VOLUME 23 · NUMBER 33 · NOVEMBER 20 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Mammography, Breast Ultrasound, and Magnetic Resonance Imaging for Surveillance of Women at High Familial Risk for Breast Cancer

*Christiane K. Kuhl, Simone Schrading, Claudia C. Leutner, Nuschin Morakkabati-Spitz, Eva Wardelmann, Rolf Fimmers, Walther Kuhn, and Hans H. Schild*

From the Departments of Radiology, Pathology, Medical Statistics and Epidemiology, and Gynecology, University of Bonn, Bonn, Germany.

Submitted November 14, 2004; accepted August 9, 2005.

Supported by a grant from the Förderverein für Radiologie an der Universität Bonn. The High Risk Clinics at the Department of Gynecology was supported by the German Cancer Aid (Deutsche Krebshilfe).

Presented in part at the Plenary Session of the 39th Annual Meeting of the American Society of Clinical Oncology, May 31-June 3, 2003, Chicago, IL.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Christiane K. Kuhl, MD, Department of Radiology, University of Bonn, Sigmund-Freud-Str 25, D-53105 Bonn, Germany; e-mail: kuhl@uni-bonn.de.



0732-183X/05/2333-8469/$20.00

DOI: 10.1200/JCO.2004.00.4960

## ABSTRACT

### Purpose
To compare the effectiveness of mammography, breast ultrasound, and magnetic resonance imaging (MRI) for surveillance of women at increased familial risk for breast cancer (lifetime risk of 20% or more).

### Patients and Methods
We conducted a surveillance cohort study of 529 asymptomatic women who, based on their family history and/or mutational analysis, were suspected or proven to carry a breast cancer susceptibility gene (*BRCA*). A total of 1,542 annual surveillance rounds were completed with a mean follow-up of 5.3 years. Diagnostic accuracies of the three imaging modalities used alone or in different combinations were compared.

### Results
Forty-three breast cancers were identified in the total cohort (34 invasive, nine ductal carcinoma-in-situ). Overall sensitivity of diagnostic imaging was 93% (40 of 43 breast cancers); overall node-positive rate was 16%, and one interval cancer occurred (one of 43 cancers, or 2%). In the analysis by modality, sensitivity was low for mammography (33%) and ultrasound (40%) or the combination of both (49%). MRI offered a significantly higher sensitivity (91%). The sensitivity of mammography in the higher risk groups was 25%, compared with 100% for MRI. Specificity of MRI (97.2%) was equivalent to that of mammography (96.8%).

### Conclusion
Mammography alone, and also mammography combined with breast ultrasound, seems insufficient for early diagnosis of breast cancer in women who are at increased familial risk with or without documented *BRCA* mutation. If MRI is used for surveillance, diagnosis of intraductal and invasive familial or hereditary cancer is achieved with a significantly higher sensitivity and at a more favorable stage.

*J Clin Oncol 23:8469-8476. © 2005 by American Society of Clinical Oncology*

## INTRODUCTION

The adequate management of women who carry a high lifetime risk for breast cancer is an issue of debate. This holds especially true if familial or hereditary breast cancer owing to a germline mutation of a breast cancer susceptibility gene (*BRCA*) is suspected or has been documented by mutational analysis.[1-4] *BRCA* mutation carriers face a lifetime risk for breast cancer of up to 65% to 80%[5,6]; they tend to develop the disease early during lifetime and to develop breast cancers that, compared with sporadic breast cancers, exhibit adverse histopathologic features suggestive of biologic aggressiveness.[7-11] Mutation carriers who were already diagnosed with the disease face a risk of up to 60% to develop second primary breast cancers.[10-12] There is evidence to suggest that bilateral preventive mastectomy reduces the incidence of breast cancer in women diagnosed with *BRCA1* and

*BRCA2* mutations compared with so-called watchful waiting.[13-16] Nonetheless, the perceived mutilating effects of mastectomy make the decision for surgical prevention difficult, and current national guidelines do not recommend it as standard management. Secondary prevention (ie, intensified surveillance) is recommended rather than preventive mastectomy for so-far healthy women and, because of the high risk of second primaries, also for women who already developed breast cancer.[11]

Current guidelines recommend screening by clinical breast examination and mammography starting by age 30 years at the latest.[1-4] However, the results that have been published on mammographic screening so far are not encouraging. This has been attributed to the dense breast tissue of young screening participants, the frequently atypical imaging presentation, and the rapid growth of hereditary breast cancers.[17-22]

Given the limited efficacy of mammographic and clinical surveillance of women at high genetic risk, other nonmammographic imaging technologies have been suggested, the most important candidates being high-frequency breast ultrasound and magnetic resonance imaging (MRI).[22-26] In particular, ultrasound has an established role to complement diagnostic mammography in young patients.[23]

We conducted a systematic intraindividual comparative cohort study to investigate the effectiveness of different imaging modalities (and combinations thereof) for secondary prevention in 529 women with increased familial risk. The objective was to compare, intraindividually, the respective diagnostic accuracies achieved with mammography, breast ultrasound, and MRI. Preliminary results of the first two screening rounds in the first 192 study participants (with nine cancers) have been published in a previous article.[22]

## PATIENTS AND METHODS

### Study Setup and Design

This cohort study was conducted at the University of Bonn Medical School, an academic tertiary care center in Germany. Cooperating institutions were the Departments of Radiology, Gynecology and Gynecologic Oncology, Epidemiology and Biostatistics, and Pathology. The protocol was reviewed and approved by the institutional review board, and written informed consent was obtained from all study participants.

