Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS)

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Summary

Background **Women genetically predisposed to breast cancer often develop the disease at a young age when dense breast tissue reduces the sensitivity of X-ray mammography. Our aim was, therefore, to compare contrast enhanced magnetic resonance imaging (CE MRI) with mammography for screening.**

Methods **We did a prospective multicentre cohort study in 649 women aged 35–49 years with a strong family history of breast cancer or a high probability of a *BRCA1*, *BRCA2*, or *TP53* mutation. We recruited participants from 22 centres in the UK, and offered the women annual screening with CE MRI and mammography for 2–7 years.**

Findings **We diagnosed 35 cancers in the 649 women screened with both mammography and CE MRI (1881 screens): 19 by CE MRI only, six by mammography only, and eight by both, with two interval cases. Sensitivity was significantly higher for CE MRI (77%, 95% CI 60–90) than for mammography (40%, 24–58; p=0·01), and was 94% (81–99) when both methods were used. Specificity was 93% (92–95) for mammography, 81% (80–83) for CE MRI (p<0·0001), and 77% (75–79) with both methods. The difference between CE MRI and mammography sensitivities was particularly pronounced in *BRCA1* carriers (13 cancers; 92% *vs* 23%, p=0·004).**

Interpretation **Our findings indicate that CE MRI is more sensitive than mammography for cancer detection. Specificity for both procedures was acceptable. Despite a high proportion of grade 3 cancers, tumours were small and few women were node positive. Annual screening, combining CE MRI and mammography, would detect most tumours in this risk group.**

Introduction

Imaging surveillance for women at high risk of breast cancer requires a solid evidence base of proven effectiveness to guide practice. Women with a strong family history of breast cancer are more likely than others to develop the disease at a young age, when breast density is higher than at older ages. Additionally, cancers in women who carry a *BRCA1* mutation are of high grade,[1] which can indicate a particularly rapidly developing tumour with a short presymptomatic phase. These factors could reduce the effectiveness of screening by mammography.

Contrast enhanced breast magnetic resonance imaging (CE MRI) has high sensitivity for cancer detection, even in dense breasts.[2] The technique might therefore be suitable for screening of young women with a family history of breast cancer. Furthermore, the cost could be justified in genetically predisposed women because of their high lifetime risk of the disease. Although results from prospective studies[3,4] of CE MRI screening in high-risk women are becoming available, some of the evidence is based on studies that include women with symptomatic breast cancer.[5] As such, there is a need for further high-quality prospective studies in a screening setting. Our aim was to compare the diagnostic accuracy of yearly CE MRI with X-ray mammography in women aged 35–49 years.

Methods

Participants

Between August, 1997, and May, 2004, we did a prospective multicentre cohort study—MARIBS (Magnetic Resonance Imaging Breast Screening)[6–8]—to which we enrolled asymptomatic women at high risk for breast cancer from 22 centres in the UK. Women were eligible if they were aged 35–49 years and fulfilled one of the following criteria: they were known carriers of a deleterious *BRCA1, BRCA2,* or *TP53* mutation (the latter were screened from age 25 years); they were a first degree relative of someone with a *BRCA1, BRCA2,* or *TP53* mutation; they had a strong family history of breast or ovarian cancer, or both; or they had a family history consistent with classic Li-Fraumeni syndrome.[9]

Our aim was to include women whose affected first-degree relative(s) had at least a 60% chance of being a *BRCA1* or *BRCA2* mutation carrier, or women with an annual risk of breast cancer of at least 0·9%. An eligibility panel composed of three members of the study advisory group (RE, GE, and DE) adjudicated on cases in doubt.[10] Women at this level of risk in the UK receive yearly mammography screening from age 35 years, or from a younger age if their first-degree relative developed cancer at an age younger than 35 years. Since the end of the MARIBS study these women have

returned to mammographic screening alone. Neither regular physical examination nor screening ultrasound has been generally applied for breast-cancer screening in the UK in normal or high-risk groups.

We excluded women with previous breast cancer and those with any other cancer such that their expected prognosis was less than 5 years. Participants who underwent predictive genetic testing during the study and whose results were negative, and women who developed cancer, were excluded from further participation.

See Lancet Online for webtable 1

Recruitment began in August, 1997, and finished in March, 2003. Screening ceased in May, 2004, by which time all women had had an opportunity for at least two annual scans. In some centres, logistical problems and a time lapse resulted in women who had agreed to participate being excluded. Furthermore, some women were screened with only one technique. The analyses presented refer only to those who had both examinations in the same screening round. Most women from Li-Fraumeni families were excluded, since they were not screened by mammography.

