MRI versus mammography for breast cancer screening in women with familial risk (FaMRIsc): a multicentre, randomised, controlled trial

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Summary

Background Approximately 15% of all breast cancers occur in women with a family history of breast cancer, but for whom no causative hereditary gene mutation has been found. Screening guidelines for women with familial risk of breast cancer differ between countries. We did a randomised controlled trial (FaMRIsc) to compare MRI screening with mammography in women with familial risk.

Methods In this multicentre, randomised, controlled trial done in 12 hospitals in the Netherlands, women were eligible to participate if they were aged 30–55 years and had a cumulative lifetime breast cancer risk of at least 20% because of a familial predisposition, but were *BRCA1*, *BRCA2*, and *TP53* wild-type. Participants who were breast-feeding, pregnant, had a previous breast cancer screen, or had a previous a diagnosis of ductal carcinoma in situ were eligible, but those with a previously diagnosed invasive carcinoma were excluded. Participants were randomly allocated (1:1) to receive either annual MRI and clinical breast examination plus biennial mammography (MRI group) or annual mammography and clinical breast examination (mammography group). Randomisation was done via a web-based system and stratified by centre. Women who did not provide consent for randomisation could give consent for registration if they followed either the mammography group protocol or the MRI group protocol in a joint decision with their physician. Results from the registration group were only used in the analyses stratified by breast density. Primary outcomes were number, size, and nodal status of detected breast cancers. Analyses were done by intention to treat. This trial is registered with the Netherlands Trial Register, number NL2661.

Findings Between Jan 1, 2011, and Dec 31, 2017, 1355 women provided consent for randomisation and 231 for registration. 675 of 1355 women were randomly allocated to the MRI group and 680 to the mammography group. 218 of 231 women opting to be in a registration group were in the mammography registration group and 13 were in the MRI registration group. The mean number of screening rounds per woman was 4·3 (SD 1·76). More breast cancers were detected in the MRI group than in the mammography group (40 *vs* 15; p=0·0017). Invasive cancers (24 in the MRI group and eight in the mammography group) were smaller in the MRI group than in the mammography group (median size 9 mm [5–14] vs 17 mm [13–22]; p=0·010) and less frequently node positive (four [17%] of 24 *vs* five [63%] of eight; p=0·023). Tumour stages of the cancers detected at incident rounds were significantly earlier in the MRI group (12 [48%] of 25 in the MRI group *vs* one [7%] of 15 in the mammography group were stage T1a and T1b cancers; one (4%) of 25 in the MRI group and two (13%) of 15 in the mammography group were stage T2 or higher; p=0·035) and node-positive tumours were less frequent (two [11%] of 18 in the MRI group *vs* five [63%] of eight in the mammography group; p=0·014). All seven tumours stage T2 or higher were in the two highest breast density categories (breast imaging reporting and data system categories C and D; p=0·0077) One patient died from breast cancer during follow-up (mammography registration group).

Interpretation MRI screening detected cancers at an earlier stage than mammography. The lower number of late-stage cancers identified in incident rounds might reduce the use of adjuvant chemotherapy and decrease breast cancer-related mortality. However, the advantages of the MRI screening approach might be at the cost of more false-positive results, especially at high breast density.

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Introduction

Approximately 15% of all breast cancers occur in women with a family history of breast cancer (familial risk) in whom no causative hereditary gene mutation has been found.[1] These women are at greater risk for breast cancer at a relatively young age.[2] In women with breast cancer,

Research in context

Evidence before this study

We searched PubMed on Nov 30, 2018, for prospective studies written in English with no restrictions in publication date, with the terms "breast cancer screening", "MRI screening", "breast cancer", "family history", and "familial risk" in several combinations. We found several screening trials in women with a familial or genetic predisposition to breast cancer, all applying MRI and mammography at the same time, and these trials have shown that the addition of MRI to mammography screening leads to detection of breast cancers at an earlier stage.

A meta-analysis showed that breast cancer screening with MRI and mammography combined resulted in a sensitivity of 98%, while sensitivity of MRI and mammography alone were 89% and 55%. Specificity of MRI and mammography combined was 79%. Unfortunately, all previous studies were non-randomised studies with a paired design in which MRI and mammography were done simultaneously. Therefore, it is unknown when an MRI-only detected tumour would have been detected by mammography, and whether this would cause a tumour stage difference that is clinically relevant. With this limited evidence, screening guidelines for women with familial risk of breast cancer differ between countries.

Added value of this study

To our knowledge, our study is the first randomised, controlled trial that shows the shift in tumour stage caused by the addition of MRI to mammography screening. We showed that the median size of invasive cancer detected under the MRI protocol was significantly smaller and cancers were less frequently node positive than those detected under the mammography protocol. Importantly, in the incident rounds, in which no interval cancers occurred with MRI, the absolute numbers of late-stage tumours (large or node positive) were also lower in the MRI group than in the mammography group. High breast density was indicative of a poorer tumour stage and lower specificity both in the MRI and mammography groups and was more informative than age to predict screening performance.

Implications of all the available evidence

In addition to previously published evidence, our study shows that MRI screening in women at high risk of developing breast cancer leads to earlier detection of breast cancer, and fewer late-stage cancers, which might reduce the need for adjuvant chemotherapy and reduce the risk of mortality. Breast density is relevant for the choice of a screening strategy. Our findings can be used to inform policy discussions about the implementation of MRI in high-risk breast screening.

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overall survival decreases considerably with increasing tumour size at detection and number of axillary lymph nodes involved, even with optimal adjuvant systemic therapy.[3,4] Screening aims to improve survival by detecting breast cancer at an early stage. However, it can also result in false-positive results.

Between 2004–18, several screening trials comparing MRI and mammography in women at high risk of developing breast cancer concluded that adding MRI to mammography screening improves early breast cancer detection in women with a familial or genetic predisposition.[5–7] As a result, guidelines for breast cancer screening were modified globally.[8–10] Unfortunately, these trials were all non-randomised studies with a paired design in which MRI and mammography were done simultaneously.[5–7,11] Therefore, it is unknown when an MRI-only detected tumour would have been detected by mammography, and whether this would have identified a difference in tumour stage that was clinically relevant. With this limited evidence, screening guidelines for women with familial risk differ between countries. American guidelines advise annual mammography, clinical breast examination, and MRI for women aged 30 years or older with a cumulative lifetime risk of at least 20%.[8] Dutch and UK guidelines omit MRI for women with familial risk without a *BRCA1/2* mutation.[9,10]

Furthermore, breast density has not been considered in these studies.[5,6] Higher breast density, caused by more glandular and connective breast tissue in relation to fat, indicates a higher cancer risk overall and in women with familial risk.[12] High-density breast tissue impairs sensitivity of mammography,[12] but has less of an effect on MRI[13] and might cause a different amount of false-positive results for mammography than for MRI. Breast density is high in about 74% of women between 40–49 years of age, and in 45% of women in their 60s.[14] MRI might not be necessary for all women with familial breast cancer risk,[15] but breast density might be a parameter to identify subgroups of women for whom MRI screening could be useful.

