 to 62.2	25/52	50.0	35.7 to 64.3	25/50	40.2	28.7 to 53.0	27/67	40.2	28.7 to 53.0	27/67
NPV	98.9	98.2 to 99.2	1,638/1,656	98.9	98.3 to 99.4	1,634/1,651	99.1	98.5 to 99.5	1,625/1,639	99.9	99.5 to 100.0	1,625/1,627	99.9	99.5 to 100.0	1,627/1,629	100.0	99.7 to 100.0	1,612/1,612	100.0	99.7 to 100.0	1,612/1,612

Abbreviations: Mx, mammography; US, ultrasound; MRI, magnetic resonance imaging; PPV, positive predictive value; NPV, negative predictive value.

breast cancer and the on average dense breast tissue of these women, but also by the specific mammographic features of *BRCA1*-associated cancers. These cancers lack mammographically detectable calcifications, and if at all visible, they exhibit benign mammographic features.[14-15] Therefore, the diagnostic benefit attributable to mammographic screening will be low. In contrast, the radiation dose will not be negligible if—per current guidelines—annual bilateral two-view screening mammography is started at age 25 to 30 years. This dose will be imposed on young fibroglandular tissue that is more susceptible to the mutagenic effects of radiation.[43-44] In addition, there is the still unsettled issue of an increased radiation sensitivity of *BRCA1* mutation carriers.[45] The risk/benefit ratio of mammographic screening has been established only for women older than 40 years of age (many radiation biologists would argue only for women older than age 49 years).[46-48] The guidelines for screening women with familial clustering of breast cancer, however, were released without prior radiobiologic modeling to estimate the risks associated with such recommendations, and none of the existing radiobiologic models would at all account for the availability of equivalent or superior diagnostic methods not associated with ionizing radiation. Current guidelines will subject high-risk women to a substantially higher lifetime glandular dose, imposed on less radiation-tolerant fibroglandular tissue, for a predictably substantially lower diagnostic benefit compared with regular mammographic screening. Therefore, although the number of mutation carriers was low in the EVA trial, existing evidence (or lack thereof; Appendix) should call for a careful reappraisal of surveillance guidelines for high-risk women younger than age 40 years, especially those with *BRCA1* mutation.

Another important finding of the EVA trial was that MRI was not only superior to mammography for diagnosing invasive breast cancers, but also for DCIS. In the EVA cohort, not only half of the invasive cancers (eight of 16), but also more than half of the DCIS (six of 11) were only MRI detected. This result contradicts earlier studies that suggested MRI to be substantially less sensitive than mammography specifically with regards to DCIS.[25,27] The discrepancy is probably best explained by the advances that have been made in the field of breast MRI since the first screening studies were conducted. The MRI diagnosis of DCIS requires the use of diagnostic criteria that have only recently been described,[32,34] and is improved by observing standards for interpretation and reporting that have only recently been introduced.

Because of the many DCISs picked up by MRI, the DCIS rate in our cohort was 53% during incidence screening. This is more than twice as high as the DCIS rate expected for mammographic screening.[49] To the best of our knowledge, it is the highest rate of preinvasive cancers stages ever reported for breast cancer screening. Although this finding could be considered a particularly successful example of secondary prevention, the high rate of DCIS also raises concerns regarding a possible overdiagnosis.

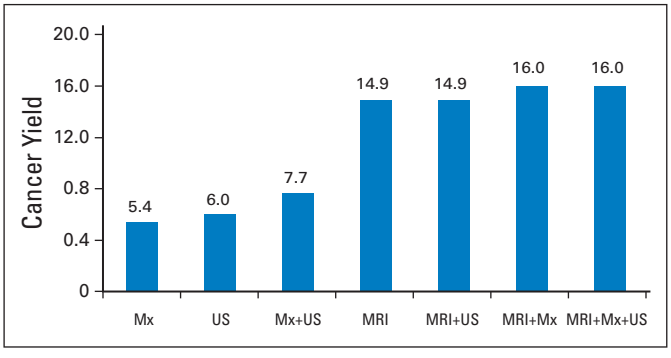

Fig 1. Cancer yield of the different imaging methods, used alone or in combination. Number of true-positive diagnoses per 1,000 complete screening rounds. Mx, mammography; US, ultrasound; MRI, magnetic resonance imaging.