See Lancet Online for webappendix 1

All women provided written informed consent, and the protocol and documentation were approved by the London Multicentre Research Ethics Committee and all the relevant local research ethics committees.

Procedures

We recruited women to centres with familial breast cancer clinics. Recruitment occurred over 6 years, resulting in a wide variation in the number of screening episodes for individuals (1–7 annual screening events). We ensured clinics were linked to suitable MRI facilities and radiological skills at the inception of the study. The MRI equipment, supplied by four manufacturers (GE Medical Systems, Slough, UK; Marconi Medical Systems and Philips Medical Systems, Reigate, UK; Siemens Medical Solutions, Bracknell, UK), had a field strength of 1·0–1·5 Tesla with a dedicated breast coil and with the systems capable of running the agreed national protocol of sequences.

Mammography was done annually and, by preference, on the same attendance day as the CE MRI examination. The examination took place either in an accredited screening centre of the National Health Service Breast Screening Programme (NHSBSP) or in a family-history clinic working to equivalent standards.[11–13] Mammography equipment in this context must conform to defined physical standards.[14,15] Physical quality assurance of the equipment and processor performance were monitored regularly. Mammographic examinations were either 2-view or 1-view (by mediolateral oblique only).

The screening CE MRI examination (protocol A) comprised high spatial resolution T1-weighted sequences before and after contrast medium injection, sandwiching a T1-weighted three dimensional coronal dynamic acquisition series with two sequences before the bolus intravenous injection of 0·2 mmol per kg bodyweight of gadopentetate dimeglumine (Gd-DTPA; Schering Healthcare, Burgess Hill, UK) and at four to six time points immediately after injection. We did an optional high resolution T1-weighted fat saturated sequence at the end of the procedure (see webtable 1 for parameters).[7] This protocol allows analysis of the time-signal intensity characteristics of any point in the imaging volume of either breast, and morphological examination of high detail images. Patients who were recalled because of an indeterminate CE MRI study, scoring suspicious (see webappendix 1), had either a high temporal resolution study with 0·1 mmol per kg Gd-DTPA (protocol B, see webtable 1), concentrating just on the area of breast where the abnormality was raised on the initial screening CE MRI study, or a repeat of the initial screening CE MRI protocol A with 0·2 mmol per kg body weight of Gd-DTPA; these alternatives were done at a different phase of the menstrual cycle. The reporting radiologist and the participant's attending doctor decided the diagnostic pathway.

For the reporting forms for CE MRI, we used a scoring system based on morphological and dynamic contrast uptake characteristics, which we devised at the time of the original protocol design in 1997 (see webappendix 1 for worksheets). This scoring system has been validated against histology, showing that the area under the receiver operator curve for the overall score was 0·88 (95% CI 0·83–0·94), higher than any component element.[16] We also developed a worksheet to ensure consistency of method in the choice of regions of interest and in their analysis. All CE MRI screening studies have been double reported and we have analysed their diagnostic accuracy on a subset of the present study examinations, enriched by 100 symptomatic cases.[17] Sensitivity of the technique was 91% (95% CI 83–96) and specificity was 81% (79–83). Single readings gave a 7% lower sensitivity (4–11) and a 7% higher specificity (6–7) than double reading. Mammography was also double reported, as is usual practice in the UK NHSBSP.[18] Radiologists unaware of the results of the other tests reported the findings of the screening studies. Once reported, the clinician taking responsibility for the screening event reviewed all the results of the diagnostic tests as an integrated whole, in the case of women recalled for additional tests or for surgical intervention. We employed an MRI physicist to ensure that the imaging protocol was correctly implemented and to do regular quality assurance checks of the MRI units, using phantom tests and other checks.[7] The pathologists from all 22 centres either participate in the UK breast screening programme or operate to equivalent standards and participate in the pathology and cytology quality assurance programme.[13] The study pathologists (SRL, AN) reviewed the pathology reports to classify lesions as benign or malignant.

Our main objective was to compare the sensitivity and specificity for malignant disease of mammography and CE MRI in women at high genetic risk of breast cancer. For every woman in every year, we compared the CE MRI score and the mammography score (both double-read, taking the more conservative score) with her true cancer status, as ascertained by pathology (where a biopsy was taken) or by the absence or presence of an interval cancer in the year after the examination. We ascertained interval cases by sending a follow-up questionnaire to participants, and by contacting the study centres. Women will be flagged at the Office of National Statistics to ascertain future cancer incidence and mortality.