### Definition of Risk

Study participants were recruited by the so-called High-Risk Clinics of the Department of Gynecology between February 1996 and February 2002. Women were recruited if they were clinically asymptomatic and met the criteria for high familial risk as defined by the Consortium on Familial Breast and Ovarian Cancer of the German Cancer Aid, corresponding to a lifetime risk for breast cancer of at least 20%.[27] In short, individuals with the following family history were included: individuals from families with two or more cases of breast cancer on the same side of the family, including at least two cases with onset before age 50 years, or with breast and ovarian cancer, irrespective of age; families with three or more cases of breast cancer on the same side of the family; families with at least one case of breast cancer diagnosed before age 35 years; and families with at least one case of male breast cancer. Women who, after additional genetic counseling, met the criteria for high familial risk were offered mutational analysis, and, irrespective of the test result or their willingness to undergo testing, were eligible for study participation. A personal history of breast cancer was no exclusion criteria provided that the patient had not undergone bilateral mastectomy, had not received chemotherapy during the last 12 months, and had no metastases. The rationale for allowing also women with a personal history of breast cancer to participate in the surveillance program is the high risk for second primary breast cancers associated with *BRCA* mutations.[10,12] Women with current clinical signs or symptoms of breast cancer, women who had undergone bilateral mastectomy, or women who were diagnosed with metastatic disease were excluded. In women without personal history of breast cancer, the individual risk was quantified according to the Claus model,[28] using the CancerGene software version 3.4 (University of Texas, Southwestern Medical Center, Dallas, TX). For further analysis of diagnostic accuracy as a function of risk status, women were stratified according to the calculated risk and mutational status in three different categories: those with moderate lifetime risk (20%), high lifetime risk (20% to 40%), and mutation carriers.

### Study Protocol

The protocol for annual surveillance consisted of clinical breast examination (CBE), ultrasound, two-view mammography, and breast MRI. The CBE and the three imaging studies were performed within a time frame of 8 weeks. Each imaging study was read and scored independently by a different radiologist who had substantial expertise with the respective breast imaging technique. The readers were informed about the clinical findings (CBE) and the risk status of the patient, but blinded to the results of the respective other imaging modalities.

In between annual surveillance rounds, half-yearly CBE and breast ultrasound were performed. If at that regular half-yearly visit, a finding suggestive of abnormality was made, additional mammography and breast MRI were obtained before biopsy was initiated.

Surveillance was started at age 30 years or 5 years before the youngest family member affected with the disease; no upper age limit was defined. In the first 2 years of the study, no mammogram was obtained in women younger than 30 years; similarly, in young women aged 30 to 39 years, no mammogram was obtained in the second surveillance round if the breast tissue had been dense at the baseline mammogram. This protocol was applied during the first 2 years of the protocol; it was abandoned thereafter in that all participants underwent mammography irrespective of age and breast density. Also in the group of women recruited during the first 2 years who were not to undergo mammography per protocol, a mammogram was always obtained in the event that a suspicious finding was made by CBE and/or by ultrasound or MRI.

### Mammography

Annual conventional film-screen mammography was performed with at least two views per breast (medio-lateral oblique and cranio-caudal views). Additional views or spot compression views were obtained where appropriate. Mammograms were obtained and interpreted in accordance with current German Radiological Practice Guidelines. Diagnoses were coded according to the Breast Imaging Reporting and Data system (BI-RADS)[29] diagnostic categories on a five-point scale, with BI-RADS 1 (negative), 2

**Table 1.** Demographic Data and Risk Profiles

| | All Women | Personal History of Breast Cancer | No Personal History of Breast Cancer | Lifetime Risk of 20%* | Lifetime Risk of 21%-40%* | Mutation Carriers |
|---|---|---|---|---|---|---|
| No. of patients | 529 | 139 | 390 | 110 | 241 | 43 |
| Age, years | | | | | | |
| Mean | 41.7 | 42.9 | 39.6 | 43.8 | 40.3 | 38.9 |
| SD | 9.4 | 8.2 | 8.9 | 10.3 | 9.3 | 4.5 |
| Median | 40 | 41 | 38 | 45 | 39 | 39 |
| Range | 27-59 | 32-57 | 27-59 | 35-59 | 31-57 | 27-51 |
| Total No. of surveillance rounds | 1,701 | 435 | 1,266 | 352 | 751 | 167 |
| No. of cancers | 43 | 12 | 31 | 6 | 20 | 8 |
| Detection rates† | | | | | | |
| Prevalence | 26.5/1,000 | 21.5/1,000 | 28.2/1,000 | 27.3/1,000 | 24.9/1,000 | 69.8/1,000 |
| Year 1 | 14/529 | 3/139 | 11/390 | 3/110 | 6/241 | 3/43 |
| Mean incidence | 25.3/1,000 | 27.6/1,000 | 24.5/1,000 | 17.1/1,000 | 26.6/1,000 | 47.9/1,000 |
| Years 2-6 | 29/1,172 | 9/296 | 20/876 | 3/242 | 14/510 | 5/124 |

Abbreviation: SD, standard deviation.
*Calculated according to the Claus model.
†Breast cancer detection rates (incidence and prevalence) per 1,000 participants.

