Diagnostic efficacy of contrast-enhanced breast MRI versus X-ray mammography in women with different degrees of breast density

Jörg Barkhausen¹, Arpad Bischof¹, Daniel Haverstock², Mark Klemens³, Guenther Brueggenwerth³, Olaf Weber⁴,⁵ and Jan Endrikat⁴,⁶

Abstract
Background: Detection of breast cancer in women with high breast densities is a clinical challenge.
Purpose: To study the influence of different degrees of breast density on the sensitivity of contrast-enhanced breast magnetic resonance imaging (CE-BMRI) versus X-ray mammography (XRM).
Material and Methods: We performed an additional analysis of two large Phase III clinical trials (G1; G2) which included women with histologically proven breast cancers, called “index cancers.” Additional cancers were detected during image reading. We compared the sensitivity of CE-BMRI and XRM in women with different breast densities (ACR A→D; Version 5). For each study, six blinded readers evaluated the images. Results are given as the “Median Reader.”
Results: A total of 774 patients were included, 169 had additional cancers. While sensitivity of CE-BMRI for detecting all index cancers was independent of breast density (ACR A→D) (G1: 83%→83%; G2: 91%→91%) the sensitivity of XRM declined (ACR A→D) (G1: 79%→62%; G2: 82%→64%). Thus, the sensitivity difference between both imaging modalities in ACR A breasts of 3% (G1) and 9% (G2) increased to 21% (G1) and 26% (G2) in ACR D breasts. Sensitivity of CE-BMRI for detecting at least one additional cancer increased with increasing breast density (ACR A→D) (G1: 50%→73%, G2: 57%→81%). XRM’s sensitivity decreased (G1: 34%→20%) or remained stable (G2: 24%→25%).
Conclusion: CE-BMRI showed significantly higher sensitivity compared to XRM.

Keywords
Dense breasts, ACR 5 density, breast magnetic resonance imaging, gadobutrol, X-ray mammography

Date received: 7 April 2020; accepted: 17 May 2020

Introduction
The introduction of mammography screening was the most important preventive achievement to reduce breast cancer mortality (1). Digital X-ray mammography (XRM) is currently the standard breast imaging method worldwide (2,3). It is a high-throughput modality for cancer screening as well as for detection and characterization of suspicious clinical findings (4).

Contrast-enhanced magnetic resonance mammography (CE-MRM) has been shown to feature higher sensitivity for the detection of breast cancer compared to conventional digital XRM (5–7).

¹Department of Radiology and Nuclear Medicine, University Hospital Schleswig Holstein, Luebeck, Germany
²Bayer HealthCare Pharmaceuticals Inc, Whippany, NJ, USA
³Bayer AG, General Clinical Imaging Services, 13353, Germany
⁴Bayer AG, Radiology R&D, Berlin, Germany
⁵Rheinische Friedrich-Wilhelms-University of Bonn, Bonn, Germany
⁶University Medical School of Saarland, Dept of Gynecology, Obstetrics and Reproductive Medicine, Homburg/Saar, Germany

Corresponding author:
Jan Endrikat, Bayer AG, Mullerstrasse 178, Berlin 13353, Germany.
Email: jan.endrikat@bayer.com
However, contrast-enhanced breast magnetic resonance imaging (CE-BMRI) is also considered to be more expensive (8), to have more false positive results (9), cause increased re-excision rates (10), cause over-detection (8), or increased mastectomy rates (11). Therefore, pertinent guidelines—e.g. American College of Radiology (ACR) (12) and the European Society of Breast Cancer Specialists (EUSOMA) (13)—recommend CE-BMRI only for a limited number of specific clinical questions. These include screening of high-risk patients (13,14), determining the extent of disease (13,14), and additional evaluation of clinical or imaging findings (14). The (routine) use in women with dense breasts is still in scientific debate (2,15). However, there is increasing evidence demonstrating the usefulness of CE-BMRI for screening women with dense breasts. In an increasing number of states in the USA, a legislation has been enacted mandating women to be directly notified of the risks associated with high breast density (16).