At the end of the study women who had developed cancer, but who had not previously had predictive genetic testing, had blood taken for anonymous testing by Myriad Genetics (Salt Lake City, Utah, USA). This testing was done solely for the purpose of this study, and the ethics committee required that the result should not be passed on to the woman or her doctor.

Statistical analysis

To compute sensitivity and specificity, we considered CE MRI scores of B—suspicious (equivalent to American College of Radiology Breast Imaging Reporting and Data System [BI-RADS]:[19] 0=requires further tests; 3=indeterminate, probably benign; 4=suspicious)—or A—malignant (BIRADS 5) to be positive. Mammography scores of M3 (indeterminate, BI-RADS[20] 0 or 3), M4 (suspicious; BI-RADS 4), or M5 (malignant; BI-RADS 5) were judged positive outcomes. We calculated 95% CIs from the exact binomial distribution. We derived a test of significance of the difference in sensitivity (and likewise specificity) between the methods by considering all cancers (or non-cancers, for specificity) that were identified by just one of the two methods. We compared the proportion of these events with a positive CE MRI score and a negative mammography score with that expected under the null hypothesis—ie, half. We determined the significance level from the exact binomial distribution. Since this test involves only examinations that were scored differently by CE MRI and mammography, it is not sensitive to the number of interval cancers. Statistical tests were two-sided. We analysed the subgroups of women with a *BRCA1* or *BRCA2* mutation, or a relative with a *BRCA1* or *BRCA2* mutation, separately. We further assessed the discrimination achieved by the two methods by comparing the areas under the non-parametric receiver operator characteristic curves, assuming a normal distribution for the area under the curve.[21] For all analyses, we used Stata version 8.2.

We originally designed the study conservatively to detect an improvement in sensitivity from 70% for mammography to 85% for CE MRI.[8] To achieve 90% power to detect this difference at $p<0\cdot01$, we needed to diagnose an estimated 84 cancers during the study. We assumed the population would include both *BRCA1* and *BRCA2* mutation carriers (approximate incidence rate 3% per year) and women with a strong family history of breast cancer (minimum estimated risk 0·9% per year), with an overall target incidence of 1·4% per annum. In the current analysis, observed incidence rate was 1·9% per year. We assumed that 5% of women would refuse the initial CE MRI scan, with a further drop out of 2% per year. To achieve the required power, we designed the study to recruit 500 women annually for 3 years, with follow-up over 5 years—ie, 2–4 follow-up scans—such that about 6000 scans would be done. In 2001, we revised our sample size calculations, assuming a 90% sensitivity for CE MRI—ie, a 20% difference—in line with more recent data than were available in 1997.[5] The revised targets were for 3300 scans in 950 women, with 46 cancers predicted.

Role of the funding source

The sponsor of the study approved proposals containing the study design, but had no role in 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

Figure 1 shows the trial profile. The age range of the 649 women analysed was 31–55 years at entry (median 40 years). One woman was aged older than 50 years. Among women who had more than one screening round, there were 1232 screening intervals of 6–54 months in length (median 12 months). 85% (1046 of 1232) of screening intervals were between 10 and 14 months. 76% (1437 of 1881) of the CE MRI and mammography examinations were done on the same day, and only 4% (71 of 1881) were more than a month apart (maximum 184 days).

Of the 649 women screened, 82 (13%) had a known *BRCA1* mutation and 38 (6%) had a *BRCA2* mutation. We identified five of the women with a known *BRCA2* mutation through anonymous testing after they developed a breast cancer during the study. A further 57 women came from families with a known *BRCA1* mutation and 48 from families with a known *BRCA2* mutation. One woman from a Li-Fraumeni family with a known *TP53* mutation, and four others who had a family history compatible with Li-Fraumeni syndrome, chose to receive mammography as well as CE MRI, and were included in our analysis. The remaining 419 women were eligible on the basis of their family history of breast or ovarian cancer. During the course of the study, 30 of these women became ineligible for further participation due to a negative predictive genetic test.

Table 1 shows the results of screening by CE MRI and mammography, and in combination. The sensitivity of

CE MRI alone, irrespective of whether the women carried a mutation in *BRCA1* or *BRCA2* or not, was greater than that of mammography alone. However, CE MRI was less specific. Use of both CE MRI and mammography gave a higher sensitivity than either method alone, but a lower specificity. The positive predictive values (PPV) of CE MRI and mammography were 7·3% (95% CI 4·9–10) and 10% (5·8–17), respectively, whereas the negative predictive value (NPV) was 99% for both (99–100 and 98–99, respectively). The area under the receiver operator characteristic curve for CE MRI scoring was 0·85 (0·84–0·87), which was higher than that for mammography (0·70, 0·68–0·72, p=0·035; figure 2).

