

evaluable and included in the current study. We examined the (combination of) detection method(s) of the diagnosed cancers and compared the characteristics of tumors detected by MRI only with those of all other and non-palpable other screen-detected tumors. Further, we compared the sensitivity of XM and MRI within subgroups according to different tumor characteristics.

**Results:** Twenty-two (49%) of the 45 BCs were detected by MRI and were not visible at XM, of which 20 (44%) were also not palpable (MRI-only detected tumors). Eight BCs (18%) were detected by XM and were not visible at MRI, 10 (22%) BCs were detected by both MRI and XM, one was only detected by CBE and 4 (9%) were detected in the interval between two screening visits. The MRI only detected tumors were more often  $\leq 1$  cm than all other screen-detected cancers (58 vs. 31%;  $p = 0.11$ ) and than non-palpable other screen detected cancers (58 vs. 22%;  $p = 0.19$ ). Also MRI only detected tumors were more often node negative than other screen detected cancers (94 vs. 59%;  $p = 0.02$ ) and than non-palpable other screen detected cancers (94 vs. 67%;  $p = 0.10$ ). MRI was more sensitive than XM for a wide spectrum of invasive tumors characteristics with respect to size, morphology, malignancy grade and ER status.

**Conclusion:** Half of the 45 BCs included in this study were detected by MRI only. MRI-only detected tumors were smaller and significantly more often node-negative than other screen-detected tumors, suggesting that MRI makes an important contribution to the early detection of hereditary BC.

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#### Factors affecting sensitivity and specificity of screening mammography and MRI in women with a hereditary risk for breast cancer

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**Introduction:** The MRISC study is a prospective screening study for breast cancer in women with a hereditary risk. Participants were screened by a 6-monthly clinical breast examination and a yearly mammography (XM) and MRI. The overall sensitivity was 33% for XM and 71% for MRI, the specificity 95% for XM and 90% for MRI. In the current study we investigate whether these results vary with respect to age, hereditary risk, breast density and menopausal status.

**Material and Methods:** From November 1999 to October 2003, 1909 women (19-72 years) were included and 50 breast cancers were detected. For the current analysis data of 4134 screening visits and 45 evaluable cancers were included. Uni- and multivariate odds ratios (ORs) of sensitivity, false-positive rate (1-specificity) and receiver operating characteristic (ROC) curves were calculated for both imaging modalities. All analyses were performed separately for subgroups according to age at entry (<40, 40-49,  $\geq 50$ ), hereditary risk (15-30%, 30-50%, 50-85% cumulative lifetime risk), menopausal status and breast density ( $\leq 50\%$ ,  $>50\%$  glandular).

**Results:** The only factor that was significantly associated with a decreased sensitivity of MRI was a high breast density (OR<sub>adjusted</sub> 0.08 [95% CI 0.01-0.84]). Sensitivity of XM was non-significantly decreased in women with a BRCA1/2 mutation, a younger age, a pre-menopausal status and a high breast density. Factors that were significantly associated with an increased false-positive rate were, for XM, a high breast density (OR<sub>adj</sub> 1.67 [1.22-2.28]), and for MRI a pre-menopausal status (OR<sub>adj</sub> 1.70 [1.23-2.36]), and a young age (OR<sub>adj</sub> 1.58 [1.17-2.13] for women 40-49 years; OR<sub>adj</sub> 1.28 [0.95-1.73] for women  $<40$  years as compared to women  $\geq 50$  years). False-positive rate of MRI was significantly decreased in women with a proven BRCA1/2 mutation (OR<sub>adj</sub> 0.74 [0.55-0.99]). In all investigated subgroups the discriminating capacity, assessed by ROC curves, was higher for MRI than for XM, with the highest difference for BRCA1/2 mutation carriers (0.237), women between 40-49 years (0.227) and women with a low breast density (0.237).

**Conclusion:** This study supports the previous recommendation that breast MRI should be a standard screening method in BRCA1/2 mutation carriers. Larger series and/or an international pooling of current MRI screening studies are needed for the development of more specific

screening recommendations according to age, genetic risk and breast density in genetically susceptible women.

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#### Clinical impact of breast MR proton spectroscopy added to a highly spatially resolved Gd-enhanced study

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**Purpose:** To evaluate feasibility and clinical impact of breast proton MR spectroscopy (1H-MRS) added to dynamic MR imaging (D-MRI).