The prevalence of women with extremely dense breasts in women aged 50+ is in the range of 3%–8% (17–19). Dense breasts constitute an increased risk for breast cancer (2,20–22), possibly because more fibro-glandular tissue bears a higher risk for development of cancerogenic mutations than fatty tissue (23). XRM has a lower sensitivity in women with extremely dense breasts (24–26) because of a masking effect of the lesions within the radio-opaque dense breast tissue (22,24,27). In addition, neovascularization is a key feature of newly developing malignant tumors. In CE-BMRI, it is the gadolinium in the vessels that triggers the MR signal. This signal is not attenuated by dense breast tissue. Thus, sensitivity of CE-BMRI remains unchanged with increasing density while sensitivity of XRM declines. As a result, CE-BMRI sensitivity is higher in women with dense breasts than XRM sensitivity (28).

Sardanelli et al. suggested that women with heterogeneously or extremely dense breasts might benefit from preoperative CE-BMRI (29,30). Later, further evidence for a higher cancer detection yield in screening women with elevated cancer risk and dense breasts by offering additional breast MRI was reported by the ACRIN 6666 study (31). Recently, in 2018 the ACR clearly recommended MRI for women with dense breast tissue (12).

Gadobutrol is a macrocyclic, extracellular gadolinium-based contrast agent (GBCA) provided in a unique 1 molar formulation (32). It is approved in 109 countries in many indications, including CNS, angiography, and breast imaging. Efficacy in lesion detection and characterizations versus other GBCAs in breast MRI has been studied by a number of other researchers (33–35). So far, 74.9 million (at 30 April 2020) gadobutrol administrations have been recorded since 1999.

The aim of the present study was to compare sensitivities of CE-BMRI versus XRM for the detection of breast cancer in women with different degrees of breast density.

Material and Methods

Data sources

We performed an additional analysis of two large Phase III studies (GEMMA-Program - Gadobutrol-Enhanced MR Mammography) registered on ClinicalTrials.gov (GEMMA1: NCT01067976; GEMMA2: NCT01104584; referred to as “G1” and “G2” below) (6).

Study population and interventions

Study population and interventions were published by Sardanelli et al. (6). In brief, in G1, 390 women (mean age = 55.7 ± 10.4 years; 74% white, 25% Asian) were included from 28 centers in seven countries in Europe, the Americas, and the Republic of Korea. In G2, 397 women (mean age = 57.1 ± 10.7 years; 71% white, 24% Asian) were included from 39 centers in Europe, Canada, Argentina, India, Taiwan, and the USA.

The “Index cancer” was defined as the lesion that triggered the diagnosis. “Additional cancers” were detected during the preoperative examinations and/or by CE-BMRI and verified by the reference standard, i.e. malignant regions were pathologically confirmed from surgical specimen and cancer-free regions by XRM together with high-frequency ultrasound or pathological examination (when available). “All cancers” were the sum of index cancers plus all additional cancers.

Study procedures

Inclusion criterion was a recently detected and histologically proven breast cancer. All patients received an additional CE-BMRI at 1.5-T. Gadobutrol (Gadovist® 1.0 mmol/mL, Bayer AG, Leverkusen, Germany) was applied intravenously at a dose of 0.1 mmol/kg body weight.

For each study, six independent readers evaluated the images: three evaluated the XRM and three evaluated the CE-BMRIs. Breast density was determined by one radiologist with > 12 years of experience in breast imaging. Histopathology results were the standard of reference.

Target variables

The primary target variable of this additional analysis was the sensitivities of CE-BMRI versus XRM for the detection of breast cancer at different degrees of breast
density according to ACR5 (36). We analyzed the index cancer and additional cancers separately. In addition, we analyzed sensitivity of both modalities of finding all cancers.

Secondary parameters were the impact of ethnicity and tumor size on the sensitivity.

**Statistics**

Sensitivity was defined as the proportion of patients for whom the readers detected all lesions identified by the standard of reference. To reduce the variability associated with multiple readers, median reader sensitivity was reported. Median reader sensitivity was calculated as the median of the sensitivity values for the three readers in each study. Patients were included in the analyses if they had at least one lesion identified by the standard of reference and had data available for the subgroup of interest. Two-sided 95% confidence intervals (CI) were calculated for within-group proportions using a normal approximation to the binomial distribution. The two-sided 95% CIs for the difference between CE-BMRI and XRM were calculated using the normal approximation based on Schwenke and Busse (37). No statistical adjustments were made for multiple comparisons and no formal threshold for statistical significance was declared.