The Familial MRI Screening study (FaMRIsc) was done to compare annual MRI and clinical breast examination plus biennial mammography versus screening with annual mammography and clinical breast examination in women with a familial breast cancer risk but without a known *BRCA1/2* or *TP53* mutation.

Methods

Study design and participants

The FaMRIsc study was a multicentre, randomised, controlled trial. Women were eligible to participate if they were aged 30–55 years and had a cumulative lifetime

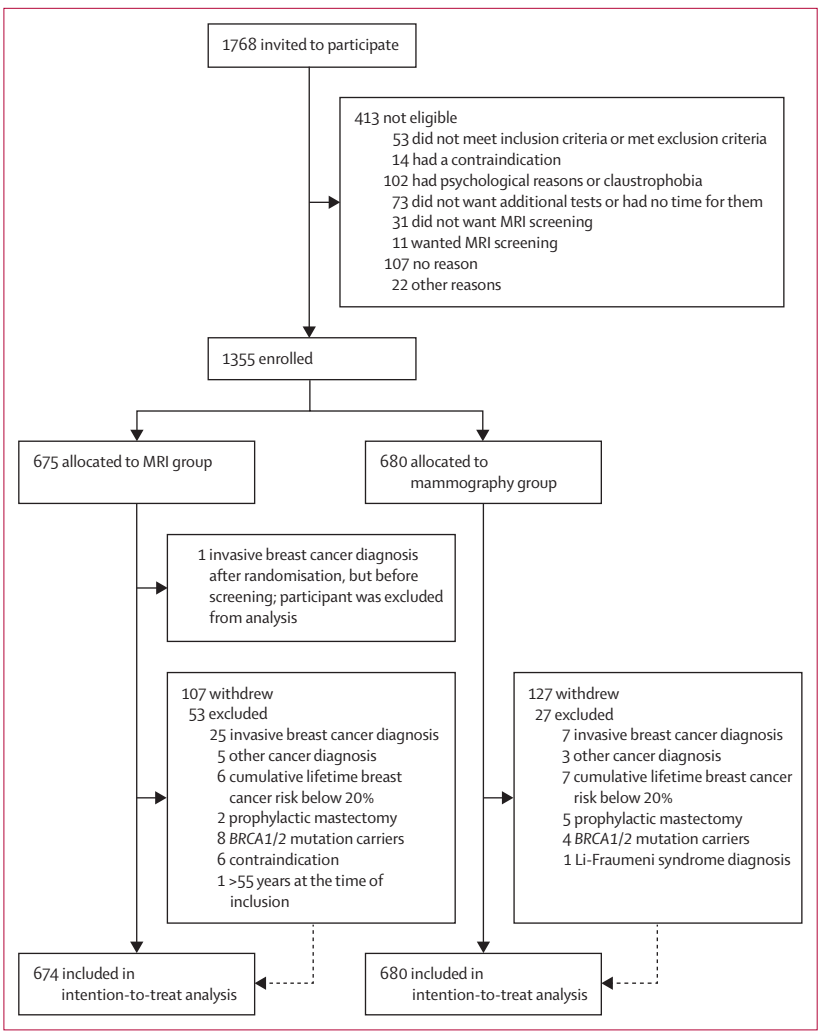

Figure 1: **Trial profile**

breast cancer risk of at least 20% because of a familial predisposition according to the modified tables of Claus,[5,16] or as assessed at a clinical genetics centre. Exclusion criteria were previous invasive cancer or *BRCA1, BRCA2,* or *TP53* mutations (proven or 50% risk of mutation), since MRI screening is already advised for these groups,[8–10] and a contraindication for contrast-enhanced MRI. Participants were removed from the study after randomisation if they met one of the exclusion criteria, or no longer met the inclusion criteria. Previous screening, a ductal carcinoma in situ diagnosis, pregnancy, and breastfeeding were permitted.

Participants were recruited from 12 outpatient breast cancer clinics or family cancer clinics at seven academic medical centres in the Netherlands and five of the larger hospitals (appendix p 3). The physician of the outpatient clinic or family cancer clinic enrolled participants after they provided written informed consent. The study follows the Declaration of Helsinki and was approved by the Institutional Review Board of the Erasmus University Medical Center (Rotterdam, Netherlands; reference number MEC-2010-292). The study protocol was published previously.[17]

See Online for appendix

Randomisation

Participants were randomly allocated (1:1) to receive either annual MRI and clinical breast examination plus biennial mammography (MRI group) or annual mammography and clinical breast examination (mammography group). Randomisation was done via a web-based system and stratified by centre. Allocation was based on a general number between 1–100 that was randomly generated by the computer. An algorithm decreased the possibility of the computer generating a number that led to allocation in an overrepresented study group by a factor of 5 minus 1. However, it remained impossible to predict what allocation would follow for the physician, participant, or researcher overseeing the randomisation.

Procedures

The mammography group received annual mammography according to Dutch guidelines[9] plus clinical breast examination. Dutch guidelines recommend clinical breast examination in women with a lifetime risk of breast cancer of at least 30%. The MRI group was screened with annual MRI and clinical breast examination, and mammography biennially. Leaving out mammography every other year was considered safe in the MRI group and might prevent overdiagnosis of low-grade ductal carcinoma in situ.[18] Women who did not provide consent for randomisation were given the option to be in a registration group, if screened via one of the same methods as either group in the study. Women in the registration group were screened according to the MRI group protocol in a joint decision with their physician.

Mammographic examination was done with full-field digital mammography. All mammography examinations were assessed according to the 4th edition of the American College of Radiology (ACR) breast imaging reporting and data system (BI-RADS) and all MRI examinations were assessed according to the 1st edition of the ACR BI-RADS.[19] MRI and mammography were preferably scheduled on the same day for participants receiving both.

A positive screening test was defined as a mammographic or MRI examination with a BI-RADS score of 3, for which additional investigation or a repeat examination at 6 months per radiological judgement followed; a mammographic or MRI examination with a BI-RADS score of 4–5, indicating histology; or a clinical breast examination with an abnormality, for which additional diagnostic testing was recommended. In the MRI group, MRI and mammography were not independently read; RMM, HMZ, MBIL, I-MO, CdM, CEL, HBWG, MNJMW, WBV, ET assessed the images. To determine mammographic density, an automated breast density

measurement with VolparaDensity (version 1.3.0, Volpara Solutions, New Zealand)[20] was done on raw data of the first digital mammogram of all participants, and estimated from the mammograms by radiologists according to the BI-RADS breast composition categories: A=fatty, B=scattered fibroglandular, C=heterogeneously dense, D=extremely dense.[19] Dynamic contrast-enhanced breast MRI examinations were done according to our study protocol.[17]

Outcomes

Primary outcomes of this study were numbers (of both ductal carcinoma in situ and invasive cancers), size, and nodal status of detected breast cancers. Secondary outcomes were false-positive results, sensitivity and specificity of each screening method, positive predictive value of a BI-RADS score of 3 or above, and positive predictive value of biopsies. Cost-effectiveness and breast cancer mortality will be reported in future analyses.