(benign finding), 3 (probably benign; short-term follow-up recommended), 4 (suspicious abnormality; biopsy recommended), and 5 (highly suggestive of malignancy). No BI-RADS 0 was assigned (assessment incomplete), because women were not recalled, but the entire diagnostic work-up (additional views, spot compression) was done ad hoc (ie, immediately in case an abnormality was identified on the standard mammographic views).

### *Breast Ultrasound*

Breast ultrasound was performed with 7.5- to 13-MHz probes (Siemens Elegra, GE Logic 500, and ATL HDI 5000; Siemens, Erlangen, Germany); the entire breast was systematically examined by the physician who interpreted the study. Diagnoses were scored on a five-point scale identical to the mammographic BI-RADS categories.

### *MRI*

Standard dynamic axial contrast-enhanced subtracted breast MRI of both entire breasts was performed on a 1.5T system (NT/INTERA; Philips, Best, the Netherlands) with a 256 × 256 or (as of January 2000) a 512 × 400 imaging matrix before and nine times (256 matrix) or four times (512 matrix) after injection of 0.1 mmol/kg body weight gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany).[22] MRI diagnoses were scored on a five-point scale identical to the mammographic BI-RADS categories.

### *Follow-Up and Validation of Imaging Diagnoses*

Validation was achieved by either histology (for positive imaging studies) or by follow-up (for negative imaging studies). If a breast cancer was identified clinically (ie, became palpable) in between surveillance rounds or at the 6-month clinical visit, the imaging studies of the respective preceding surveillance round were considered false negative and the respective cancer was considered as interval cancer. Data of the last surveillance round were validated as follows: a total of 428 women opted to continue surveillance at our institution; another 52 were followed up by a standardized telephone interview. In six women who opted to undergo prophylactic mastectomy, the imaging findings of the last surveillance round were validated by thin-section analysis of the mastectomy specimen.

### *Clinical Management and Biopsy*

The actual clinical management was defined according to current clinical practice guidelines (ie, on the basis of the combined analysis of all three imaging studies) as follows: in mammographic findings categorized as BI-RADS 4 or 5, biopsy was recommended

**Table 2.** Diagnostic Sensitivities for the Different Imaging Modalities in the Entire Cohort and in the Different Risk Categories

| | Mammography | | Ultrasound | | Mammography + Ultrasound | | MRI | | Mammography + MRI | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Sensitivity (%) | TP/TP + FN | Sensitivity (%) | TP/TP + FN | Sensitivity (%) | TP/TP + FN | Sensitivity (%) | TP/TP + FN | Sensitivity (%) | TP/TP + FN |
| All women | 32.6 | 14/43 | 39.5 | 17/43 | 48.8 | 21/43 | 90.7 | 39/43 | 93.0 | 40/43 |
| With personal history of breast cancer | 33.3 | 4/12 | 41.7 | 5/12 | 41.7 | 5/12 | 66.6 | 8/12 | 75.0 | 9/12 |
| Without personal history of breast cancer | 32.3 | 10/31 | 38.7 | 12/31 | 51.6 | 16/31 | 100.0 | 31/31 | 100.0 | 31/31 |
| Risk 20% | 50.0 | 3/6 | 67.7 | 4/6 | 83.3 | 5/6 | 100.0 | 6/6 | 100.0 | 6/6 |
| Risk 21%-40% | 25.0 | 5/20 | 30.0 | 6/20 | 45.0 | 9/20 | 100.0 | 20/20 | 100.0 | 20/20 |
| Mutation carriers | 25.0 | 2/8 | 25.0 | 2/8 | 37.5 | 3/8 | 100.0 | 8/8 | 100.0 | 8/8 |

Abbreviations: MRI, magnetic resonance imaging; TP, true positive diagnoses (No. of cancer detected); FN, true positive and false negative diagnoses (total No. of cancers).

**Table 3.** Diagnostic Specificities for the Different Imaging Modalities in the Entire Cohort and in the Different Risk Categories

| | Mammography | | Ultrasound | | Mammography + Ultrasound | | MRI | | Mammography + MRI | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Specificity (%) | TN/TN + FP | Specificity (%) | TN/TN + FP | Specificity (%) | TN/TN + FP | Specificity (%) | TN/TN + FP | Specificity (%) | TN/TN + FP |
| All women | 96.8 | 1,364/1,409 | 90.5 | 1,275/1,409 | 89.0 | 1,254/1,409 | 97.2 | 1,370/1,409 | 96.1 | 1,354/1,409 |
| With personal history of breast cancer | 95.5 | 252/264 | 88.3 | 233/264 | 87.1 | 230/264 | 96.2 | 254/264 | 95.1 | 251/264 |
| Without personal history of breast cancer | 97.1 | 1,112/1,145 | 91.0 | 1,042/1,145 | 89.4 | 1,024/1,145 | 97.5 | 1,116/1,145 | 96.3 | 1,103/1,145 |
| Risk 20% | 96.5 | 302/313 | 90.4 | 283/313 | 88.2 | 276/313 | 97.4 | 305/313 | 95.5 | 299/313 |
| Risk 21-40% | 97.4 | 676/694 | 91.2 | 633/694 | 89.9 | 624/694 | 97.7 | 678/694 | 97.0 | 673/694 |
| Mutation carriers | 96.9 | 154/159 | 91.2 | 145/159 | 88.7 | 141/159 | 97.5 | 155/159 | 94.4 | 150/159 |