Analysis restricted to the prevalence screen (20 cancers, 629 non-cancers) gives CE MRI sensitivity of 75% (51–91) and mammography sensitivity of 40% (19–64; p=0·12 for the difference between tests) and specificities of 82% (78–85) and 93% (91–95), respectively (p<0·0001). Since some women had mammographic screening before entering the study, the mammogram was not necessarily a prevalence screen. The equivalent values for incidence (all subsequent MARIBS examinations, 15 cancers, 1217 non-cancers) are CE MRI sensitivity 80% (52–96) and mammography sensitivity 40% (16–68; p=0·11), with specificities of 81% (79–83) and 94% (92–95), respectively (p<0·0001).

We diagnosed only two cancers in the screening interval—ie, they were not detected by either CE MRI or mammography (figure 1). Excluding the six DCIS-only cancers (one interval cancer, two detected by both methods, and three detected by mammography alone) increased the CE MRI sensitivity to 86% (68–96) but reduced the mammography sensitivity to 31% (15–51, p=0·0009 for the difference between CE MRI and mammography). The sensitivity using both methods was 97% (82–100). 1743 (93%) mammographic examinations were 2-view, and 138 (7%) were 1-view by mediolateral oblique only.

The sensitivity of CE MRI was also higher than that of mammography in the group of women with a mutation in *BRCA1*, or with a relative having a mutation in *BRCA1* (p=0·004, Fisher's exact test; table 1). However, if these women are excluded, the sensitivities of CE MRI and mammography are 68% (45–86) and 50% (28–72), respectively (p=0·45 comparing CE MRI with mammography). The specificity of CE MRI was lower than that of mammography in the *BRCA1* group, but both tests were comparable with the results for the complete study group. In the *BRCA1* group, the PPV for CE MRI is 14% (7·2–23) and for mammography is 9·1% (1·9–24). Both tests together gave a sensitivity of 92% (64–100) and a specificity of 72% (65–78). Excluding the one DCIS-only case (an interval cancer) the CE MRI sensitivity was 100% (74–100) and the mammography sensitivity was 25% (5·5–57).

The sensitivity of CE MRI was similar to that of mammography in the group of women with a *BRCA2*