Statistical analysis

The sample size was calculated on the basis of the breast cancer incidence of 7 per 1000 person-years at risk among women with familial risk screened in the Dutch MRI screening study.[5] We expected a sensitivity of 70% for MRI and 40% for mammography on the basis of previous studies.[5] After 4000 woman-years at risk in both study groups—eg, 1000 women in each group for 4 years—we expected the detection of 32 tumours in the MRI group and 18 tumours in the mammography group. With these 50 cancers, a difference in tumour size of 8 mm (SD 9) was expected to be significant (with a two-sided α-level of 0·05 and a power of 80%). A difference of 8 mm in tumour size was also considered to be clinically relevant. Accrual and the number of detected cancers were evaluated after 2, 4, and 6 years. Fewer women were enrolled and randomly assigned than expected and 50 breast cancers were not reported after 4 years; therefore, the study was continued for 3 additional years to reach this threshold. The study ended Dec 30, 2017.

All women who provided consent for randomisation and were screened at least once were included in all analyses (done by intention to treat). Data from participants who were excluded (eg, after they no longer met inclusion criteria) were included in the analyses up until exclusion. Data from participants who withdrew were included in the analyses up until withdrawal.

Tumour type (invasive or ductal carcinoma in situ), tumour stage, lymph node status, Bloom-Richardson grade, oestrogen receptor status, progesterone status, *HER2* status, and ductal carcinoma in situ grade were compared between the screening groups with two-sided Fisher's exact tests. Age at detection, tumour size, and ductal carcinoma in situ size were compared with Mann-Whitney *U* tests.

Numbers of cancers were calculated per 1000 screening rounds or woman-years at risk and compared with exact rate ratio tests, assuming Poisson counts. Corresponding 95% CIs were calculated with a Poisson distribution. Woman-years at risk were calculated from the date of first screening examination to the date of discontinuation from the study, bilateral prophylactic mastectomy, detection of invasive cancer, death, or to the date at which the participant reached 60 years of age. To account for interval cancers, woman-years at risk were also calculated from the date of first screening examination to 1 year after the last screening visit; this calculation included women lost to follow-up after a screening visit. We defined interval cancers as cancers diagnosed between

	MRI group (n=674)	Mammography group (n=680)
Mean age (years)	44·7 (6·3)	44·7 (6·3)
Menopausal status		
Premenopausal	512 (76%)	505 (74%)
Postmenopausal	109 (16%)	116 (17%)
Unknown	53 (8%)	59 (9%)
Hormonal contraceptive use		
Present	103 (15%)	111 (16%)
In the past	462 (69%)	442 (65%)
Never	55 (8%)	50 (7%)
Unknown	54 (8%)	77 (11%)
Hormone replacement therapy use		
Present	7 (1%)	10 (2%)
In the past	14 (2%)	12 (2%)
Never	593 (88%)	577 (85%)
Unknown	60 (9%)	81 (12%)
Previous screening		
No screening	58 (9%)	53 (8%)
Unknown	13 (2%)	21 (3%)
Mammography		
Up to 2 years ago	535 (79%)	542 (80%)
More than 2 years ago	23 (3%)	29 (4%)
Unknown	14 (2%)	7 (1%)
MRI		
Up to 2 years ago	62 (9%)	81 (12%)
More than 2 years ago	90 (13%)	89 (13%)
Unknown	1 (<1%)	1 (<1%)
BI-RADS density category*		
A (entirely fat)	88 (13%)	92 (14%)
B (scattered densities)	248 (37%)	229 (34%)
C (heterogeneously dense)	237 (35%)	243 (36%)
D (extremely dense)	98 (15%)	102 (15%)
Unknown	3 (<1%)	14 (2%)
Number of first-degree relatives with a history of breast cancer below the age of 50		
One	362 (54%)	397 (58%)
Two	44 (7%)	37 (5%)
Three or more	2 (<1%)	2 (<1%)

Data are mean (SD) or n (%). BI-RADS=breast imaging reporting and data system. *As determined by the radiologist.

Table 1: **Baseline characteristics of study population**

two screening rounds because of symptoms when the result of the previous screening round was negative. We retrieved data on interval cancers from the Dutch national pathology registry (PALGA) between Jan 17, 2017, and Jan 1, 2019.

We used the exact rate ratio test to compare biopsy frequency and false positive frequency between screening groups. Sensitivity was defined as the number of screen-detected breast cancers divided by the total number of breast cancers. Specificity was defined as the number of negative screens divided by all screens in women without breast cancer. Positive predictive value was calculated by dividing the number of screen-detected cancers by the number of positive screening tests (BI-RADS ≥3). Positive predictive value for biopsy was calculated by dividing the number of breast cancers by the number of biopsies. To compare sensitivity, specificity, and positive predictive value between the screening groups, we used Fisher's exact test, and CIs were calculated with the Clopper-Pearson interval. We repeated these analyses including incident screens only (all screens after the first screening round).

Analyses were also stratified by mammographic density (with BI-RADS breast composition categories A–D). They included both randomly allocated and registration participants; participants from the MRI registration group were combined with the MRI group and participants from the mammography registration group were combined with the mammography group.

To test for linear trends in numbers of breast cancers, interval cancers, or false-positive results, or in tumour stage, sensitivity, or specificity when stratified by both BI-RADS breast density and automated breast (Volpara) density, we used linear-by-linear association tests.

To determine the level of agreement between the automated density measures and BI-RADS density estimates by the radiologists, Cohen's Kappa coefficient (κ) was calculated. A post-hoc analysis of tumour stage, lymph node status, and specificity stratified by age (<50 years *vs* ≥50 years) was done per screening group.

Statistical analyses were done with IBM SPSS Statistics (version 24) and RStudio (version 1.0.44). p values less than or equal to 0·05 were deemed significant. No independent data monitoring committee oversaw the study. This trial is registered with the Netherlands Trial Register, number NL2661.

	MRI group (n=674)	Mammography group (n=680)	p value
Mean age at detection (years)	49·4 (7·1)	50·0 (4·6)	0·88
Cancers diagnosed during study	..	..	0·0017
No cancer	634 (94%)	665 (98%)	..
Invasive breast cancer	24 (4%)	8 (1%)	..
Ductal carcinoma in situ	16 (2%)	7 (1%)*	..
Size of invasive cancer (mm)	..	..	0·010
Mean	11·9 (12·3)	18·0 (8·1)	..
Median	9 (5–14)	17 (13–22)	..
Tumour stage	..	..	0·065†
T1a	7/24 (29%)	0	..
T1b	7/24 (29%)	1/8 (13%)	..
T1c	7/24 (29%)	5/8 (63%)	..
T2	2/24 (8%)	2/8 (25%)	..
T3	1/24 (4%)	0	..
T4	0	0	..
Node status	..	..	0·023
Positive	4/24 (17%)	5/8 (63%)	..
Negative	20/24 (83%)	3/8 (38%)	..
Bloom-Richardson grade	..	..	0·50
1	10/24 (42%)	2/8 (25%)	..
2	9/24 (38%)	3/8 (38%)	..
3	4/24 (17%)	3/8 (38%)	..
Unknown	1/24 (4%)	0	..
Oestrogen-receptor status	..	..	0·25
Positive	22/24 (92%)	6/8 (75%)	..
Negative	2/24 (8%)	2/8 (25%)	..
Progesterone-receptor status	..	..	0·65
Positive	18/24 (75%)	5/8 (63%)	..
Negative	6/24 (25%)	3/8 (38%)	..
HER2 status	..	..	1·00
Positive	2/24 (8%)	0	..
Negative	22/24 (92%)	8/8 (100%)	..
Ductal carcinoma in situ grade	..	..	1·00
1	5/16 (31%)	2/7 (29%)	..
2	8/16 (50%)	4/7 (57%)	..
3	3/16 (19%)	1/7 (14%)	..
Ductal carcinoma in situ size (mm)	..	..	1·00
Mean	34·18 (43·8)	30·29 (26·9)	..
Median	14 (9–35)‡	20 (7–60)	..
Tumour stage incident rounds	..	..	0·035
Tis	7/ 25 (28%)	7/15 (47%)	..
T1a + T1b	12/25 (48%)	1/15 (7%)	..
T1c	5/25 (20%)	5/15 (33%)	..
T2 or higher	1/25 (4%)	2/15 (13%)	..

(Table 2 continues on next page)

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Inclusion and follow-up of participants took place between Jan 1, 2011, and Dec 30, 2017. 1355 women provided consent for randomisation and 231 for registration (figure 1). 675 of 1355 women who provided consent for randomisation were allocated to the MRI group, and 680 to the mammography group. One woman in the MRI group had a breast cancer diagnosis after randomisation, but before the first MRI screening, and was excluded from the analysis; therefore, 1354 women

were included in the intention-to-treat population. She was excluded from the analysis because an invasive cancer before the first screening round was an exclusion criterion; furthermore, the cancer was neither screen-detected nor an interval cancer, as the first screening round had not been completed. 13 women were excluded after randomisation because they ultimately proved to have a cumulative lifetime risk of breast cancer below 20%, twelve were excluded because they were found to carry a *BRCA1/2* mutation, and one was excluded because they were found to carry a *TP53* mutation (figure 1); these participants were included in the analysis. 218 of 231 women opting to be in a registration group were in the mammography registration group and 13 were in the MRI registration group. The mean number of screening rounds per woman was 4·3 (SD 1·76), and the median follow-up after inclusion was 5·2 years for both screening groups (IQR 3·4–6·2 in the MRI group and 3·6–6·3 in the mammography group). Of the women who were randomly allocated, 57 requested the screening protocol of the other group during follow-up (45 [7%] of 675 in the MRI group and 13 [2%] of 680 in the mammography group); these participants were still analysed by intention to treat. 13 of the 45 requests in the MRI group were because of gadolinium retention information we sent to all participants in the MRI group in 2016. Before the end of follow-up, 234 women withdrew from the study (107 [16%] of 675 in the MRI group; 127 [19%] of 680 in the mammography group). Table 1 shows the characteristics of the participants by screening group (see appendix p 4 for baseline characteristics of participants in registration groups). MRIs and mammograms were mostly done on the same day, in incident rounds with a median 1 day (IQR 0–14) and a mean 12·8 days (SD 26·6) between the MRI and the mammogram.

55 cancers were detected in the randomly allocated participants (32 invasive cancers, 23 ductal carcinomas in situ; table 2). No bilateral breast cancers were detected and none had metastasised. Two triple-negative cancers were detected in the mammography group and one was detected in the MRI group. Invasive cancers in the MRI group were smaller than those in the mammography-group (median size 9 mm [5–14] in the MRI group *vs* 17 mm [13–22] in the mammography group; p=0·010; table 2). 14 (58%) of 24 invasive cancers were up to 10 mm in size in the MRI group, compared with only one (13%) of eight in the mammography group. Fewer invasive breast cancers were node positive in the MRI group than in the mammography group (four [17%] of 24 *vs* five [63%] of eight; p=0·023; table 2). Tumour stage of all incident cancers was significantly different between groups (p=0·035; table 2). In incident rounds, MRI screening resulted in lower numbers of late-stage cancers (one [6%] of 18 were ≥T2 in the MRI group *vs* two [25%] of eight in the mammography group; p=0·035 for stage difference) and node-positive cancers (two [11%] of 18 *vs* five [63%] of eight; p=0·014). Bloom-Richardson grade, oestrogen receptor status, progesterone receptor status, and *HER2* status, ductal carcinoma in situ grade, and ductal carcinoma in situ size were not significantly different between screening groups (table 2). Descriptions of detected cancers including participants in the registration groups are shown in the appendix (p 5).

	MRI group (n=674)	Mammography group (n=680)	p value
(Continued from previous page)			
Node status incident rounds	..	..	0·014
Positive	2/18 (11%)	5/8 (63%)	..
Negative	16/18 (89%)	3/8 (38%)	..
Tumour stage in women <50 years	..	..	0·13
Tis	7/18 (39%)	5/8 (63%)	..
T1a+T1b	6/18 (33%)	0	..
T1c	4/18 (22%)	1/8 (13%)	..
T2 or higher	1/18 (6%)	2/8 (25%)	..
Tumour stage in women ≥50 years	..	..	0·18
Tis	9/22 (41%)	2/7 (29%)	..
T1a+b	8/22 (36%)	1/7 (14%)	..
T1c	3/22 (14%)	4/7 (57%)	..
T2 or higher	2/22 (9%)	0	..
Node status in women <50 years	..	..	0·011
Positive	1/11 (9%)	3/3 (100%)	..
Negative	10/11 (91%)	0	..
Node status in women ≥50 years	..	..	0·58
Positive	3/13 (23%)	2/5 (40%)	..
Negative	10/13 (77%)	3/5 (60%)	..

Data are mean (SD), n (%), median (IQR), or n/N (%). Tis=tumour in situ. *One ductal carcinoma in situ was detected after the woman requested screening with MRI and mammography. The ductal carcinoma in situ was detected by both MRI and mammography. †Based only on categories T1a+T1b, T1c, and T2 or higher. ‡Contains missing values. Tumour stage in MRI group (<50 years *vs* ≥50 years): p=0·93. Tumour stage in mammography group (<50 years *vs* ≥50 years): p=0·092. Node status in MRI group (<50 years *vs* ≥50 years): p=0·60. Node status in mammography group (<50 years *vs* ≥50 years): p=0·20.