Abbreviations: MRI, magnetic resonance imaging; TN, true negative diagnoses; TN + FP, true negative + false positive diagnoses.

irrespective of imaging findings in breast ultrasound or MRI. Mammographic findings categorized as BI-RADS 3 were managed by a short-term (6 months) follow-up until they received either a BI-RADS 2 category or were clarified by biopsy. Ultrasound findings categorized as BI-RADS 3 (probably benign) were managed by short-term sonographic follow-up. Ultrasound findings categorized as suggestive of abnormality (categories 4 and 5) were managed by ultrasound-guided biopsy (14G, semi-automatic or automatic biopsy gun) except for the following constellation: if an ultrasound finding that was suspicious had a clearly benign correlate on mammography and/or breast MRI (ie, findings that would explain the respective sonographic lesion appearance such as fat necrosis, scar tissue, or collapsed cyst), no biopsy was performed. MRI findings that were scored as suspicious (4 and 5) and that were not visible on mammography and/or on ultrasound were managed by magnetic resonance–guided biopsy.[30] In MRI findings that were categorized as BI-RADS 3 (probably benign), short-term follow-up after 6 months was recommended, with further management corresponding to the management of mammographic BI-RADS 3 lesions.

### *Data Analysis and Statistical Analysis*

The diagnoses established in the independent readings were used to calculate the sensitivities, specificities, and positive predictive values (PPVs) of the three different imaging studies under evaluation. In addition, to evaluate the utility of the combined use of mammography plus ultrasound and of MRI combined with mammography and/or ultrasound, further analyses were made by combining the respective imaging studies.

In accordance with the BI-RADS lexicon and current clinical practice,[29] all BI-RADS categories 1 to 3 were taken as negative, and the categories 4 and 5 were taken as positive test results. This means that studies that required short-term follow-up examinations (BI-RADS 3) were not considered positive for the calculation of sensitivity or PPV. A diagnosis of invasive cancer or ductal carcinoma-in-situ (DCIS) was accepted as a malignant diagnosis; others, including lobular carcinoma-in-situ and atypical ductal hyperplasia, were categorized as benign.

To account for repeated observations made in the same patients, we used generalized estimation equations under a logistic model to calculate confidence limits for sensitivity, specificity, and PPV.

## RESULTS

### *Study Cohort and Study Period*

A total 590 women met the criteria of high familial risk. Of those, 12 patients presented with a clinical abnormality suggestive of breast cancer at their first visit; after undergoing therapy for breast cancer, these women were followed

**Table 4.** Positive Predictive Value for the Different Imaging Modalities in the Entire Cohort and in Different Risk Categories

| | Mammography | | Ultrasound | | Mammography + Ultrasound | | MRI | | Mammography + MRI | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Positive Predictive Value (PPV) | TP/ TP + FP | Positive Predictive Value (PPV) | TP/ TP + FP | Positive Predictive Value (PPV) | TP/ TP + FP | Positive Predictive Value (PPV) | TP/ TP + FP | Positive Predictive Value (PPV) | TP/ TP + FP |
| All women | 23.7 | 14/59 | 11.3 | 17/151 | 11.9 | 21/176 | 50.0 | 39/78 | 42.1 | 40/95 |
| With personal history of breast cancer | 25.0 | 4/16 | 13.9 | 5/36 | 12.8 | 5/39 | 44.4 | 8/18 | 40.9 | 9/22 |
| Without personal history of breast cancer | 23.3 | 10/43 | 10.4 | 12/115 | 11.7 | 16/137 | 51.7 | 31/60 | 42.5 | 31/73 |
| Risk 20% | 21.4 | 3/14 | 11.8 | 4/34 | 11.9 | 5/42 | 42.9 | 6/14 | 30.0 | 6/20 |
| Risk 21-40% | 21.7 | 5/23 | 9.0 | 6/67 | 11.4 | 9/79 | 55.6 | 20/36 | 51.2 | 21/41 |
| Mutation carriers | 28.6 | 2/7 | 17.6 | 3/17 | 14.3 | 3/21 | 66.7 | 8/12 | 47.1 | 8/17 |

Abbreviations: MRI, magnetic resonance imaging; TP, true positive diagnoses (No. of cancers detected); TP + FP, true positive + false positive diagnoses (total No. of biopsy recommendations).

up with the same imaging protocol as the study participants, but their data were excluded from further analysis. A total of 578 women were clinically asymptomatic and therefore eligible for study participation. Of those, 49 women underwent only one surveillance round and were lost to follow-up thereafter. The data sets of these women were discarded from analysis because of lack of validation. Accordingly, the final study cohort consisted of a total of 529 clinically asymptomatic high-risk women. Demographic data, mutational status, fraction of women with or without personal history of breast cancer, and familial risk levels of the final cohort are listed in Table 1.

Women were observed for a mean observation period of 5.3 years (range, 2 to 7 years) per participant, yielding a total 1,701 woman-years in the 529 participants. Prevalence and incidence of breast cancer in the cohort were calculated for the entire observation period of 1,701 woman-years.