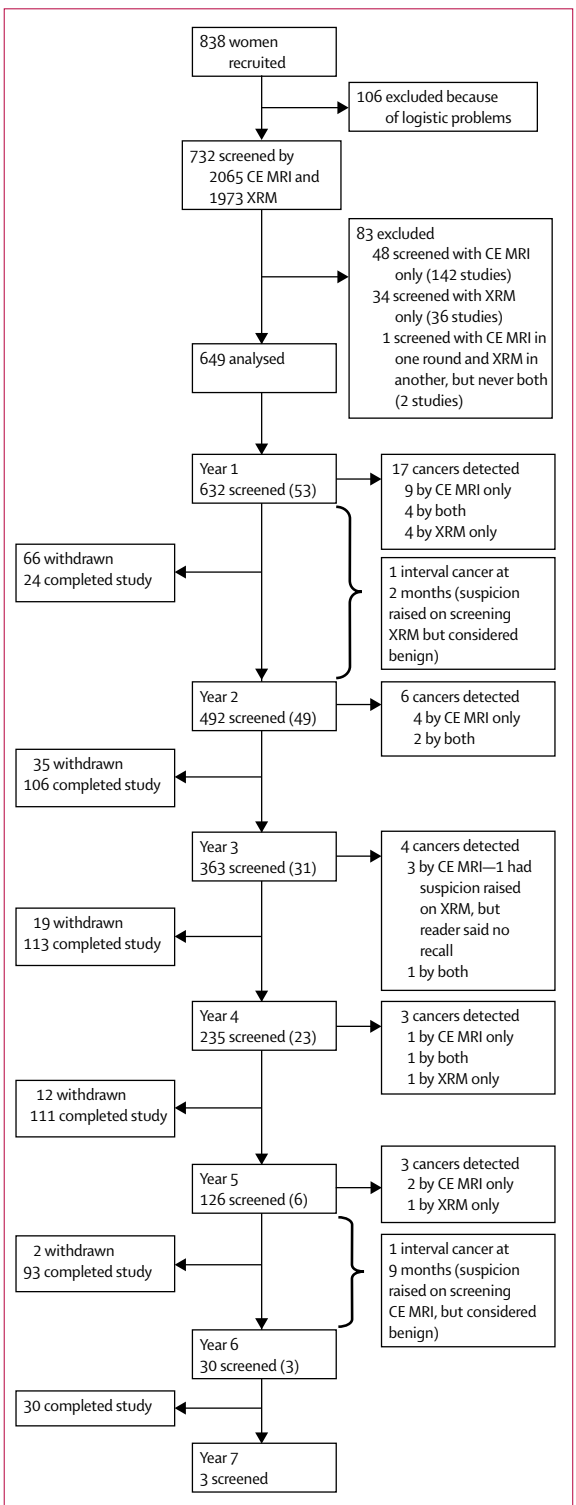

Figure 1: **Trial profile**
Numbers in parentheses are women who did not complete the full screening round this year. There were 41 screening rounds in which CE MRI only was used, 55 in which only X-ray mammography was used, and 33 in which both were declined. These rounds were, therefore, excluded, although these women were invited again the next year. XRM= X-ray mammography.

mutation, or a relative with a mutation in *BRCA2* (p=1·0). Excluding these women, the sensitivities of CE MRI and mammography are 87% (66–97) and 35% (16–57), respectively, rising to 96% (78–100) when both were combined. Excluding the three DCIS-only cancers increased the CE MRI sensitivity in the *BRCA2* group to 67% (30–93) and reduced the mammography sensitivity to 33% (7·5–70), although the numbers are small and the difference between CE MRI and mammography remained non-significant (p=0·45).

All breast cancers in the *BRCA1* and *BRCA2* groups were in known mutation carriers, including five women whose *BRCA2* mutation was identified during the anonymous genetic testing of women who developed breast cancer during the study. However, since the anonymous testing has, to date, been restricted to women with breast cancer, 57 of the 126 women without cancer in the *BRCA1* group have not been tested, but have a first degree relative with a mutation (49 of 74 women without cancer in the *BRCA2* group). Hence, though the sensitivities quoted for these groups refer exclusively to tested mutation carriers, the specificities do not, and should be interpreted as preliminary estimates.

Table 2 shows details of the cancers that arose during the study with their pathological and prognostic features and method of detection. 11 invasive cancers were less than 10 mm in greatest dimension, four were 10–14 mm, five were 15–19 mm, and nine were 20 mm or larger; average invasive tumour size was 15 mm. There were six cases of DCIS alone, of which four were less than 10 mm in diameter. Of the 29 invasive tumours, three were grade 1, seven were grade 2, and 19 were grade 3. Of cancers detected by screening or in a screening interval, 21 of 26 were node negative. Cancer detection rates were 26·9 per 1000 women at first examination (ie, prevalence) and 12·8 per 1000 women-years at subsequent examinations (ie, incidence). Most tumours from *BRCA1* carriers (seven of 11 with known status) were oestrogen-receptor negative, whereas most of the non-*BRCA1* tumours (14 of 18 with known status) were oestrogen-receptor positive. Double reading was used throughout, and of 14 cancers detected by mammography, seven were detected by one reader only. For the 19 cases diagnosed by CE MRI, four were detected by only one reader.

Webtable 2 shows why participants withdrew from the study. The five most common causes for withdrawal were a negative predictive genetic test (n=30), the development of breast cancer (n=35), personal reasons or stress (n=19), claustrophobia (n=12), and prophylactic mastectomy (n=28).

279 examinations resulted in a woman being recalled for further assessment, with recall rates of 3·9% per woman year for mammography and 10·7% per woman year for CE MRI (see webappendix 2). Use of both techniques together gave a recall rate of 12·7% per woman year (40 of the recalls were not justified by either the CE MRI or the mammography score, and thus were purely on the basis of the reader's judgment). Results of a previous study[22] in the first 726 screening episodes showed a recall rate of 11·8% and a surgical biopsy rate of 0·6%. Of the 245 women recalled who did not have cancer, 73% were diagnosed as healthy by doing further non-invasive tests—fine needle aspiration cytology, core