**Results**

**Study population**

A total of 774 patients were included (G1: n = 386 G2: n = 388), 169 had additional cancers (G1: n = 86; G2: n = 83). The detailed demographics of the study population have been reported by Sardanelli et al. (6).

**Index cancers**

While the median reader sensitivity of CE-BMRI for detecting all index cancers remained stable with increasing breast density (i.e. from ACR Density A → ACR D) (G1: 83% → 83%; G2: 91% → 91%) the sensitivity of XRM declined (G1: 79% → 62%; G2: 82% → 64%). As a consequence, the difference in sensitivities between both imaging modalities increased with increasing breast density (from ACR Density A → ACR D) (G1: 3% → 21%; G2: 9% → 26%) (Fig. 1a).

**Additional cancers**

While the sensitivity of CE-BMRI for detecting at least one additional cancer increased with increasing breast density (G1: 50% → 73%; G2: 57% → 81%) the sensitivity of XRM decreased (G1: 34% → 20%) or remained stable (G2: 24% → 25%). These findings resulted in remarkably higher sensitivity differences for the additional tumors than for the index cancers reaching > 50% for ACR D (Fig. 1b).

**All cancers**

A similar picture is seen when looking at patients where all cancers have been detected. The sensitivity differences are increasing with increasing ACR grade and highest in ACR D: 24% in G1 and 36% in G2 (Fig. 1c).

**Ethnicity**

While the sensitivity for detecting index or additional cancers was higher in Asian patients for both imaging modalities, the difference between the two imaging modalities was similar for Caucasian and Asian patients. The difference was highest for the additional cancers (Table 1).

**Tumor size**

The vast majority of all tumors were in the size categories 1.0–1.9 cm and 2.0–4.9 cm. The sensitivity of CE-BMRI was constantly ~13% higher than XRM independent of tumor size, only with the exception of tumors ≥ 5 cm in G1 (4%). Thus, the 95% CIs excluded zero, consistent with a result of CE-BMRI superiority in the two major size brackets (Table 2).

**Discussion**

We compared sensitivities of CE-BMRI versus XRM for the detection of breast cancer in women with different degrees of ACR 5 breast density in a large dataset of two Phase III studies. While the sensitivity of CE-BMRI was almost unaffected by breast density, the sensitivity of XRM decreased remarkably with increasing breast density.

The primary inclusion criterion was a histologically proven newly diagnosed breast cancer, called index cancer, an XRM was also required for comparison (6). All blinded readers were asked to find the diagnosis solely based on the images. They had no access to the patients' medical history or results of clinical examination and/or ultrasound, which usually provide important additional information in “normal clinical routine.” As the CE-BMRI readers were also limited to the images, both datasets, i.e. XRM and CE-BMRI, were well comparable.

While the sensitivity of CE-BMRI for detecting all index cancers was independent of the breast density, the sensitivity of XRM sensitivity declined by around 20% with increasing density (Fig. 1). The higher sensitivity of CE-BMRI was even more pronounced in detection of additional cancers. In the ACR D
This advantage of CE-BMRI over XRM in detecting malignant breast lesions is in line with findings of other groups, although the clinical trial settings are not always exactly comparable with respect to study population (patients with elevated breast cancer risk (38,39), dense breasts, proven breast cancer (40)) and imaging purpose (screening (39,41), preoperative staging (40), recurrence detection).

Berg et al. (31) added a single screening CE-BMRI to XRM in 2662 women with elevated risk of breast cancer and dense breasts. By applying supplemental CE-BMRI in 612 women with ACR density 3 and 4 plus ≥1 other risk factor, they identified nine additional cancer cases.

Kuhl et al. (5) investigated 2120 women with average risk of breast cancer. Sixty percent featured ACR breast density C or D. All had normal XRM findings. In this prospective observational study, 37/61 (61%) MR-detected additional cancers were in women with the ACR breast density category C or D.

An intriguing approach to assess the benefits of CE-BMRI in women with dense breasts has recently been reported by Bakker et al. (42) (DENSE study protocol by Emaus et al. (25)). They evaluated CE-BMRI as an additional screening modality in 40,373 women aged 50–75 years with extremely dense breasts. A total of
8061 were offered an additional CE-BMRI after a negative XRM result and 32,312 women served as controls. After two years of follow-up, they found an interval-cancer rate of 2.5 per 1000 screenings in the CE-BMRI group compared to 5.0 per 1000 screenings in the control group. The difference of 2.5 per 1000 screenings was significant ($P < 0.001$). While Bakker et al. (42) focus on women with extremely dense breasts, i.e. ACR D, our study confirms the higher sensitivity of CE-BMRI versus XRM by showing the “almost linear correlation” between increasing breast density—ACR A to B to C to D—and increasing sensitivity advantage of CE-BMRI.

The fact that CE-BMRI detects additional cancers besides the index cancer is of paramount clinical importance as eventually the totality of cancers determines the clinical course of the disease. Identification of additional cancers confirms a multifocal and/or multicentric cancer situation. This feature of CE-BMRI is already known independently of breast density (43). Ioacconi et al. (43) claim that these additional cancers are potentially more biologically relevant because of the presence of unsuspected invasion or a higher histological tumor grade. There is no need to say that multiple cancer lesions, either uni- or bi-lateral, heavily impact the treatment strategy.

Finally, Kuhl (44) states, that XRM is primarily detecting slow-growing, less aggressive cancers. This might explain the persistently high rates of interval cancers and high mortality rates of breast cancer despite decades of mammographic screening. CE-BMRI, instead, detects the fast-growing, more aggressive, and thus most clinically relevant cancers. The question of whether the higher sensitivity of CE-BMRI impacts re-excision rates, recurrence rates, recurrence-free survival, or overall survival is subject to scientific debate (45).

The sensitivities of CE-BMRI and XRM were higher in Asian women compared to Caucasians but the difference between both imaging modalities was independent of ethnicity. Interestingly, the sensitivity difference between both modalities was highest for the additional cancers. A possible reason for this might be that in our study the percentage of Asian

### Table 1. Sensitivities of CE-BMRI vs. XRM by ethnicity.

| Study | Cancer | Ethnicity | n | CE-BMRI (%) | XRM (%) | Difference % | 95% CI |
|-------|--------|-----------|---|-------------|---------|--------------|-------|
| G1    | Index  | White     | 283 | 84 | 71 | 13 | 7.1–18.3 |
|       |        | Asian     | 96 | 91 | 76 | 15 | 4.9–24.3 |
|       | Additional | White | 41 | 44 | 19 | 25 | 2.9–50.8 |
|       |        | Asian     | 16 | 66 | 39 | 27 | 6.6–28.4 |
|       | All    | White     | 288 | 69 | 54 | 15 | 9.4–20.4 |
|       |        | Asian     | 97 | 80 | 63 | 17 | 4.4–21.4 |
| G2    | Index  | White     | 275 | 86 | 71 | 15 | 8.9–20.9 |
|       |        | Asian     | 93 | 97 | 84 | 13 | 4.4–21.4 |
|       | Additional | White | 54 | 65 | 24 | 41 | 24.0–57.5 |
|       |        | Asian     | 26 | 77 | 35 | 42 | 13.0–71.6 |
|       | All    | White     | 277 | 78 | 59 | 19 | 12.9–24.7 |
|       |        | Asian     | 93 | 91 | 69 | 22 | 13.4–31.8 |

CE-BMRI, contrast-enhanced breast magnetic resonance imaging; CI, confidence interval; XRM, X-ray mammography.

### Table 2. Sensitivities of CE-BMRI vs. XRM by tumor size, all tumors.

| Study | Size (cm) | n | CE-BMRI (%) | XRM (%) | Difference (%) | 95% CI |
|-------|-----------|---|-------------|---------|----------------|-------|
| G1    | 0–0.5     | 20 | 65 | 50 | 15 | $-7.9–37.9$ |
|       | 0.6–0.9   | 56 | 79 | 64 | 15 | $-0.5–29.1$ |
|       | 1.0–1.9   | 156 | 83 | 69 | 14 | $5.8–21.1$ |
|       | 2.0–4.9   | 134 | 87 | 74 | 13 | $5.4–21.5$ |
|       | $\geq$5   | 23 | 78 | 74 | 4 | $-16.2–24.9$ |
| G2    | 0–0.5     | 26 | 88 | 73 | 15 | $-3.4–34.1$ |
|       | 0.6–0.9   | 73 | 84 | 63 | 21 | $7.7–33.4$ |
|       | 1.0–1.9   | 118 | 86 | 67 | 19 | $9.4–27.9$ |
|       | 2.0–4.9   | 134 | 89 | 75 | 14 | $6.9–21.5$ |
|       | $\geq$5   | 21 | 90 | 62 | 29 | $7.5–49.6$ |

CE-BMRI, contrast-enhanced breast magnetic resonance imaging; CI, confidence interval; XRM, X-ray mammography.
patients with additional cancers was much higher than for Caucasians, e.g. in G1, 41/96 Asians had additional cancers (43%) compared to 16/283 whites (5.7%). A potential reason for this may be the fact that the Asians have generally higher breast density than Caucasians, although paradoxically they appear to have a lower risk of breast cancer (46). A limitation of these considerations might be the smaller number of Asian women in our cohort, just about one-third the number of Caucasians (Table 1), and further studies would be needed to confirm above hypothesis.

CE-BMRI showed a higher sensitivity than XRM independent of tumor size. There was no advantage seen in a group of very small tumors, i.e. 0–0.5 cm. We did not find any research investigating this aspect.

The breast cancer risk factor “dense breast” (20,21) is prevalent in up to 8% of the female population aged 50+ years (17–19). As dense breast tissue potentially masks malignant breast lesions in XRM, CE-BMRI shows higher sensitivity with increasing degree of breast density. This analysis provides strong evidence for the usefulness of CE-BMRI, especially in women with dense breasts.

The present study has some limitations. First, this was an additional analysis, not primarily planned for this dataset. Second, as both studies were evaluated by six different blinded radiologists (three for XRM and three for CE-BMRI, each), pooling of the two studies was not possible. Third, breast density of all images was determined by only one reader (with > 12 years of experience). Fourth, the number of patients in some subgroups (e.g. additional cancers in ACR A and D) is small. Fifth, all blinded readers were asked to find the diagnosis solely based on the images. They did not have access to additional clinical information as in clinical routine, a somewhat artificial situation. Sixth, Roman et al. (47) recently reported changes of density over time. As breast density was determined at the time of cancer diagnosis and tumor growths take time, breast density at the time of cancer initiation remains unknown. Lastly, ultrasound is frequently used as an adjunct to ambiguous XRM findings, also in dense breasts (48,49). We did not perform a comparison to this modality.

In conclusion, CE-BMRI showed significantly higher sensitivity compared to XRM in women with dense breasts.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: JB received research funding and speaker honoraria from multiple companies, including Bayer; AB received funding and honoraria from various medical companies, including Bayer; MK, GB, OW, and JE are employees of Bayer AG.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Jan Endrikat https://orcid.org/0000-0001-6063-5014

References

1. Strand F, Zackrisson S. Breast cancer imaging - A rapidly evolving discipline. Breast 2019;46:58–63.
2. Smetana GW, Elmore JG, Lee CI, et al. Should this woman with dense breasts receive supplemental breast cancer screening? Grand rounds discussion from Beth Israel Deaconess Medical Center. Ann Intern Med 2018;169:474–484.
3. You C, Zhang Y, Gu Y, et al. Comparison of the diagnostic performance of synthesized two-dimensional mammography and full-field digital mammography alone or in combination with digital breast tomosynthesis. Breast Cancer 2020;27:47–53.
4. Renz DM, Durmus T, Bottcher J, et al. Comparison of gadoteric acid and gadobutrol for detection as well as morphologic and dynamic characterization of lesions on breast dynamic contrast-enhanced magnetic resonance imaging. Invest Radiol 2014;49:474–484.
5. Kuhl CK, Strobel K, Bieling H, et al. Supplemental breast MR imaging screening of women with average risk of breast cancer. Radiology 2017;283:361–370.
6. Sardanelli F, Newstead GM, Putz B, et al. Gadobutrol-Enhanced Magnetic Resonance Imaging of the Breast in the Preoperative Setting: Results of 2 Prospective International Multicenter Phase III Studies. Invest Radiol 2016;51:454–461.
7. Mann RM, Kuhl CK, Moy L. Contrast-enhanced MRI for breast cancer screening. J Magn Reson Imaging 2019;50:377–390.
8. O’Flynn EA, Ledger AE, deSouza NM. Alternative screening for dense breasts: MRI. AJR Am J Roentgenol 2015;204:W141–149.
9. Houssami N, Ciatto S, Macaskill P, et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol 2008;26:3248–3258.
10. Peters NH, van Esser S, van den Bosch MA, et al. Preoperative MRI and surgical management in patients with nonpalpable breast cancer: the MONET - randomised controlled trial. Eur J Cancer 2011;47:879–886.
11. Pettit K, Swatske ME, Gao F, et al. The impact of breast MRI on surgical decision-making: are patients at risk for mastectomy? J Surg Oncol 2009;100:553–558.
12. Monticciolo DL, Newell MS, Moy L, et al. Breast cancer screening in women at higher-than-average risk: recommendations from the ACR. J Am Coll Radiol. 2018;15:408–414.
13. Sardanelli F, Boetes C, Borisch B, et al. Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. Eur J Cancer 2010;46:1296–1316.

14. ACR Practice Parameter for the Performance of Contrast Enhanced Magnetic Resonance Imaging (MRI) of the Breast. Amended 2014 (Resolution 39). Available at: https://studylib.net/doc/8742935/-mri–of-the-breast—american-college-of-radiology.

15. Nadler M, Al-Attar H, Warner E, et al. MRI surveillance for women with dense breasts and a previous breast cancer and/or high risk lesion. Breast 2017;34:77–82.

16. Houssami N, Lee CI. The impact of legislation mandating breast density notification - Review of the evidence. Breast 2018;42:102–112.

17. Wanders JO, Holland K, Veldhuis WB, et al. Volumetric breast density affects performance of digital screening mammography. Breast Cancer Res Treat 2017;162:195–103.

18. Lee CI, Chen LE, Elmore JG. Risk-based breast cancer screening: implications of breast density. Med Clin North Am 2017;101:725–741.

19. Sprague BL, Gangnon RE, Burt V, et al. Prevalence of mammographically dense breasts in the United States. J Natl Cancer Inst 2014;106:duj255.

20. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2006;15:1159–1169.

21. Berg WA, Zhang Z, Lehrer D, et al. Detection of multicentric, multifocal breast cancer in fatty and dense breasts using the whole-breast pathologic examination as a gold standard. AJR Am J Roentgenol 2004;183:1149–1157.

22. Pinsky RW, Helvie MA. Mammographic breast density: How it affects performance indicators in diagnostic studies. Methods Inf Med 2007;46:548–552.

23. Albert M, Schnabel F, Chun J, et al. The relationship of breast density in mammography and magnetic resonance imaging in high-risk women and women with breast cancer. Clin Imaging 2013;39:987–992.

24. Boyd NF, Guo H, Martin LJ, et al. Mammographic density, breast cancer risk and risk prediction. Breast Cancer Res 2007;9:217.

25. Emaus MJ, Bakker MF, Peeters PH, et al. MR Imaging as an Additional Screening Modality for the Detection of Breast Cancer in Women Aged 50-75 Years with Extremely Dense Breasts: The DENSE Trial Study Design. Radiology 2015;277:527–537.

26. Posso M, Louro J, Sanchez M, et al. Mammographic breast density: How it affects performance indicators in screening programmes? Eur J Radiol 2019;110:81–87.

27. Boyd NF, Martin LJ, Yaffe MJ, et al. Mammographic density and breast cancer risk: current understanding and future prospects. Breast Cancer Res 2011;13:223.

28. Sardanelli F, Giuseppetti GM, Panizza P, et al. Sensitivity of MRI versus mammography for detecting foci of multifocal, multicentric breast cancer in fatty and dense breasts using the whole-breast pathologic examination as a gold standard. AJR Am J Roentgenol 2004;183:1149–1157.

29. Sardanelli F. Overview of the role of pre-operative breast MRI in the absence of evidence on patient outcomes. Breast 2010;19:3–6.

30. Lee J, Tanaka E, Eby PR, et al. Preoperative Breast MRI: Surgeons’ Patient Selection Patterns and Potential Bias in Outcomes Analyses. AJR Am J Roentgenol 2017;208:923–932.

31. Berg WA, Zhang Z, Lehrer D, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. JAMA 2012;307:1394–1404.

32. Scott Lj. Gadobutrol: A Review in Contrast-Enhanced MRI and MRA. Clin Drug Investig 2018;38:773–784.

33. Pediconi F, Kuhik-Huch R, Chilla B, et al. Intra-individual randomised comparison of gadobutrol 1.0 M versus gadobenate dimeglumine 0.5 M in patients scheduled for preoperative breast MRI. Eur Radiol 2013;23:84–92.

34. Escribano F, Sentis M, Oliva JC, et al. Dynamic magnetic resonance imaging of the breast: Comparison of gadobutrol vs. Gd-DTPA. Radioligia 2018;60:49–56.

35. Fallenberg EM, Renz DM, Karle B, et al. Intraindividual, randomized comparison of the macrocyclic contrast agents gadobutrol and gadoterate meglumin in breast magnetic resonance imaging. Eur Radiol. 2015;25:837–849.

36. American College of Radiology. Reporting System. Reston, VA: ACR. Available at: https://www.acr.org/-/media/ACR/Files/RADS/BI-RADS/Mammography-Reporting.pdf

37. Schwenke C, Busse R. Analysis of differences in proportions from clustered data with multiple measurements in diagnostic studies. Methods Inf Med 2007;46:548–552.

38. Pick U, Engel C, Krug B, et al. High-risk breast cancer surveillance with MRI: 10-year experience from the German consortium for hereditary breast and ovarian cancer. Breast Cancer Res Treat 2019;217–228.

39. Roark AA, Dang PA, Niell BL, et al. Performance of screening breast MRI after negative full-field digital mammography versus after negative digital breast tomosynthesis in women at higher than average risk for breast cancer. AJR Am J Roentgenol 2019;212:271–279.

40. Gonzalez-Huebra I, Elizalde A, Garcia-Baizan A, et al. Is it worth to perform preoperative MRI for breast cancer after mammography, tomosynthesis and ultrasound? Magn Reson Imaging 2019;57:317–322.

41. Heller SL, Moy L. MRI breast screening revisited. J Magn Reson Imaging 2019;49:1212–1221.

42. Bakker MF, de Lange SV, Pijnappel RM, et al. Supplemental MRI screening for women with extremely dense breast tissue. N Engl J Med 2019;381:2091–2102.

43. Iaconi C, Galman L, Zheng J, et al. Multicentric cancer detected at breast MR imaging and not at mammography: important or not? Radiology 2016;279:378–384.

44. Kuhl CK. Abbreviated Magnetic Resonance Imaging (MRI) for Breast Cancer Screening: Rationale,
45. Houssami N, Turner RM, Morrow M. Meta-analysis of pre-operative magnetic resonance imaging (MRI) and surgical treatment for breast cancer. Breast Cancer Res Treat 2017;165:273–283.

46. Rajaram N, Mariapun S, Eriksson M, et al. Differences in mammographic density between Asian and Caucasian populations: a comparative analysis. Breast Cancer Res Treat 2017;161:353–362.

47. Roman M, Sala M, Bare M, et al. Changes in mammographic density over time and the risk of breast cancer: An observational cohort study. Breast 2019;46:108–115.

48. Golatta M, Zeegers D, Filippatos K, et al. LECANDUS study (LEsion CANdidate Detection in UltraSound Data): evaluation of image analysis algorithms for breast lesion detection in volume ultrasound data. Arch Gynecol Obstet 2016;294:423–238.

49. Maier A, Heil J, Lauer A, et al. Inter-rater reliability and double reading analysis of an automated three-dimensional breast ultrasound system: comparison of two independent examiners. Arch Gynecol Obstet 2017;296:571–582.