The analysis of the diagnostic accuracy of the three imaging techniques under investigation was based on a total 1,452 annual surveillance rounds for which data on all three imaging modalities were available. Data of another 249 annual surveillance rounds that were collected in 86 of 529 participants during the first 2 years of the study were incomplete in that no mammogram was obtained in accordance with the protocol (specified below); these data sets were not considered for analysis of diagnostic accuracies.

### Breast Cancers

In the entire cohort of 529 participants, a total of 43 breast cancers were identified in 41 patients: 34 invasive cancers and nine DCIS. Thirty-one cancers were identified in 30 women without previous history of cancer, and another 12 cancers in 11 women with history of breast cancer. Of the latter 12 cancers, three cancers were classified as local recurrences, and nine cancers occurred in the contralateral breast and/or were histologically categorized as second primary cancers (Table 1).

Two cancers were palpable at the time of diagnosis (one at the regular screening interval; one was the interval cancer diagnosed in-between screening rounds); the remaining cancers were clinically asymptomatic (ie, not palpable). None of the 43 cancers were diagnosed by CBE alone; the two cancers that were clinically palpable at the time of diagnosis were also visualized with breast ultrasound and MRI (yet not with mammography).

Additional separate multifocal or multicentric invasive and/or intraductal cancers were identified in 19 (44%) of 43 patients with breast cancer. The diagnostic indices of the three imaging modalities were, however, calculated per breast with cancer, not per single cancer.

### Performance of the Screening Methods

Forty (93%) of the 43 breast cancers were diagnosed by imaging studies. The diagnostic indices of the different imaging modalities in the different risk categories are listed in Tables 2 through 4. TNM stages and nuclear gradings of primary cancers are listed in Table 5. Prognostically relevant details of the cancers itemized by imaging mode of detection are listed in Table 6.

Of the 40 cancers that were diagnosed by imaging studies, 14 cancers were identified by mammography, 17 cancers were identified by ultrasound, 21 cancers were identified if mammography and ultrasound were combined, 39 cancers were identified by MRI, and all 40 cancers were identified if MRI was combined with mammography.

The one additional cancer that was diagnosed only by means of mammography was a recurrent DCIS plus microinvasive component in a 36-year-old patient. This lesion had been correctly classified as suggestive of abnormality (BI-RADS 4) on mammography due to clustered calcifications that had newly developed compared with previous films. The lesion had also been identified, but falsely categorized as probably benign on MRI.

No additional cancer was diagnosed only by means of ultrasound at the regular annual surveillance rounds. However, two of the 43 cancers were diagnosed at the half-yearly ultrasound screening study. Both cancers were not palpable;

**Table 5.** Stages of 31 Primary Breast Cancers Diagnosed During the Study Period in Women Without Personal History of Breast Cancer

| | Study Participants Without Personal History of Breast Cancer (n = 390) | |
|---|---|---|
| | No. | % |
| pT stage, n = 31 | | |
| pTis | 7 | 23 |
| pT1 | 22 | 71 |
| T1a | 2 | 6 |
| T1b | 7 | 23 |
| T1c | 13 | 42 |
| pT2 | 2 | 6 |
| pT3 | — | — |
| pT4 | — | — |
| pN stage, n = 31 | | |
| N0 | 26 | 84 |
| N+ | 5 | 16 |
| N1 | 5 | 16 |
| N2 | — | — |
| N3 | — | — |
| M stage, n = 30* | | |
| M0 | 29 | 97 |
| M+ | 1 | 3 |
| Grading of invasive cancers, n = 24 | | |
| G1 | 3 | 12 |
| G2 | 10 | 42 |
| G3 | 11 | 46 |
| Grading of intraductal cancers, n = 7 | | |
| Non–high grade | 2 | 29 |
| High grade | 5 | 71 |

*Calculated per patient at the time of breast cancer diagnosis (one patient had synchronous bilateral breast cancer).

**Table 6.** Comparison of Diagnostic Yield of the Different Imaging Modalities Regarding Prognostically Relevant Tumor Features

| | Detected by Mx | Detected by US | Detected by Mx Combined With US | Detected by MRI | Only MRI Detected (not diagnosed with Mx and US) |
|---|---|---|---|---|---|
| No. of primary invasive cancers | 10 | 12 | 16 | 31 | 14 |
| Node-positive primary invasive cancers* | | | | | |
| No. | 4/10 | 5/12 | 5/16 | 5/31 | 0/14 |
| % | 40 | 42 | 31 | 16 | 0 |
| Size of invasive cancers, mm | | | | | |
| Mean | 13.2 | 15.1 | 13.9 | 12.4 | 9.0 |
| SD | 7.8 | 8.1 | 6.4 | 6.7 | 4.3 |
| Median | 12.0 | 13.0 | 13.0 | 11.0 | 7.5 |
| Minimal cancers† | | | | | |
| No. | 5/25 | 3/25 | 6/25 | 23/25 | 18/25 |
| % | 20 | 12 | 24 | 92 | 72 |
| Intraductal cancers | | | | | |
| No. | 3/9 | 0/9 | 3/9 | 8/9 | 5/9 |
| % | 33 | 0 | 33 | 89 | 56 |

Abbreviations: Mx, mammography; US, ultrasound; MRI, magnetic resonance imaging; SD, standard deviation.
*Rate refers to the number of breast cancers with positive axillary lymph nodes over the total number of primary breast cancers diagnosed with the respective imaging modality.
†Minimal cancer is defined as ductal carcinoma-in-situ or small invasive cancers with a size < 10 mm and with negative axillary lymph nodes (N0). Data represent the number of minimal cancers detected by the respective imaging modality over the total number of minimal cancer stages in the entire study cohort.

repeat mammograms at the time of diagnosis were negative (BI-RADS 1 and 2, respectively), and MRI studies were positive (BI-RADS 5) in the two cases.