	Cancer	No cancer	Sensitivity of test (95% CI)	Specificity of test (95% CI)
All women (n=649)				
CE MRI+, XRM+	8	37		
CE MRI+, XRM–	19	307		
CE MRI–, XRM+	6	84		
CE MRI–, XRM–	2	1418		
CE MRI+	27	344	77% (60–90)	81% (80–83)
XRM+	14	121	40% (24–58)	93% (92–95)
CE MRI+ or XRM+	33	428	94% (81–99)	77% (75–79)
p value (CE MRI *vs* XRM)			0·01	<0·0001
Women with mutation in *BRCA1* or with a first-degree relative with mutation in *BRCA1* (n=139)				
CE MRI+, XRM+	3	11		
CE MRI+, XRM–	9	65		
CE MRI–, XRM+	0	19		
CE MRI–, XRM–	1	270		
CE MRI+	12	76	92% (64–100)	79% (75–83)
XRM+	3	30	23% (5–54)	92% (88–94)
CE MRI+ or XRM+	12	95	92% (64–100)	74% (69–78)
p value (CE MRI *vs* XRM)			0·004	<0·0001
Women with mutation in *BRCA2* or with a first-degree relative with mutation in *BRCA2* (n=86)				
CE MRI+, XRM+	2	3		
CE MRI+, XRM–	5	38		
CE MRI–, XRM+	4	10		
CE MRI–, XRM–	1	181		
CE MRI+	7	41	58% (28–84)	82% (77–87)
XRM+	6	13	50% (21–79)	94% (91–97)
CE MRI+ or XRM+	11	51	92% (62–100)	78% (72–83)
p value (CE MRI *vs* XRM)			1·0	0·0001

Table 1: **Occurrence of breast cancer in women grouped by result of CE MRI and mammography (XRM) examinations**

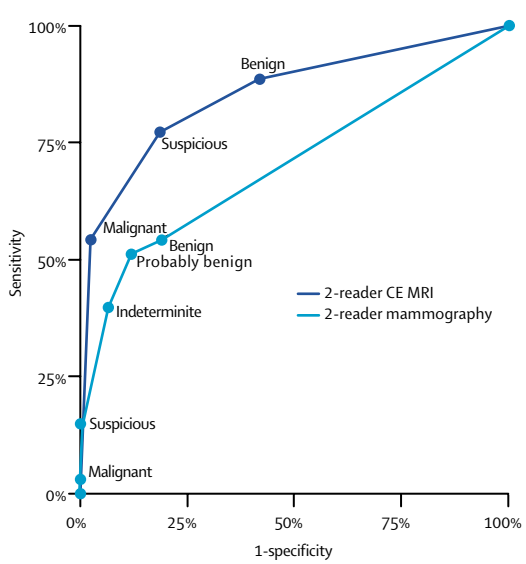

Figure 2: **Receiver operator characteristic curves for two-reader CE MRI and mammography**