Table 2: **Characteristics of detected breast cancers by study group**

Table 3 shows the performance of the two screening strategies within the randomisation groups.

The number of breast cancers per 1000 screening rounds was significantly higher in the MRI group than in the mammography group (14·2 [95% CI 10·0–18·8] *vs* 4·9 [2·6–7·5]; p<0·00030). This difference in breast cancer incidence decreased and was no longer significant in the incident screening rounds (p=0·722). Figure 2 shows the incidence per group per screening round. One (3%) of the 40 cancers in the MRI group and two (13%) of the 15 cancers in the mammography group were interval cancers (table 3). The interval cancer in the MRI group occurred 10 months after screening (T2, node positive, BI-RADS density D). One interval cancer in the mammography group occurred 9 months after screening (T2, node positive, BI-RADS density C), and the second occurred in the year after closure of the study (T1c, node negative, BI-RADS density B).

Sensitivity was higher in the MRI group than in the mammography group, but this difference was not

	MRI group (n=674)	Mammography group (n=680)	p value
Screening rounds	2812	3075	..
Person-years at risk	3220	3326	..
Screen-detected cancers	39/40 (98%)*	13/15 (87%)†	..
Interval breast cancers	1/40 (3%)	2/15 (13%)	0·18
Breast cancers (per 1000 screening rounds)			
All breast cancers	14·2 (10·0–18·8)	4·9 (2·6–7·5)	0·00030
Screen-detected cancers	13·9 (9·6–18·5)	4·2 (2·0–6·8)†	0·00012
Invasive screen-detected cancers	8·2 (5·0–11·7)	2·0 (0·7–3·6)	0·0010
Ductal carcinoma in situ	5·7 (3·2–8·5)*	2·3 (0·7–4·3)†	0·058
Interval cancers (per 1000 person-years at risk)	0·3 (0·0–0·9)	0·6 (0·0–1·5)	1·00
Invasive cancer detection technique			
Mammography	3/23 (13%)	6/6 (100%)	..
MRI	14/23 (61%)	NA	..
Mammography and MRI	5/23 (22%)	NA	..
Clinical breast examination only	1/23 (4%)	0	..
Biopsies	..	..	<0·0001
N	149	54	..
Incidence (per 1000 screening rounds)	53·0	17·6	..
False positives (BI-RADS ≥3)	..	..	<0·001
N	449	276	..
Incidence (per 1000 screening rounds)	159·7	89·8	..
By mammography	98/449 (22%)	157/276 (57%)	..
By MRI	275/449 (61%)	9/276 (3%)‡	..
By mammography and MRI	19/449 (4%)	0	..
By clinical breast examination only	57/449 (13%)	110/276 (40%)	..
Sensitivity	97·5% (86·8–99·9)	86·7% (59·5–98·3)	0·18
Specificity	83·8% (82·4–85·2)	91·0% (89·9–92·0)	<0·0001
Positive predictive value (BI-RADS ≥3)	8·0% (5·7–10·7)	4·5% (2·4–7·6)	0·074
Positive predictive value (biopsy)	26·8% (20·0–34·7)	27·8% (16·5–41·6)	1·00
Incident screening rounds	2141	2407	..
Breast cancers in incident rounds (per 1000 screening rounds)	10·0 (6·4–14·0)	5·9 (3·2–9·1)	0·72
Screen-detected cancers in incident rounds	25/25 (100%)*	13/15 (87%)	..
Interval cancers in incident rounds	0	2/15 (13%)	0·14
Biopsies in incident rounds	..	..	<0·0001
N	82	38	..
Incidence (per 1000 screening rounds)	38·3	15·8	..
False positives in incident rounds (BI-RADS ≥3)	..	..	<0·0001
N	266	176	..
Incidence (per 1000 screening rounds)	124·2	73·1	..
Sensitivity in incident rounds	100·0% (86·3–100·0)	86·7% (59·51–98·3)	0·14
Specificity in incident rounds	87·4% (85·9–88·8)	92·6% (91·5–93·7)	<0·0001
Positive predictive value in incident rounds (BI-RADS ≥3)	8·6% (5·6–12·4)	6·9% (3·7–11·5)	0·61
Positive predictive value in incident rounds (biopsy)	30·5% (20·8–41·6)	39·5% (24·0–56·6)	0·54
Specificity in women <50 years	81·9% (80·1–83·6)	89·6% (88·2–90·9)	<0·0001
Specificity in women ≥50 years	87·7% (85·4–89·8)	93·5% (91·9–94·9)	<0·0001

Data are n, n/N (%), n (95% CI), or n% (95% CI). BI-RADS=breast imaging reporting and data system.*One ductal carcinoma in situ was detected after the woman discontinued the trial protocol and went to the national breast cancer screening programme. Within the trial, this lesion was given a BI-RADS score of 3 and was considered stable over time. During the first screening at the national screening programme, this lesion was given a BI-RADS score of 4, and ultimately was diagnosed as ductal carcinoma in situ. †One ductal carcinoma in situ was detected after the woman requested screening with MRI and mammography. The ductal carcinoma in situ was detected by both MRI and mammography. ‡These false positives occurred in women who requested the MRI protocol while being assigned to the mammography group. Specificity in MRI group (<50 years *vs* ≥50 years): p=0·00010. Specificity in mammography group (<50 years *vs* ≥50 years): p=0·00026. Positive predictive value in MRI group (<50 years *vs* ≥50 years): p<0·0001 . Positive predictive value in mammography group (<50 years *vs* ≥50 years): p=0·107.

***Table 3*: Performance of the two screening strategies within the study groups**

significant (table 3). Specificity was significantly lower in the MRI group than in the mammography group, although specificity improved for both groups in the incident screening rounds (table 3). 14 (61%) of the 23 invasive screen-detected cancers in the MRI group were detected by MRI only: eight were T1a/T1b, five were T1c (two of which were node positive), and one was T2. Three (13%) were detected by mammography only: one was T1a, two were T1b. Five (31%) of the 16 ductal carcinomas in situ detected in the MRI group were grade 1: one was detected by MRI only, one by mammography only, and three by both MRI and mammography.

Of the 449 false-positive results in the MRI group, 98 (22%) resulted from a positive mammogram while MRI was negative. Positive predictive value (for BI-RADS ≥3) was higher in the MRI group than in the mammography group, but this difference was not significant, whereas positive predictive value for biopsy was similar between screening groups (table 3), both for prevalent and incidence screens.

When we combined registration group data and randomisation group data (appendix pp 5–6), numbers of detected breast cancers increased significantly with increasing breast density for the mammography protocol (p=0·018) but not for the MRI protocol (p=0·92; table 4). All seven tumours stage T2 or higher and three of five interval cancers were in the two highest density categories (table 4). Automated breast density measurements were available for 537 (78%) of 687 participants in the MRI registration and MRI groups and for 733 (82%) of 898 participants in the mammography registration and mammography groups and were in slight agreement with the density assessments by radiologists, with a κ of 0·205.[21] However, results stratified by automated density grades (appendix p 7) were in accordance with those of BI-RADS breast density stratification.[19] According to estimates made by the radiologists, MRI detected more early-stage cancers, and more cancers with negative nodes than mammography in the three lowest breast density categories (A–C), in which MRI performs best (table 4). However, with automated (Volpara) breast density measurements, MRI detected more early-stage cancers in all density categories. Sensitivity did not differ significantly with increasing breast density in either protocol (table 4). Specificity decreased with increasing breast density for both screening protocols, as false positives increased (table 4).

In a post-hoc analysis, stratifying our results by age (<50 years *vs* ≥50 years), we observed no difference in tumour or nodal stage in either screening group (table 2), but higher specificity in both screening groups for women aged 50 years or older than for women younger than 50 years (table 3).

Median follow-up of patients after a breast cancer diagnosis was 4·3 years (IQR 3–6) and none of the patients in the randomisation groups died during follow-up, but one patient in the mammography registration group died due to breast cancer.

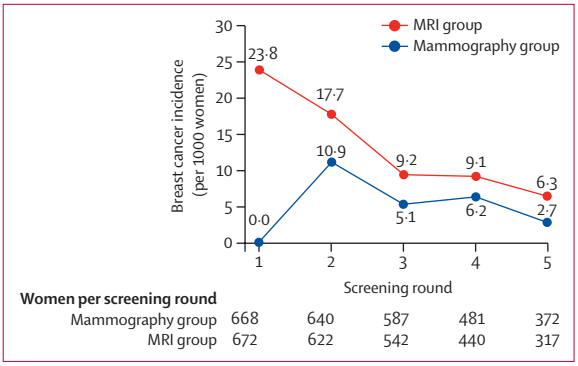

Figure 2: **Breast cancer incidence per screening round by study group**

Discussion

To our knowledge, this randomised controlled trial is the first to compare MRI screening with mammography in women with familial risk of breast cancer. The number of cancers detected was significantly higher in the MRI group than in the mammography group. However, in incident rounds, this difference in breast cancer incidence was no longer significant. Median tumour size of the invasive breast cancers was smaller, and fewer invasive cancers were node positive in the MRI group than in the mammography group. To assess the effectiveness of the screening protocols in the long run, the results of the incident rounds are important: MRI screening resulted in lower numbers of late-stage cancers and node-positive cancers than mammography screening, thus both tumour stage and nodal status were significantly more favourable in the MRI group.

MRI screening might lead to a substantial reduction in mortality compared with mammography screening. In a study[4] of 93 569 patients diagnosed with primary breast cancer in the Netherlands in 2006–12, 5-year relative survival for patients with T1c tumours was 98%, and for patients with T2 tumours it was 92%; for patients with N0 tumours 5-year relative survival was 98%, but for patients with N2 tumours, it was 86% despite up-to-date adjuvant therapy. Furthermore, with substantially fewer patients with node-positive disease, less adjuvant chemotherapy will be needed, sparing many women the early and late side-effects and cost. As prespecified, we intend to publish 10-year mortality results after linkage with our national database, since mortality reduction is the aim of screening. The current follow-up is too short, but tumour stage is a reliable proxy.[3,4]

Participants screened using the MRI protocol had a favourable shift in tumour stage in detected tumours compared with participants screened with the mammography protocol; tumour stages detected in the mammography group were very similar to stages detected by MRI screening in older multicentre studies in women with familial risk.[5–7] This result shows how both mammography and MRI have improved over the past decade, and suggests that we should no longer use

the results of those older studies[6] for screening guidelines, as already shown by Obdeijn and colleagues.[22]

The MRI protocol had a clear disadvantage of more false-positive results and lower specificity, as was expected. Despite improvements in incident rounds for both screening groups, the difference in specificity between the groups remained significant and substantial. These results are in accordance with other high-risk MRI screening studies.[6] The false-positive frequency is potentially explained by the relatively young age of our participants, as the frequency of false positives clearly decreased in women aged 50 years or older and increased with increasing breast density, and might furthermore be the consequence of the very early stage at detection. The ACR expects a positive predictive value of 24% for biopsies, and the positive predictive value for biopsies we found in this study was just above this.[19] Our positive predictive values for BI-RADS scores of 3 or higher and for biopsies

	Density A	Density B	Density C	Density D	p value
All participants in screening and registration groups*	206	549	562	239	..
Screening rounds	993	2412	2413	1022	..
All breast cancers	..	..	..	..	0·13
N	5	22	27	11	..
Incidence (per 1000 screening rounds)	5·0	9·1	11·2	10·8	..
Interval cancers	..	..	..	..	0·47
N	0	2	2†	1	..
Incidence (per 1000 screening rounds)	0	0·8	0·8	1·0	..
Tumour stage					
Tis	1 (20%)	8 (36%)	11 (41%)	5 (50%)	0·11
T1a+T1b	2 (40%)	5 (23%)	8 (30%)	1 (9%)	0·98
T1c	2 (40%)	9 (41%)	4 (15%)	2 (18%)	0·49
T2 or higher	0	0	4 (15%)	3 (27%)	0·0077
Node status					
Positive	1 (25%)	3 (21%)	6 (38%)	3 (50%)	..
Negative	3 (75%)	11 (79%)	10 (63%)	3 (50%)	..
Participants in MRI group and MRI registration group	86	249	238	105	..
Screening rounds	403	1033	973	440	..
All breast cancers	..	..	..	..	0·92
N	5	15	17	5	..
Incidence (per 1000 screening rounds)	12·4	14·5	17·5	11·4	..
Interval cancers	..	..	..	..	0·10
N	0	0	0	1	..
Incidence (per 1000 screening rounds)	0	0	0	2·3	..
Sensitivity	100·0% (47·8–10·0)	100·0% (78·2–100·0)	100·0% (80·5–100·0)	80·0% (28·4–99·5)	0·080
Specificity	90·5% (87·1–93·2)	85·3% (82·9–87·4)	82·8% (80·3–85·2)	77·0% (72·8–80·9)	<0·0001
False positives	..	..	..	..	<0·0001
N	38	150	164	100	..
Incidence (per 1000 screening rounds)	94·3	145·2	168·6	227·3	..
Tumour stage					
Tis	1 (20%)	7 (47%)	7 (41%)	1 (20%)	0·97
T1a+T1b	2 (40%)	5 (33%)	7 (41%)	0	0·54
T1c	2 (40%)	3 (20%)	2 (12%)	1 (20%)	0·42
T2 or higher	0	0	1 (6%)	3 (60%)	0·0068
Node status					
Positive	1 (25%)	0	2 (20%)	2 (50%)	..
Negative	3 (75%)	8 (100%)	8 (80%)	2 (50%)	..

(Table 4 continues on next page)

	Density A	Density B	Density C	Density D	p value
(Continued from previous page)					
Participants in mammography group and mammography registration group	120	300	324	134	..
Screening rounds	590	1379	1440	582	..
All breast cancers	..	..	..	..	0·018
N	0	7	10†	6	..
Incidence (per 1000 screening rounds)	0	5·1	6·9	10·3	..
Interval cancers	..	..	..	..	0·99
N	0	2	2	0	..
Incidence (per 1000 screening rounds)	0	1·5	1·4	0	..
Sensitivity	NA	71·4% (29·0–96·3)	80·0% (44·4–97·5)	100·0% (54·1–100·0)	0·18
Specificity	93·7% (91·5–95·5)	93·0% (92·3–93·6)	89·0% (87·3–90·6)	86·3% (83·2–90·0)	0·00015
False positives	..	..	..	..	<0·0001
N	37	96	157	79	..
Incidence (per 1000 screening rounds)	62·7	69·6	109·0	135·7	..
Tumour stage					
Tis	0	1 (14%)	4 (40%)	4 (67%)	0·0065
T1a+T1b	0	0	1 (10%)	1 (17%)	0·12
T1c	0	6 (86%)	2 (20%)	1 (17%)	0·84
T2 or higher	0	0	3 (30%)	0	0·35
Node status					
Positive	0	3 (50%)	4 (67%)	1 (50%)	..
Negative	0	3 (50%)	2 (33%)	1 (50%)	..

Data are n, n (%), or n% (95% CI). BI-RADS breast density was estimated at baseline. Tis=tumour in situ. BI-RADS=breast imaging reporting and data system.*30 participants did not have density measurements. †One ductal carcinoma in situ was detected after the woman requested screening with MRI and mammography. The ductal carcinoma in situ was detected by both MRI and mammography.

Table 4: **All breast cancers, tumour staging, and false positives stratified by BI-RADS breast density category**

are also similar to the positive predictive values found in two recent cohort studies of MRI screening.[11,23]

Another drawback of screening is overdiagnosis. The incidence of all cancers detected was higher in the MRI group than in the mammography group. The difference in cancer incidence decreased after the first screening round and was no longer significant, although incidence remained higher in the MRI group until the fourth round of screening. However, with a mean age of 49 years at detection (the average Dutch life expectancy is 84 years), hardly any of the invasive cancers are expected to be a result of overdiagnosis, as even early-stage oestrogen-positive breast cancers might metastasise within 20 years.[3] Nevertheless, the detection of ductal carcinoma in situ is expected to be partly overdiagnosis; especially ductal carcinoma in situ grade 1, for which trials are ongoing to investigate whether active surveillance is safe.[24,25] In incident rounds, we detected an equal number of ductal carcinoma in situ with MRI and mammography.

A possible unwanted side-effect of MRI screening is retention of minute amounts of gadolinium in the brain and other tissues, although no harmful effect has been identified with the macrocyclic gadolinium products used in our 12 hospitals so far. A letter we sent to all participants in the MRI group in 2016 with evidence[26] that gadolinium could be retained in tissues, did not lead to a substantial withdrawal of participants.

Whether breast density measurements were estimated by radiologists or fully automated with Volpara, all tumours stage T2 or higher and most of the interval cancers were only detected in the two highest breast-density categories. MRI proved however, to be capable of detecting relevantly more early-stage cancers especially at categories A–C, and according to our automated density assessment, also in the highest-density category D, resulting in fewer late-stage cancers is incident rounds. With increasing breast density, specificity decreased both in the MRI and mammography groups, consistent with the results of Kerlikowske and colleagues.[12] Based on our results, density seems to be more important than age when choosing a screening strategy.

Previous studies have concluded that mammography is of limited additional value to MRI screening in women with familial risk.[27] Of the false-positive results in the MRI group, 98 (22%) of 449 were caused by mammography only. On the other hand, three (12%) minimal cancers (≤1 cm) were only detected by our

low-frequency mammography. We do not know at which stage these minimal tumours would have been detected with MRI, but either an even lower frequency of mammography screening should be considered, or mammography should be omitted entirely. Clinical breast examination generated a substantial amount of false-positive results in both screening groups and detected only one cancer, making the additional value of clinical breast examination negligible.

Studies have shown that digital breast tomosynthesis has the potential to increase screening sensitivity and specificity in comparison with digital mammography.[28] If digital breast tomosynthesis would have replaced mammography in this study, we would expect a gain in diagnostic accuracy in the mammography group. However, the average additional cancer yield for digital breast tomography is 1·2 per 1000 cases, compared with 3·5–4·4 per 1000 cases for ultrasound (with a considerable accompanying increase in false-positive frequency; thus, ultrasound is not recommended in Dutch screening guidelines)[9,29] but 15·5 per 1000 cases for MRI.[28,30,31]

One limitation of our study was that the numbers of detected cancers were small when stratified according to density or age categories, because the study was powered to show a difference in tumour size between the two screening groups. Therefore, we did not see a significant decrease in sensitivity with increasing breast density, which has been shown in previous studies.[12] Importantly, in the MRI group, the number of late-stage cancers detected decreased in incident rounds, but we also have to evaluate long-term survival and cost-effectiveness.

Another limitation was that previous screening might have affected cancer incidence; however, a nearly equal amount of previous MRI screening was done in both screening groups. Previous screening might have affected cancer incidence more in the mammography group because there was more previous mammography screening in the study population, although it was also dsitributed equally in both screening groups. Fortunately, the study continued for 7 years, with an average of 4·3 screening rounds per person. The highest cancer incidence in the mammography group was in the second year, and a nearly equally steep decline in cancer incidence can be seen in both groups thereafter. This suggests that the effect of previous screening on the complete study must have been limited and will not have affected our primary endpoints, tumour size and nodal status.

The biggest strength of our study (aside from the randomised design) is that the results are representative of daily, real-life practice, as patients were not only included at university hospitals with specialised high-risk breast screening units, but also at five larger, general hospitals throughout the Netherlands. However, better specificity might be achievable if MRIs are done in expert clinics. Further improvements might come from abbreviated MRI and, for specificity, artificial intelligence-based assistance.

We conclude that in real-life practice, MRI screening can result in an important and favourable shift in tumour stage at time of breast cancer detection compared with mammography screening, reducing the incidence of late-stage cancers and thus reducing the need for adjuvant chemotherapy and the risk of mortality. Especially in breast density category D, MRI screening would come at the cost of lower specificity. Clinical breast examinations could be omitted, and the frequency of combined MRI and mammography screenings could be further reduced.

Contributors

MMAT-L, I-MO, MJH, and HJdK were responsible for the study design. SS and HAG did the literature search. SS, HAG, I-MO, EAMH, HJdK, and MMAT-L were responsible for data analyses, data interpretation, and writing of the first draft of the manuscript. SS, HAG, EJTR, RMM, DBWdRvZ, HMZ, RAEMT, MBIL, MGEMA, Mv'tR, MJH, IM-E, EJTL, EAMH, CV, NK, WM, KK, CC, EM, LBK, JR, JCO, I-MO, HJdK, and MMAT-L were involved in data collection, and contributed to critical reading and final approval of the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

De-identified participant data will be made available 6 months after the trial primary and secondary endpoints have been published. Any requests for trial data and supporting material (data dictionary, protocol, and statistical analysis plan) will be reviewed by the trial principal investigator group in the first instance. Requests that have a methodologically sound proposal, do not interfere with planned analyses, and have been approved by the trial steering committee—eg, cost-effectiveness and 10-year mortality results, will be considered in the first instance. To gain access, data requestors will need to sign a data access agreement.

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References

1 Margolin S, Johansson H, Rutqvist LE, Lindblom A, Fornander T. Family history, and impact on clinical presentation and prognosis, in a population-based breast cancer cohort from the Stockholm County. *Fam Cancer* 2006; **5:** 309–21.

2 Brandt A, Bermejo JL, Sundquist J, Hemminki K. Age of onset in familial breast cancer as background data for medical surveillance. *BR J Cancer* 2010; **102:** 42–47.

3 Pan H, Gray R, Braybrooke J, et al. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. *N Engl J Med* 2017; **377:** 1836–46.

4 Saadatmand S, Bretveld R, Siesling S, Tilanus-Linthorst MMA. Influence of tumour stage at breast cancer detection on survival in modern times: population based study in 173797 patients. *BMJ* 2015; **351:** h4901.

5 Kriege M, Brekelmans CTM, Boetes C, et al. Efficacy of MRI and mammography for breast-cancer screening in women with familial or genetic predisposition. *N Engl J Med* 2004; **351:** 427–37.

6 Phi XA, Houssami N, Hooning MJ, et al. Accuracy of screening in women at familial risk of breast cancer without a known gene mutation: individual patient data meta-analysis. *Eur J Cancer* 2017; **85:** 31–38.

7 Leach MO, Boggis CR, Dixon AK, et al. Screening with magnetic resonance imaging and mammography of a UK population at high risk of breast cancer: a prospective multicenter cohort study (MARIBS). *Lancet* 2005; **365:** 1769–78.

8 Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2017: A review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin* 2017; **67:** 100–21.

9 Richtlijn borstkanker: versie 2.0. 2017. https://www.oncoline.nl/borstkanker (accessed Sept 15, 2018).

10 NICE clinical guideline 164. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. National Institute for Health and Care Excellence. June 25, 2017. https://www.nice.org.uk/guidance/cg164/chapter/Recommendations#surveillance-and-strategies-for-early-detection-of-breast-cancer (accessed April 15, 2018).

11 Bick 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; published online Feb 6.

12 Kerlikowske K, Scott CG, Mahmoudzadeh AP, et al. Automated and clinical breast imaging reporting and data system density measures predict risk for screen-detected and interval cancers: a case-control study. *Ann Intern Med* 2018; **168:** 757–65.

13 Lehman CD, Gatsonis C, Kuhl CK, et al. MRI evaluation of the contralateral breast in women with recently diagnosed breast cancer. *N Engl J Med* 2007; **356:** 1295–303.

14 Checka CM, Chun JE, Schnabel FR, Lee J, Toth H. The relationship of mammographic density and age: implications for breast cancer screening. *AJR Am J Roentgenol* 2012; **198:** W292–95.

15 Saadatmand S, Tilanus-Linthorst MM, Rutgers EJ, et al. Cost-effectiveness of screening women with familial risk for breast cancer with magnetic resonance imaging. *J Natl Cancer Inst* 2013; **105:** 1314–21.

16 Claus EB, Risch NR, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. *Cancer* 1994; **73:** 643–51.

17 Saadatmand S, Rutgers EJ, Tollenaar RA, et al. Breast density as indicator for the use of mammography or MRI to screen women with familial risk for breast cancer (FaMRIsc): a multicenter randomized controlled trial. *BMC Cancer* 2012; **12:** 440.

18 Kuhl CK, Schrading S, Bieling HB, et al. MRI for diagnosis of pure ductal carcinoma in situ: a prospective observational study. *Lancet* 2007; **370:** 485–92.

19 American College of Radiology. ACR BI-RADS Atlas, 4th edn. Reston, VA: American College of Radiology, 2003.

20 van Engeland S, Snoeren PR, Huisman H, Boetes C, Karssemeijer N. Volumetric breast density estimation from full-field digital mammograms. *IEEE Trans Med Imaging* 2006; **25:** 273–82.

21 Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; **33:** 159–74.

22 Obdeijn IM, Winter-Warnars GA, Mann RM, Hooning MJ, Hunink MG, Tilanus-Linthorst MMA. Should we screen *BRCA1* mutation carriers only with MRI? A multicenter study. *Breast Cancer Res Treat* 2014; **144:** 577–82.

23 Lee JM, Ichikawa L, Valencia E, et al. Performance Benchmarks for screening breast MR imaging in community practice. Radiology 2017; **285:** 44–52.

24 Elshof LE, Tryfonidis K, Slaets L, et al. Feasibility of a prospective, randomized, open-label, international multicentre, phase III, non-inferiority trial to assess the safety of active surveillance for low risk ductal carcinoma in situ – the LORD study. *Eur J Cancer* 2015; **51:** 1497–510.

25 Francis A, Thomas J, Fallowfield L, et al. Addressing overtreatment of screen-detected DCIS; the LORIS trial. *Eur J Cancer* 2015; **51:** 2296–303.

26 Huckle JE, Altun E, Jay M, Semelka RC. Gadolinium deposition in humans: when did we learn that gadolinium was deposited in vivo? *Invest Radiol* 2016; **51:** 236–40.

27 Vreemann S, van Zelst JCM, Schlooz-Vries M, et al. The added value of mammography in different age-groups of women with and without BRCA mutation screened with breast MRI. *Breast Cancer Res* 2018; **20:** 84.

28 Zackrisson S, Lang K, Rosso A, et al. One-view breast tomosynthesis versus two-view mammography in the Malmo Breast Tomosynthesis Screening Trial (MBTST): a prospective, population-based, diagnostic accuracy study. *Lancet Oncol* 2018; **19:** 1493–503.

29 Berg WA, Blume JD, Cormack JB, et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. *JAMA* 2008; **299:** 2151–63.

30 Gilbert FJ, Tucker L, Young KC. Digital breast tomosynthesis (DBT): a review of the evidence for use as a screening tool. *Clin Radiol* 2016; **71:** 141–50.

31 Kuhl CK, Strobel K, Bieling H, Leutner C, Schild HH, Schrading S. Supplemental breast MR imaging screening of women with average risk of breast cancer. *Radiology* 2017; **283:** 361–70.