Nineteen cancers were diagnosed only by means of MRI (Fig 1); these included five intraductal (all high grade) and 14 invasive cancers with a median size of 7.5 mm; all 14 invasive cancers were staged pT1, and all had negative axillary lymph nodes (Table 6).

MRI was significantly ($P < .001$) more sensitive than mammography, ultrasound, and the combination of both (Table 2). MRI offered approximately the same specificity as mammography ($P > .5$), and both MRI and mammography were significantly more specific ($P < .001$) than ultrasound alone or in combination with mammography (Table 3).

Diagnostic sensitivities of mammography and breast ultrasound declined further in the subgroup of 241 women

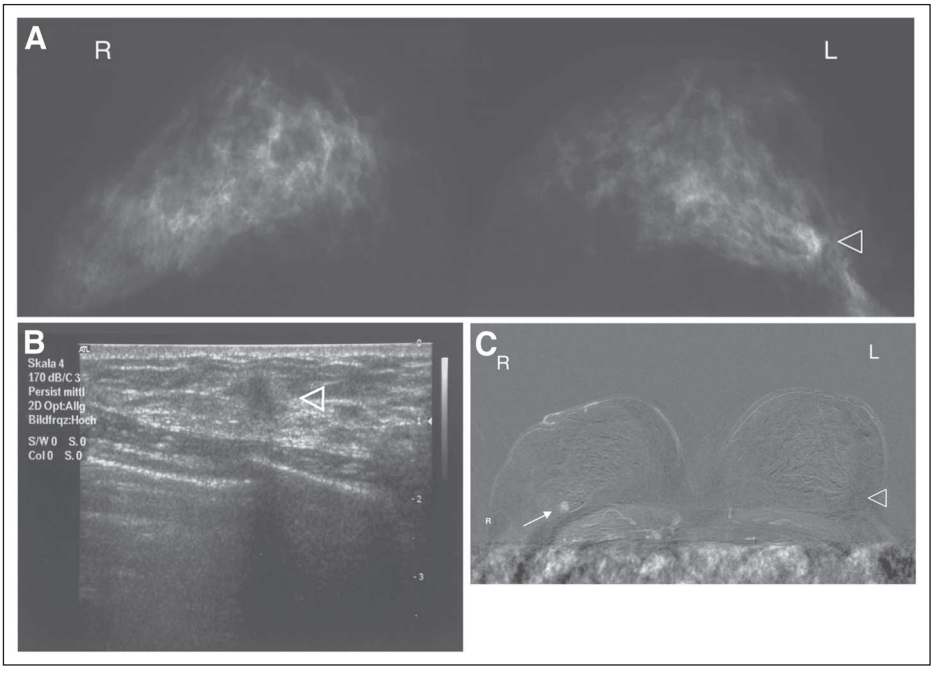


**Fig 1.** First screening of a 53-year-old patient with a family history suggestive of familial breast cancer and personal history of benign breast biopsy on the left breast revealed no clinical findings. Her mammogram (A) and her ultrasound (B) were read as suggestive of cancer in the left breast (arrowhead); the right breast appeared normal. MRI (C) showed only scar tissue on the left (arrowhead), but revealed a suspicious lesion in the right breast (long arrow). Biopsy of the right breast revealed an invasive ductal cancer, pT1b, G3, N0, M0. Absence of cancer in the left breast was confirmed by follow-up for 4 years.

at lifetime risk of 20% to 40% according to Claus model; mammographic and breast ultrasound sensitivity was lowest in the group of 43 mutation carriers. In both groups, MRI maintained its high sensitivity level (Table 2).

A diagnosis of category BI-RADS 3 (short-term follow-up recommended) was assigned by mammography in 9.5% (139 of 1,452), by ultrasound in 16.7% (243 of 1,452), and by breast MRI in 11.5% (167 of 1,452) of surveillance rounds. The rate of recommendations for short-term follow-up did not differ statistically significantly between mammography and MRI; both (mammography and MRI) had significantly lower rates of BI-RADS 3 categories compared with breast ultrasound.

False-positive diagnoses (BI-RADS 4 or 5) were made by mammography in 45 women, by ultrasound in 134 women, and by MRI in 39 women. If mammography and ultrasound were read in combination, the number of false-positive diagnoses increased to 155. Seventy-eight of the 134 ultrasound category BI-RADS 4 or 5 findings were not biopsied because a clearly benign correlate had been identified on the respective mammogram and/or breast MRI studies. None of these findings turned out to be breast cancer on follow-up.

## DISCUSSION

In this prospective cohort study comparing three different breast imaging modalities (mammography, high-frequency breast ultrasound, and MRI) in patients at high familial risk for breast cancer, we found that MRI had the highest sensitivity, specificity, and positive predictive value for the detection of invasive as well as of intraductal cancer. Indeed, even when we used mammography and breast ultrasound in combination, not even half of all cancers were prospectively diagnosed, whereas breast MRI alone enabled us to diagnose 91% (39 of 43 cancers). Among the total study population, 19 cancers were diagnosed by means of MRI alone, whereas only one (a second primary) cancer was diagnosed by means of mammography alone. By adding mammography to MRI, sensitivity did not improve to a statistically significant degree (from 39 of 43 cancers, or 91%, to 40 of 43 cancers, or 93%). In the subgroup of women with higher-risk profiles or in documented mutation carriers, sensitivity of MRI increased to 100%, whereas that of mammography decreased further to 25%.

Our results demonstrate that systematic surveillance with MRI allows an early diagnosis of familial or hereditary breast cancer. Tumor stage at the time of diagnosis in our cohort compares favorably with published data regarding surveillance in high-risk women without systematic MRI: the node-positive rates for mammographic surveillance of women at high genetic risk range between 35% and 44%, compared with 16% in our cohort. The rate of interval cancers (ie, cancers that become clinically obvious after a normal or benign screening examination) with mammographic surveillance has been reported to range between 43% and 60%, compared with 2% in our cohort.[19-21]

MRI of the breast has already been demonstrated to be of clinical value for local staging before breast cancer surgery and for the assessment of patients with inconclusive conventional imaging findings.[32,33] However, MRI is still considered an investigational technique for surveillance and screening of asymptomatic women with normal conventional imaging findings. Apart from cost, the most important reason has been the reported low PPV and specificity of breast MRI and its allegedly low sensitivity for DCIS. However, MRI in our hands offered the highest sensitivity for invasive as well as intraductal cancers (Table 6). This high sensitivity was not achieved at the expense of specificity, which was equivalent to that achieved with mammography, and significantly higher than that achieved with breast ultrasound. We suppose that this is mainly due to the fact that in our cohort, all imaging studies—notably including MRI—were interpreted by readers who had substantial expertise with the respective imaging modalities.

Our own primary results,[22] currently published material on MRI screening in women at increased genetic risk,[24-26] as well as these results after several years of follow-up are concordant in that MRI seems to be significantly more sensitive compared with mammography. If breast ultrasound is used in combination with mammography, it can help compensate for some but by far not for all of the shortcomings of mammography, and it causes a substantial number of false-positive diagnoses. If MRI is available for surveillance, mammography proved to be of limited and ultrasound of no additional value. Screening ultrasound may, however, be useful to bridge the relatively long time interval between the annual surveillance rounds.

In view of the insufficient diagnostic accuracy of mammography and breast ultrasound, we propose that breast MRI should be considered an integral part of surveillance programs for women at high familial risk—in particular in documented carriers of pathogenic *BRCA* mutations, but also for women without documented mutation.

The number of cancers in the subgroup at moderately (20%) increased risk was too low to make valid recommendations regarding appropriate surveillance strategies. However, it is noteworthy that also in this group, MRI offered the highest sensitivity while maintaining its high specificity—findings that may be used to justify further studies. Further work is also needed to assess the risk/benefit ratio of mammography and MRI in young *BRCA1* mutation carriers who may exhibit an increased radiosensitivity.[34,35]

Our data suggest that, compared with mammography or even the combined use of mammography and high-frequency breast ultrasound, surveillance with MRI does allow an earlier diagnosis of familial breast cancer. We want to underscore, however, that early diagnosis is only a surrogate marker for the efficacy of a surveillance program.

Whether or not an earlier diagnosis will ultimately translate into a reduced morbidity and mortality is still unclear[36] and needs to be investigated in further clinical trials.

## Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

## REFERENCES


**1.** Pichert G, Bolliger B, Buser K, et al: Evidence-based management options for women at increased breast/ovarian cancer risk. Ann Oncol 14:9-19, 2003

**2.** National Comprehensive Cancer Network: Clinical Practice Guidelines in Oncology, version 1, 2003. http://www.nccn.org/physician_gls/f_guidelines.html

**3.** Vasen HF, Haites NE, Evans DG, et al: Current policies for surveillance and management in women at risk of breast and ovarian cancer: A survey among 16 European family cancer clinics—European Familial Breast Cancer Collaborative Group. Eur J Cancer 34:1922-1926, 1998

**4.** Burke W, Daly M, Garber J, et al: Recommendations for follow-up care of individuals with an inherited predisposition to cancer: II. BRCA1 and BRCA2—Cancer Genetics Studies Consortium. JAMA 277:997-1003, 1997

**5.** Ford D, Easton DF, Bishop DT, et al: Risks of cancer in BRCA1-mutation carriers: Breast Cancer Linkage Consortium. Lancet 343:692-695, 1994

**6.** Antoniou A, Pharoah PD, Narod S, et al: Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: A combined analysis of 22 studies. Am J Hum Genet 72:1117-1130, 2003

**7.** Armes JE, Egan AJ, Southey MC, et al: The histologic phenotypes of breast carcinoma occurring before age 40 years in women with and without BRCA1 or BRCA2 germline mutations: A population-based study. Cancer 83: 2335-2345, 1998

**8.** Lakhani SR, Jacquemire J, Sloane JP, et al: Multifactorial analysis of differences between sporadic breast cancers and cancers involving BRCA1 and BRCA2 mutations. J Natl Cancer Inst 90:1138-1145, 1998