See Lancet Online for webtable 2

See Lancet Online for webappendix 2

	Year of study	Genetic status	Type	DCIS size (mm)	Invasive tumour size (mm)	Grade	Nodes	Oestrogen-receptor status	Progesterone-receptor status	MRI score		XRM score		Detected by
										Reader 1	Reader 2	Reader 1	Reader 2	
1	1	*BRCA2* (FM)*	IDC+DCIS	N/K	15	3	0/12	+	+	A	A	M5	M5	Both
2	1	Br/ov (FH)*	IDC+DCIS	N/K	12	3	0/14	−	−	A	A	M4	M4	Both
3	1	*BRCA1* (T)	IDC+DCIS	4	7	3	0/12	NT	NT	N	B	N	M3	Both
4	1	Br/ov (FH)*	DCIS only	5		N/A	N/A	NT	NT	B	B	M3	M3	Both
5	1	*BRCA1* (T)	IDC+DCIS	N/K	8	2	0/10	+	NT	A	A	M2	N	MRI
6	1	*BRCA1* (T)	IDC+DCIS	N/K	6	3	0/7	−	−	B	B	N	N	MRI
7	1	*BRCA2* (T)	DCIS only	9		N/A	N/A	+	NT	N	N	M4	M4	XRM
8	1	*BRCA2* (T)	IDC		22	3	11/21	+	NT	B	A	N	N	MRI
9	1	*BRCA1* (T)	IDC		31	1	0/8	−	−	A	A	M2	N	MRI
10	1	Br/ov (FH)*	IDC+DCIS	N/K	9	2	0/12	+	+	B	A	N	N	MRI
11	1	*BRCA1* (T)	IDC+DCIS	N/K	16	2	0/4	+	NT	B	B	N	N	MRI
12	1	*BRCA1* (T)	IDC		21	3	0/23	−	NT	A	A	N	N	MRI
13	1	*BRCA1* (T)	IDC		18	3	0/16	+	NT	A	B	M1	M1	MRI
14	1	*BRCA2* (T)	IDC		20	3	0/17	+	−	A	A	N	N	MRI
15	1	Br/ov (FH)*	DCIS only	4		N/A	N/A	NT	NT	C	C	N	M3	XRM
16	1	Br/ov (FH)*	IDC		6	3	1/7	+	+	N	N	M3	M3	XRM
17	1	Br/ov (FH)*	IDC+DCIS	N/K	5	2	3/9	+	+	N	N	M4	N	XRM
18	1	*BRCA1* (T)	DCIS only	6		N/A	0/4	−	NT	N	N	M3	M3	Interval†
19	2	*BRCA2* (T)	DCIS only	17		N/A	N/A	NT	NT	N	A	M3	M3	Both
20	2	*BRCA1* (T)	IDC+DCIS	N/K	31	3	0/13	-	NT	C	B	M2	M3	Both
21	2	*BRCA1* (T)	IDC		10	3	N/K	NT	NT	C	B	N	N	MRI
22	2	Br/ov (FH)*	IDC+DCIS	1	15	3	0/29	−	−	B	A	N	N	MRI
23	2	*BRCA1* (T)	IDC+DCIS	10	20	3	0/13	−	−	A	A	N	N	MRI
24	2	Br/ov (FH)*	IDC		11	3	0/8	+	+	N	B	N	N	MRI
25	3	Br/ov (FH)*	IDC+DCIS	N/K	20	3	0/16	−	NT	A	N	M3	N	Both
26	3	Br/ov (FH)*	IDC		6	1	0/16	+	NT	A	B	N	N	MRI
27	3	*BRCA2* (T)	IDC+DCIS	N/K	8	3	1/4	+	+	A	B	N	N	MRI
28	3	Br/ov (FH)*	ILC		30	2	N/A	+	+	N	A	M1	M3‡	MRI
29	4	*BRCA1* (T)	IDC+DCIS	N/K	30	3	3/16	−	−	A	A	M3	M3	Both
30	4	*BRCA1* (T)	ILC		15	1	N/K	+	NT	A	C	N	N	MRI
31	4	*BRCA2* (T)	DCIS only	18		N/A	N/A	NT	NT	C	C	N	M3	XRM
32	5	Br/ov (FH)*	IDC+DCIS	3	10	3	0/4	+	NT	B	B	N	N	MRI
33	5	Br/ov (FH)*	IDC+DCIS	N/K	8	2	N/K	+	+	A	A	N	N	MRI
34	5	Br/ov (FH)*	IDC+DCIS	7	6	2	0/4	+	+	C	C	M2	M4	XRM
35	5	*BRCA2* (T)	IDC+DCIS	8	8	3	0/16	−	NT	C	C	N	N	Interval§

XRM=X-ray mammography. Br/ov=breast or ovarian cancer, or both. FM=mutation in family. T=tested mutation. FH=family history. ILC=invasive lobular cancer. IDC=invasive ductal cancer. N/A=not applicable. NK=not known. NT=not tested. N=normal (no lesions seen, no recall). C=benign lesion (no recall). B=equivocal lesion (recall). A=malignant lesion (recall). M1=benign lesion/normal tissue (no recall). M2=probably benign lesion (no recall). M3=indeterminate lesion (recall). M4=suspicious lesion (recall). M5=malignant lesion (recall). *These 15 women have been tested by Myriad Genetics: five are positive for a *BRCA2* deleterious mutation; no mutation was found in the other ten (testing was anonymous, so results cannot be linked to individual women). †2 months (suspicion raised on year 1 screening XRM but returned to normal screening). ‡XRM reader said no recall. §9 months (suspicion raised on year 5 screening CE MRI but both readers noted no change since previous year).

Table 2: **Details of the 35 breast cancers that arose during the study**

biopsy, or surgery were not required. Additional diagnostic procedures included ultrasound (93 cases), core biopsy (32 cases), and fine needle aspiration cytology (47 cases), to resolve diagnostic queries. Surgery was necessary to establish a diagnosis for 3% of recalled women with subsequent normal or benign results and in 27% of those with a cancer. The number of women per 1000 screening episodes that needed a diagnostic surgical biopsy, rather than fine needle aspiration or core biopsy, was 0·4% (seven of 1881) for benign lesions and 0·5% (nine of 1881) for malignant disease, giving a PPV for diagnostic surgical biopsy of 56%.