**Subjects and Methods:** From January 2003 to November 2004, 244 consecutive patients underwent breast MRI using (1.5 T, Sonata, Siemens) 128 T1-weighted 3D GE sequence (coronal 1-mm partitions; TR/TE = 11/4.8 ms; FA = 25°; FOV = 384 mm; matrix 384 x 192 mm; 1-mm<sup>3</sup> voxel; 0.1 mmol/kg Gd-DOTA; 120-s time resolution; 1 pre- and 4 postcontrast phases; second week of the cycle); 115 negative (foci of CE smaller than 5 mm or without CE), 2 interrupted D-MRI. Thereafter, in 127 patients (4 male, 56  $\pm$  14 y.o., range 15-92) single-voxel water- and fat-suppressed spin-echo (TR/TE = 1500/136 ms) proton spectroscopy was obtained. For the dynamic MR interpretation a multimodal score system was used. Proton spectra was processed using water reference, filtering, zero-filling, frequency shift, baseline/phase correction, and curve fitting. An intensity choline peak integral equal or higher than 2.0 was considered a sign of malignancy. Gold standard was pathological examination obtained with core/open biopsy or one year follow up.

**Results:** One hundred fifty-one 1H-MRS voxels were obtained, one in 98 patients, two in 25, three in 1 of them (voxel size: 2.9  $\pm$  2.2 cm; range 1-8 cm<sup>3</sup>; median acquisition time: 13'). No reliable spectrum (low signal-to-noise ratio) resulted in 3 cases (2 IDCs and 1 benign enhancement). In the remaining 148 spectra, pathology demonstrated 68 malignancies and 80 benignancies. Seven cancers were false negative both at 1H-MRS and D-MRI, three of them in different patients. Nine benignancies at 1H-MRS and 15 at D-MRI were false positive. Sensitivity was 90% for both for 1H-MRS (63/70) and D-MRI (63/70), specificity was 89% (70/79) and 81% (63/78), PPV 87% (62/71) and 81% (63/78), NPV 91% (70/77) and 90% (63/70), respectively, giving a 8% gain in specificity. Combining the two technique, lesion with a suspicious morphodynamic score or with a significant choline peak integral, a sensitivity of 97% (66/68) was reached.

**Conclusion:** 1H-MRS can be routinely performed after breast D-MRI. The absence/presence of choline peak strengthen the diagnosis.

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#### Diagnosis of intraductal pathology by breast duct micro-endoscopy (BDME)

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**Aim:** Breast tissue is affected by benign and malignant conditions; most of these originate in the ductal system. Breast duct micro-Endoscopy (BDME) is a new technique that allows direct visualisation of the mammary ductal epithelia and has the potential to provide greater accuracy in the diagnosis of benign and malignant breast conditions.

The aim of our project is to identify and classify the benign and malignant intraductal lesions, develop endoscopic instruments and assess the use of this technique as a screening tool in the early detection of breast cancer.

**Materials and Methods:** The phase 1 of our study was to assess the feasibility of BDME in 35 ex vivo mastectomy specimens. (Acuity Inc. USA, Polydiagnost GmbH, Germany systems).

In phase 2, BDME was offered to all patients undergoing surgery for nipple discharge (microdochectomy/total duct excision). A micro-cytology-brush was developed and used to collect samples whenever an endoluminal papilloma was seen on Endoscopy. The result of micro-brush cytology samples was compared to ductal lavage samples.

In phase 3, the endoscopic lesions observed were compared to final histopathology and a simple classification of benign, inflammatory lesions was developed.

**Results:** In the feasibility study, an average of 3.3 (median 3) mammary ducts could be identified and cannulated in 35 mastectomy specimens (Total of 115 ducts). Abnormalities were visualised in 40% of the ducts.

In the second phase of our study, 50 consecutive patients undergoing microdochectomy or total duct excision for nipple discharge had breast microendoscopy. Visualisation of discharging ducts was accomplished in 100% cases. Endoluminal abnormalities were seen in 33(66%) patients, 15 had single papilloma, 3 multiple papilloma and 15 had signs of inflammation. Seven out of eight patients with an intraductal papilloma who