**9.** Marcus JN, Watson P, Page DL, et al: Hereditary breast cancer: Pathobiology, prognosis, and BRCA1 and BRCA2 gene linkage. Cancer 77:697-709, 1996

**10.** Breast Cancer Linkage Consortium: Pathology of familial breast cancer: Differences between breast cancers in carriers of BRCA1 or BRCA2 mutations and sporadic cases. Lancet 349:1505-1510, 1997

**11.** Metcalfe K, Lynch HT, Ghadirian P, et al: Contralateral Breast Cancer in BRCA1 and BRCA2 Mutation Carriers. J Clin Oncol 22:2328-2335, 2004

**12.** Hoskins KF, Stopfer JE, Calzone KA, et al: Assessment and counseling for women with a family history of breast cancer: A guide for clinicians. JAMA 273:577-585, 1995

**13.** Metcalfe KA, Goel V, Lickley L, et al: Prophylactic bilateral mastectomy: Patterns of practice. Cancer 95:236-242, 2002

**14.** Hartmann LC, Schaid DJ, Woods JE, et al: Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med 340:77-84, 1999

**15.** Meijers-Heijboer H, van Geel B, van Putten WL, et al: Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 345:159-164, 2001

**16.** Rebbeck TR, Friebel T, Lynch HT, et al: Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: The PROSE Study Group. J Clin Oncol 22:1055-1062, 2004

**17.** Kerlikowske K, Grady D, Barclay J, et al: Positive predictive value of screening mammography by age and family history of breast cancer. JAMA 270:2444-2450, l993

**18.** Tilanus-Linthorst M, Verhoog L, Obdeijn IM, et al: A BRCA1/2 mutation, high breast density and prominent pushing margins of a tumor independently contribute to a frequent false-negative mammography. Int J Cancer 102: 91-95, 2002

**19.** Brekelmans CT, Seynaeve C, Bartels CC, et al: Rotterdam Committee for Medical and Genetic Counseling: Effectiveness of breast cancer surveillance in BRCA1/2 gene mutation carriers and women with high familial risk. J Clin Oncol 19:924-930, 2001

**20.** Scheuer L, Kauff N, Robson M, et al: Outcome of preventive surgery and screening for breast and ovarian cancer in BRCA mutation carriers. J Clin Oncol 20:1260-1268, 2002

**21.** Komenaka IK, Ditkoff BA, Joseph KA, et al: The development of interval breast malignancies in patients with BRCA mutations. Cancer 100: 2079-2083, 2004

**22.** Kuhl CK, Schmutzler RK, Leutner CC, et al: Breast MR imaging screening in 192 women proved or suspected to be carriers of a breast cancer susceptibility gene: Preliminary results. Radiology 215:267-279, 2000

**23.** Kolb TM, Lichy J, Newhouse JH: Occult cancer in women with dense breasts: Detection with screening US—Diagnostic yield and tumor characteristics. Radiology 207:191-199, 1998

**24.** Stoutjesdijk MJ, Boetes C, Jager GJ, et al: Magnetic resonance imaging and mammography in women with a hereditary risk of breast cancer. J Natl Cancer Inst 93:1095-1102, 2001

**25.** Warner E, Plewes DB, Hill KA, et al: Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA 292:1317-1325, 2004

**26.** Kriege M, Brekelmans CT, Boetes C, et al: Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 351:427-437, 2004

**27.** Meindl A: Comprehensive analysis of 989 patients with breast or ovarian cancer provides BRCA1 and BRCA2 mutation profiles and frequencies for the German population: German Consortium for Hereditary Breast and Ovarian Cancer. Int J Cancer 97:472-480, 2002

**28.** Claus E, Risch N, Thompson W: Autosomal dominant inheritance of early-onset breast cancer: Implications for risk prediction. Cancer 73:643-651, 1994

**29.** American College of Radiology: Breast Imaging Reporting and Data System (BI-RADS) Atlas. Reston, VA, American College of Radiology, 2003

**30.** Kuhl CK, Elevelt A, Leutner C, et al: Interventional breast MR imaging: Clinical use of a stereotactic localization and biopsy device. Radiology 204:667-675, 1997

**31.** Lazovich D, Solomon CC, Thomas DB, et al: Breast conservation therapy in the United States following the 1990 National Institutes of Health Consensus Development Conference on the treatment of patients with early stage invasive breast carcinoma. Cancer 86:628-637, 1999

**32.** Morris EA: Breast cancer imaging with MRI. Radiol Clin North Am 40:443-466, 2002

**33.** Fischer U, Kopka L, Grabbe E: Breast carcinoma: Effect of preoperative contrast-enhanced MR imaging on the therapeutic approach. Radiology 213:881-888, 1999

**34.** Zhong Q, Chen CF, Chen PL, et al: BRCA1 facilitates microhomology-mediated end joining of DNA double strand breaks. J Biol Chem 277:28641-28647, 2002

**35.** Somasundaram K: Breast cancer gene 1 (BRCA1): Role in cell cycle regulation and DNA repair—Perhaps through transcription. J Cell Biochem 88:1084-1091, 2003

**36.** Foulkes WD, Metcalfe K, Hanna W, et al: Disruption of the expected positive correlation between breast tumor size and lymph node status in BRCA1-related breast carcinoma. Cancer 98:1569-1577, 2003