Of 137 supplementary CE MRI screening studies, only seven were done in women later shown to have cancer. 13 MRI-guided biopsies were undertaken. In one of these cancer was diagnosed and in the remainder the biopsy was used to exclude cancer in indeterminate lesions, one of which was in the contralateral breast of a woman with cancer. 62% (172 of 279) of suspicious findings on CE MRI were resolved without any invasive procedure, and 16 women had diagnostic surgery to complete their diagnosis. 91 participants had to have some form of percutaneous biopsy procedure. The preoperative diagnosis of cancer was made in 24 of 33 (73%) cases of screen-detected cancer. In this study 279 women were recalled for 33 screen-detected cancers with seven benign surgical biopsies and rates of 8·5 recalls and 0·21 benign surgical biopsies per cancer detected.

Discussion

Our findings show that, in women with a high risk of breast cancer by virtue of a strong family history, screening with CE MRI is more sensitive than mammography. However, as reported in other studies,[3,4] specificity was higher for mammography. Increased sensitivity was achieved by combining both modalities, but with some concomitant loss of specificity.

The gain in sensitivity of CE MRI over mammography was greatest in women with either a germline mutation

for *BRCA1* or with a first degree relative with such a mutation. Since these women also have a higher absolute risk in the age-range studied than the other risk groups, CE MRI screening might be particularly productive in this group. In women with a *BRCA2* mutation, and in women without any identified mutation, the gain was smaller and not significant. There were few cancers in these subgroups, however, and combined analyses with other studies are needed to fully assess the sensitivity of CE MRI in these women. Combining CE MRI and mammography increased sensitivity in all groups.

Our original power calculations were conservative and assumed that the sensitivity of yearly mammography would be 70%. The findings of studies published since the start of our trial[3–5] have, however, shown much lower sensitivities in high-risk groups, with 30–40% being a typical finding. For mammography in our study, which was double read and undertaken by doctors working to UK NHSBSP standards, sensitivity was 40% and specificity was 93%. Our results show that our policy of double reading was especially effective for mammography, where only one reader observed the subtle features in half the cases. The low sensitivity is likely to indicate underlying biological factors in this young high-risk group, including a higher proportion of rapidly developing tumours, particularly in *BRCA1* mutation carriers, and possibly a higher proportion of dense breasts in these women.[23–25] A related factor could be that CE MRI screening is able to detect tumours earlier in their development than mammography, thus reducing the apparent sensitivity of mammography by comparison with other studies.[26] The double reading policy for both modalities resulted in higher sensitivities than would be the case for single reading, but at the cost of higher recall and biopsy rates.

We chose the dose of Gd-DTPA contrast of 0·2 mmol per kg bodyweight for the CE MRI in 1996 to increase sensitivity to a maximum, since the evidence[27] at the time showed greater sensitivity with a higher dose. More recent publications[28] suggest that a lower dose of contrast (0·16 or 0·1 mmol per kg) might achieve the same sensitivity, though these used new gadolinium preparations and are therefore not strictly comparable with our study.

The tumour characteristics show that many were small and node negative, though a high proportion of women had grade 3 cancers. Nevertheless, despite annual screening with two modalities, we did identify some large, node-positive tumours, notably in the incident cases. This finding could reflect the rapid growth characteristics of the cancers that arose in women with germline mutations.[24] Our study was not designed to address the most effective screening interval, but resource use is likely to preclude screening with CE MRI more frequently than yearly.

Participant acceptability is a key factor in a screening programme. Most of the women who withdrew from our study did so because they became ineligible for CE MRI—eg, they had a negative predictive genetic test, developed cancer, or chose prophylactic mastectomy. Some women found the CE MRI scan uncomfortable or claustrophobic, but such reasons for withdrawal were rare. Stress or personal reasons were also cited for not wanting to continue with the study. Such problems have the potential to limit the usefulness of CE MRI screening. Mammography is well established and, though not fully acceptable to some women, the unpleasant features are known. A parallel psychological study will look at the features of both modalities that women find difficult to accept and at the temporal associations of such anxieties around the screening event. Although some women did not attend individual screening events because they could not be contacted, the rate of loss to follow up was low.

Recall for additional tests after screening causes anxiety.[29] Results of a previous study,[22] however, indicate that our recall and surgical biopsy rates were not unduly high for women at increased risk of cancer. Furthermore, our rates of preoperative diagnosis, recall, and benign surgical biopsies were similar to those reported by the UK NHSBSP,[30] where the preoperative diagnosis rate for women aged 50–64 years was 80%; the recall rate and the benign surgical biopsy rate per cancer detected were, respectively, 7·8 and 0·19 for 2002–03. