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The Value of Quality-Assured Magnetic Resonance Imaging of the Breast for the Early Detection of Breast Cancer in Asymptomatic Women

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Purpose: The aim of this study was to evaluate the exclusive performance of quality-assured high-resolution breast magnetic resonance imaging (MRI) for early detection of breast cancer in a population of asymptomatic women.

Materials and Methods: A total of 1189 MRI examinations performed in 789 asymptomatic women (mean age, 51.1 years) were evaluated. All examinations were performed using open bilateral surface coil, dedicated compression device, and high spatial resolution (matrix, 512 × 512). Digital mammography was available for all participants. AQ3 Assessment included density types, artifact level, and BIRADS classifica- AQ4 tion. Evaluation was performed by 2 readers. In addition, a CAD system was used for image assessment.

Results: Breast MRI showed density types I and II in 87.6% and artifacts AQ5 categories III and IV in 3.1%. Study included 32 carcinomas (8 DCIS, 24 invasive tumors). Both readers detected 29 of 32 correctly (sensitivity 90.6%). The variation between the readers was low (reader 1: specificity, AQ6 94.4% and PPV, 25.7%; reader 2: specificity, 97.6% and PPV, 34.1%). Sensitivity of CAD was 62.5% (specificity, 84.4%; PPV, 5.2%). Digital mammography detected 13 of 32 carcinomas (sensitivity, 56.3%; specificity, 98.4%; PPV, 32.1%).

Conclusions: The exclusive use of quality-assured breast MRI allows the early detection of breast cancer with a high sensitivity and specificity. The CAD analysis of MRI does not give additional information but shows results comparable with digital mammography.

Key Words: MRI of the breast, breast cancer, DCIS, screening, CAD

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KEY POINTS

- Magnetic resonance imaging (MRI) of the breast is superior to mammography in breast cancer screening.
- Exclusive performance of MRI of the breast is an ideal screening tool.
- Actually, costs, availability, quality assurance, and expertise do not make MRI screening feasible.

To date, the indication for MRI of the breast is usually in preoperative local staging of patients with breast cancer, the follow-up after breast-conserving therapy to differentiate between scar and tumor relapse, and the search for the primary cancer in patients with metastases in axillary lymph node in absence of a mammographic abnormality.[1–5]

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For breast cancer screening, conventional or digital mammography has, however, usually been used. In this context, breast cancer screening with mammography has been proven to reduce the breast cancer mortality in a normal risk population.[6] Advantages of mammographic imaging are the reliable detection of suspicious microcalcifications that can be associated with breast cancer and the visualization of suspicious masses within fatty or fibroglandular breasts.

Sole mammography is significantly limited, however, in the detection of noncalcified malignant masses within inhomogeneous dense or dense breasts type c or d according to the new classification of the American College of Radiology. In this constellation, the sensitivity of mammography decreases to 30% to 50%.[7] High breast tissue density on mammography is the main reason for the rate of 20% to 35% interval carcinomas in population-based screening programs.[8]

The MRI of the breast works in another way than mammography: MRI shows tumor enhancement especially due to pathologic angiogenesis. This is the main reason why MRI is clearly superior to mammography in women with breast density type ACR c and d. In the group of women aged from 50 to 60 years, AQ7 the rate of mammographic dense breasts ranges up to 46%.[7,9] In women younger than 50 years, this rate is even higher. In comparison with the data of mammography, MRI shows increased physiological enhancement (magnetic resonance [MR] density type III and IV) in only 10% to 15% of women.[10]

Quality-assured contrast-enhanced (CE) MRI of the breast is unquestionably the most reliable method for the detection of preinvasive and invasive breast cancer.[1–5,11,12] Regarding the image quality of CE MRI of the breast, artifacts caused by movement during the dynamic measurements are, however, a major problem. In this context, high quality presupposes the use of open breast surface coils and integrated MR-compatible compression device. Their use can reduce the rate of unacceptable examinations (artifact level III and IV) to less than 3%.[10] Moreover, the performance of sequences with high spatial resolution (slice thickness of 2–3 mm, matrix of 512 × 512 without interpolation) is essential for high image quality.[9]

Thus, the purpose of this study was to evaluate the exclusive performance of quality-assured MRI of the breast for the early detection of breast cancer in a population of asymptomatic women.

MATERIAL AND METHODS

In this retrospective study, the images of asymptomatic women who underwent MRI of the breast from 2004 to 2008 were evaluated by 2 readers in a stand-alone manner with respect to the density type of enhanced images, the range of artifacts, and the BIRADS classification. In addition, an assessment was performed by a computer-assisted MR-CAD system.

All MRI examinations were performed on a 1.5T whole-body scanner Signa HDX (Fa. GE Healthcare, Milwaukee, WI)

by using a dedicated open 4-channel breast surface coil (Fa. MRI Device, Knaresborough, NY) with an integrated device for the fixation of both breasts in craniocaudal orientation (Fa. Noras, Hoechberg, Germany). The MRI examination included a fat-saturated T2-weighted inversion-recovery sequence with the following parameters: repetition time/echo time, 6925/67 milliseconds; field of view, 380 mm; 50 slices of 2.0 to 2.5 mm; matrix of 512 × 224, and a measurement time of 4 hours and 51 minutes. Subsequently, a 3-dimensional T1-weighted gradient-echo sequence was performed repetitively once before and 5 times after administration of contrast material the following: repetition time/echo time 8.4/4.1 milliseconds; field of view, 380 mm; 50 slices of 2.0 to 2.5 mm; matrix of 512 × 512 without interpolation; and a measurement time of 86 seconds per sequence. The phase-encoding gradient was in the mediolateral orientation for all measurements. The Gd-DTPA (Magnevist, Schering company, Berlin, Germany) was administered with a dosage of 0.1 mmol/kg body weight via a peripheral vein by using an automatic injector (flow 3 mL/s).

Postprocessing included the subtraction of the precontrast image from the first and second measurements after contrast administration on a pixel-to-pixel base and the presentation of these subtraction images and the T2 images as maximum intensity projections.

Women in this study underwent a bilateral digital full-field mammography on a Senographe 2000D (GE Healthcare, Milwaukee, WI). Mammograms from outside the facilities were not included. Concerning the density type and the BIRADS categorizations of the mammograms were taken from the primary medical report. A reevaluation of the mammograms was not performed.

The evaluation of the MR images was performed by 2 readers: reader 1 had minor experience (2 years) in analyzing breast MR images, and reader 2 had a very high-level experience (>20 years). Image evaluation was done in a stand-alone matter. Reader 1 received all MR images for evaluation, whereas reader 2 evaluated only the subtraction and the maximum intensity projection images. Both readers were not allowed access to the results of digital mammography.

The MR density type was categorized by reader 2 depending on the enhancement of the parenchymal tissue in the second image subtraction. Four types were differentiated (MRI density type I: no parenchymal enhancement; type II: focal areas of enhancement, not confluent; type III: confluent focal areas of enhancement; type IV: confluent diffuse parenchymal enhancement).[10]

Motion artifacts on MRI were also classified by reader 2 into to 4 different levels (level I: no motion artifacts; level II: intramammary motion artifacts with a maximum width of 2 mm; level III: intramammary motion artifacts with a maximum width of 4 mm; level IV: intramammary motion artifacts with a maximum width of more than 4 mm).[10]

Breast MRI findings were categorized for each breast individually into 1 of the 5 categories according to the BIRADS lexicon of the American College of Radiology (MR-BIRADS 1: negative finding; MR-BIRADS 2: benign finding; BIRADS 3: probably benign finding; MR-BIRADS 4: suspicious abnormality; MR-BIRADS 5: highly suggestive of malignancy). Within this study, MR-BIRADS 1 to 3 were classified as "benign," and MR-BIRADS 4 and 5 were classified as "malignant" lesions.

Evaluation also included a computer-assisted analysis of the MR images by using a CADstream in the version 5.0.2.521 (Confirma, Nashua, NH). This system is based on a pixel-to-pixel analysis of the signal enhancement in the initial phase (3 minutes after contrast material) and in the post–initial phase (3 minutes after contrast material until the end of the examination). A color-encoded marker is placed if the initial signal enhancement exceeds a defined threshold. Depending on the desired sensitivity, 2 threshold levels for color encoding are applicable: an initial signal increase of more than 50% (CAD50%, higher sensitivity) or an initial signal increase of more than 100% (CAD100%, lower sensitivity). The color (blue, yellow, or red) of the placed marker is dependent on the findings: A color-encoded initial enhancement followed by a continuous increase in the post–initial phase is signified by a blue colored marker. An initial increase followed by a plateau is signified by a yellow marker, and a post–initial washout is signified by the color red.

For statistical analysis, the presence of 1 or 2 red-colored regions within a breast was classified as "malignant," separately for CAD50% and for CAD100%. Blue and yellow markers as well as the presence of more than 2 red markers were classified as "benign."

RESULTS

A total of 1189 MRI examinations of the breast in asymptomatic women were included in this study (mean age, 51.1 years; min/max, 22/79 years). A total of 789 women underwent their first MRI examination. The other 400 women had had previous MRI examinations.

In 87.6% of all MRI examinations, the MR density was low (MR density type I: 787, MR density type II: 255). A high MR density type, limiting the informative value of the examination, was found in 147 of 1189 cases (12. 4%) (MR density type III: 109, MR density type IV: 38). For comparison, in digital mammography, 1047 cases (88%) demonstrated high MX density type c and d in the same collective. Low mammographic density type a was found in only 10 women (Fig. 1).

In 868 MRI examinations of the breast (73%), there were no motion artifacts (artifact level I). Artifacts (level III and IV) in MRI, lessening the information value of the examination, were present in 3.1%. Excellent images for assessment (MRI density type I and MRI motion artifact level I) were found in 45.7%. Good prerequisites for a high information value conditions (MRI density type I + II and MRI motion artifact level I + II) were found in 84.4% of cases.

The study included 32 malignant breast tumors (8 DCIS and 24 invasive carcinomas). Histology of DCIS showed 2 low-grade tumors (grading 1), 3 intermediate type DCIS (grading 2; one was minimally invasive), and 3 high-grade DCIS (grading 3). The invasive carcinomas were predominantly ductal type (IDC, n = 18). The others were 5 lobular types (ILC, n = 5) and 1 tubular carcinoma.

Both readers detected 29 of 32 carcinomas (sensitivity, 90.6%) and missed the 3 same tumors: 2 DCIS (1, grading 2; 1, grading 3) and 1invasive ductal breast cancer of 15 mm. The

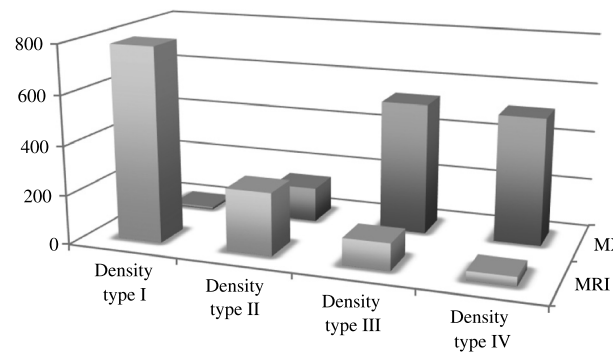

FIGURE 1. Comparison of the parenchymal density in digital mammography (red) and MRI of the breast (blue) (1189 examinations).

density type of MRI was I (type of artifacts, I) and II (artifact type II) for the two missed DCIS lesions. The missed invasive carcinoma (false-negative) was located in the very lateral aspect of the breast, where it was masked by the phase-encoding gradient in the CE measurement. In this case, the density type of MRI was III (artifact type I).

Reader 1, who was less experienced, categorized more lesions as BIRADS 3, 4, and 5 than reader 2. Reader 1 classified 232 MR examinations as BIRADS 3 and 113 MR examinations as BIRADS 4 and 5. In contrast, reader 2 correctly classified more findings as BIRADS 2 (benign findings). Compared with reader 1, his rate of BIRADS 3 to 5 was clearly lower (BIRADS 3: 39 cases, BIRADS 4 and 5: 85 cases).

The CAD analysis showed best results using a signal increase threshold of 50% and 2 markers were placed. In this constellation, CAD50% depicted 4 of 8 (50%) of the DCIS and 16 of 27 (67.7%) of the invasive carcinomas. An increase of the threshold to 100% led to an expected worsening of the results; CAD100% marked none of the DCIS and only 10 of 27 of the invasive lesions.

Digital mammography depicted all the 3 malignant tumors that were missed on MRI. In contrast, 3 of the DCIS were not found on mammography (1, grading 1; 1, grading 2 with microinvasive component; 1, grading 3), and 11 of the invasive breast carcinomas were missed on mammography (7 IDC, 3 IL,C and the tubular cancer). Tumor stages of the false-negative carcinomas on MX were 5 pT1b, 4 pT1c, and 2 pT2. In conclusion, the different imaging modalities demonstrated sensitivities, specificities, T1 positive, and negative predictive value as shown in Table 1.

DISCUSSION

There have been many reports about the high value of MRI for the detection of breast cancer in high-risk women who are in Italy, Austria, Germany, and Australia.[9,11–19] In all studies, MRI of the breast has been shown to be superior to all other imaging modalities including breast ultrasound and/or digital mammography, when performed with a quality-assured technique and a high spatial resolution. Moreover, MR imaging screening improves early diagnosis of prognostically relevant breast cancer also in women at average risk for breast cancer.[20]

Kriege et al[13] compared different imaging modalities in 1909 AQ13 women with high-risk profile, 358 with BRCA gene mutation. Examinations included palpation, mammography, and MRI. In this collective, they found 6 DCIS, 44 invasive lesions, and 1 lymphoma. Sensitivity of mammography was 33.3%, compared with 79.5% for MRI, whereas the specificity was equivalent for both methods (MX 95.0%, MR 89.8%).[13]

AQ14 The results of a prospective multicenter study (4 sites, EVA study) were presented by Kuhl et al[9] in 2010. They evaluated 1.687 annual screening rounds in 687 women with a defined high-risk profile. Clinical evaluation, mammography, ultrasound, and MRI of the breast were performed. They found 11 DCIS and 16 invasive carcinomas. The detection rate for malignant tumors was 5.4% for mammography, 6.0% for ultrasound, and 7.7% for the combination of both methods. In contrast, the exclusively use of MRI depicted 14.9% of carcinomas. According to the presented study, MRI did not find all breast cancers. Mammography depicted 1 low-grade DCIS and another 3-mm microinvasive cancer that were not visible with MRI. A total of 14 breast cancers, however, were seen only on MRI. The combination of MRI with mammography allowed the highest detection rate (16%). The performance of palpation or ultrasound in a 6-month interval detected no additional cancers. No interval carcinomas occurred in the study.[9] These excellent results of the EVA study have since been confirmed by other working groups.[11,12]

Since this study, further studies dealing with the value of the different imaging modalities in the early detection of breast cancer in a high-risk population have been performed. Sung et al[14] reported on imaging with mammography and MRI in 91 patients with chest irradiation therapy. Although the spatial resolution was low in this study, the results were comparable with the other presented results: 4 of 5 invasive breast carcinomas were detected by MRI alone, whereas 3 of 5 DCIS were depicted in mammography alone.[14] It is unclear, if the missed DCIS on MRI here are caused by the reduced spatial resolution (matrix 256 × 192).

Passaperuma et al[15] showed that MRI was clearly superior to all other imaging modalities in BRCA1 and BRCA2 carriers (sensitivity of MRI vs MX: 86% vs 19%). Moreover, the excellent MRI results increased the second part of the study (sensitivity, 94%) compared with the first 6 years.[15]

The presented study demonstrates that quality-assured high-resolution MRI of the breast is superior to all other imaging modalities in the early detection of breast cancer in asymptomatic women. The rate of missed intraductal carcinomas is comparable with that reported in other studies, when a quality-assured technique was used.[21]

Of all DCIS, 25% were not depicted with MRI in spite of high image quality. Apparently, these DCIS did not yet have sufficient angiogenesis to result in an increased enhancement after administration of contrast material. A preponderance of DCIS grade I was not observed in the missed DCIS. This study, however, included only a small number of DCIS and therefore may not be representative. Furthermore, it is not clear whether enhancement on MRI allows a reliable assessment of the aggressiveness and prognostic relevance of DCIS. Further studies with larger patient numbers are necessary to assess this aspect.

Only one of all invasive ductal carcinomas in this study was missed by MRI. The location of this tumor was close to the axilla, and the mediolateral artifacts of the phase-encoding gradient masked this lesion. The cause of this false-negative finding was methodical. It was not based on the lack of tumor enhancement. The problem of nonvisualization of lesions that are positioned in

TABLE 1. Sensitivity, Specificity, PPV, and NPV of Digital Mammography and MRI of the Breast in Different Evaluation Modalities (Reader 01, Reader 02, CAD) AQ16

	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Mammography	56.3	98.4	32.1	99.4
MRI-reader 01	90.6	96.4	25.7	99.9
MRI-reader 02	90.6	97.6	34.1	99.9
CAD MR50 marker 1	43.8	88.8	4.7	99.6
CAD MR50 marker 1 + 2	62.5	84.4	5.2	99.4
CAD MR100 marker 1	28.2	96.6	10.1	99.0
CAD MR100 marker 1 + 2	31.3	95.6	8.8	99.0

the axillary extension of the breast has been solved. We now use a protocol including a switch of the direction of the phase-encoding gradient from mediolateral to ventrodorsal and back to mediolateral. This switch allows a prompt artifact-free presentation of the axillary portion of the breast tissue (so-called zebra protocol).[7] Neglecting this case, only intraductal carcinomas were missed by MRI in this study.

Suspicious findings, which are only visible with MRI, should be investigated further by MR-guided vacuum biopsy and/or open biopsy after MR-guided wire localization. The required MR-compatible tools are comparable with the equipment that is used for ultrasound- or mammographic-guided interventions. Highly experienced breast units allow the percutaneous assessment of MR findings according to the categories BIRADS 4 and 5 with a low complication rate and a short expenditure of time.[22,23]

Taking only medical aspects into account, MRI of the breast is an ideal diagnostic tool for the early detection of breast cancer, if the method is quality assured and the MR density type is low. MR density (type I and II) will be found in approximately 85% of all examinations. In case of higher MR density types (III and IV), additional mammography and/or sonography are recommended. The MRI of the breast allows a reliable detection of invasive breast cancer in stages with an excellent prognosis for long time survival. Moreover, intraductal malignant tumors will be depicted at an acceptable rate. It is important to realize that not all intraductal carcinomas will progress to invasive breast cancer. Moreover, missing a DCIS will usually not lead to a worsening of prognosis within a 2-year examination interval.

High sensitivity, acceptable specificity, lack of radiation exposure, and breast compression are motivating criteria for the development of an effective MRI screening program. There are, however, other circumstances that limit the development of such a program: the number of MRI systems is too limited to offer a population-based concept; there is a limited number of well-experienced MRI readers; and the examination costs are high. The number of breast experts could easily be increased by introducing more teaching and quality assurance. Conditions to certify readers at a moderate or a high level have been defined years ago.[24] Usually, screening programs are characterized by low costs and short examination times. In this context, there are first publications and clinical studies dealing with short MRI protocols to increase the flow rate of patients using first-pass MRI or abbreviated protocols with a time slot of 3 to 6 minutes per examination.[25,26] Another concept describes the combination of an MRI system with 2 to 3 tables to reduce the patient's table-changing time and to increase the number of examinations per hour.[25]

In conclusion, nonmedical aspects such as the limited capacity of MRI systems and reader's experience prevent the introduction of a sufficient MRI breast screening at the moment. Changes begin, however, in the mind. More acceptances to MRI of the breast, rethinking screening concepts, and introducing a high-quality assurance of breast MRI are necessary to achieve a more effective breast cancer screening program in the future.

AQ17
- *MRI of the breast is superior to mammography in breast cancer screening.*
- *Considering medical aspects alone, exclusive performance of MRI of the breast is an ideal screening tool.*
- *At present, aspects like costs, availability, quality assurance, and expertise do not make MRI screening feasible.*

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