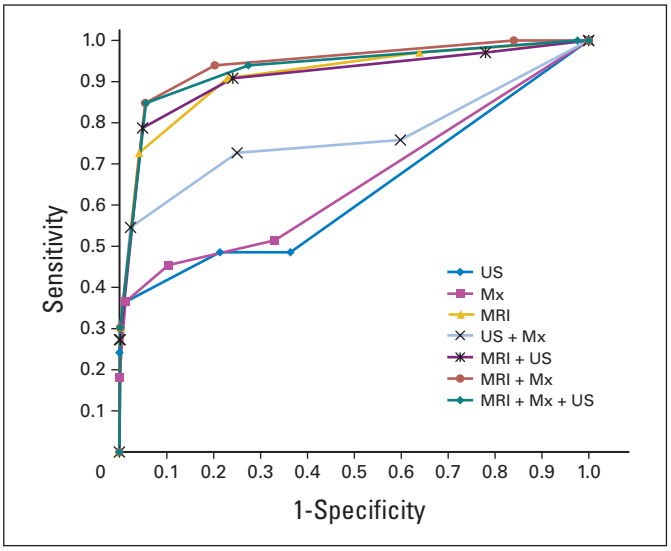

Fig 2. Receiver operating characteristic analysis. Mx, mammography; US, ultrasound; MRI, magnetic resonance imaging.

Table 5. Receiver Operating Characteristics Analysis

Imaging Method	Area	95% CI	Comparison *v* MRI Alone		
			Difference	95% CI	*P*
Mx	0.66	0.55 to 0.77	−0.26	−0.38 to −0.14	< .0001
US	0.63	0.52 to 0.75	−0.28	−0.40 to −0.16	< .0001
Mx + US	0.77	0.55 to 0.88	−0.15	−0.02 to −0.28	< .003
MRI	0.91	0.86 to 0.97	NA	NA	NA
MRI + Mx	0.94	0.90 to 0.98	0.03	0.08 to 0.02	.29
MRI + US	0.91	0.85 to 0.98	0.00	−0.02 to 0.01	.50
MRI + Mx + US	0.93	0.88 to 0.98	0.02	−0.04 to 0.07	.53

Abbreviations: MRI, magnetic resonance imaging; Mx, mammography; US, ultrasound; NA, not available.

For mammographic screening, estimates on overdiagnosis range between 1% and 30% of screen-detected cancers.[50-53] The rate of overdiagnosis of MRI-only detected cancers is unknown. On pathophysiologic grounds, it should be lower. This is because the mammographic hallmarks of cancer (ie, architectural distortions and calcifications) are caused by regressive changes (ie, fibrosis, necrosis)—one reason for the fact that mammographic screening preferably identifies slowly-growing cancers,[54-56] an effect referred to as length time bias, of which overdiagnosis is an extreme form. As opposed to this, a cancer's detectability in MRI is determined by its angiogenic activity (ie, by tissue alterations that have been implicated in carcinogenesis, cancer proliferation, and metastatic growth).[57-61] MRI characteristics can therefore serve as biomarkers for cancer vitality.[62-64] MRI-only cancers tend to exhibit histopathologic evidence of biologic aggressiveness.[14,34,65] This was also true for the DCIS identified in this cohort: all MRI-only detected DCIS exhibited intermediate or high nuclear grading, whereas the only DCIS missed by MRI (picked up by mammography) was the only low-grade DCIS in the cohort. Moreover, the breast cancer incidence observed in this cohort—notably with the DCIS cases included—matched with expectations, although an accurate quantitative incidence prediction is difficult due to the inclusion of women with a personal history of breast cancer in the EVA cohort.[66-68] Finally, this report is one of the first screening trials to report on an interval cancer rate of 0%.[29] Studies on comparable screening cohorts that did not use MRI for screening (eg, the recent American College of Radiology Imaging Network 6666 trial) or that did use MRI, but did not employ the MR-BIRADS DCIS criteria, reported on interval cancer rates between 8% to 55%.[8-12,24-25]

We conclude, therefore, that the DCIS in our cohort do not (or not mainly) represent overdiagnosis. Based on the histopathologic features of the DCIS, based on the expected incidence rates in our cohort, and based on the absence of expected interval cancers, it is probable that the DCIS would indeed have progressed to invasive cancers (and had not it been for MRI, to interval cancers) if we had not diagnosed their respective intraductal precursors.

In close agreement with the recently published American College of Radiology Imaging Network 6666 study,[31] adding ultrasound to mammography increased the cancer yield by almost 50%. However, the direct comparison with MRI in the same patients reveals that even if ultrasound is added to mammography, only about half of the breast cancers are detected. Accordingly, ultrasound appears to be complementary to mammography, but not to MRI, and is no equivalent replacement for MRI. Additional half-yearly ultrasound and CBE did not contribute to an earlier diagnosis of breast cancer, either.

The use of MRI, and even more so the use of ultrasound, led to additional short-term follow-up examinations and additional core biopsies. This may cause harm and unnecessary anxieties. However, there is evidence to suggest that women at elevated risk perceive the additional work-up of (false-positive) diagnoses as an acceptable part of intensified surveillance.[69]

For this multi-institutional study, quality assurance was implemented for MRI by enforcing the use of standardized MR-BIRADS interpretation criteria, and by accepting only sites that interpret at least 200 breast MRI studies per year and have verifiable experience with MR-guided biopsies. Although these requirements are still substantially lower than those for mammographic screening,[70] the positive predictive value of breast MRI was not lower, but higher than that of mammography. This is in keeping with more recent results on MRI for screening[28,29,34] and suggests that the low positive predictive value reported in early publications on screening breast MRI does not constitute a modality-inherent limitation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Christiane Kuhl, Heribert Bieling, Andrea Rieber-Brambs, Maximilian Reiser, Hans H. Schild
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CORRECTIONS

Author Correction

The May 20, 2010, abstract by Attal et al, entitled, "Lenalidomide maintenance after transplantation for myeloma" [J Clin Oncol 28:15S, 2010 (suppl; abstr 8018)], contained an error.

In the Methods section, the first sentence was given as: "Patients, under 65 years of age, with non-progressive disease after a first line ASCT (performed within the last 6 months) were randomized to receive a consolidation with lenalidomide (25 mg/d, 21 days/month, for 2 months) followed by a maintenance with either lenalidomide (10 to 15 mg/d) until relapse (Arm A) or placebo (Arm B)."

whereas it should have been:

"Patients, under 65 years of age, with non-progressive disease after a first line ASCT (performed within the last 6 months) were randomized to receive a consolidation with lenalidomide (25 mg/d, 21 days/month, for 2 months) followed by a maintenance with either **placebo until relapse (Arm A) or lenalidomide (10 to 15 mg/d) until relapse (Arm B)**."

The online version has been corrected in departure from the print. The authors apologize to the readers for the mistake.

Journal Corrections

The February 20, 2010, article by Gore et al, entitled, "Single Cycle of Arsenic Trioxide–Based Consolidation Chemotherapy Spares Anthracycline Exposure in the Primary Management of Acute Promyelocytic Leukemia" (J Clin Oncol 28: 1047-1053, 2010), contained errors.

In Figure 2, the dosage for cytarabine was given as 0.667 **mg**/m^2/d, whereas it should have been 0.667 **g**/m^2/d.

In the first paragraph of the Discussion section, reference 23 was cited in the first sentence, whereas it should have been reference 25. Also, references 23 and 24 were cited in the second sentence, whereas it should have been references 25 and 26.

The online version has been corrected in departure from the print. *Journal of Clinical Oncology* and the authors apologize to the readers for the mistakes.

DOI: 10.1200/JCO.2010.32.4202

The March 20, 2010, article by Kuhl et al entitled, "Prospective Multicenter Cohort Study to Refine Management Recommendations for Women at Elevated Familial Risk of Breast Cancer: The EVA Trial" (J Clin Oncol 28:1450-1457, 2010), contained errors.

In the Results section, the third sentence of the first paragraph was given as: "Annual breast cancer incidence was 15.5% (27 of 1,741), with 13.9% (10 of 718) in the first, 16.2% (10 of 617) in the second and 17.2% (seven of 406) in the third year (Appendix Fig A1, online only)."

whereas it should have been:

"Annual breast cancer incidence was 15.5‰ (27 of 1,741), with 13.9‰ (10 of 718) in the first, 16.2‰ (10 of 617) in the second and 17.2‰ (seven of 406) in the third year (Appendix Fig A1, online only)."

In Figure A1, the *y*-axis was labeled as "Breast Cancer Incidence (%)," whereas it should have been "Breast Cancer Incidence (‰)."

The online version has been corrected in departure from the print. *Journal of Clinical Oncology* apologizes to the authors and readers for the mistakes.

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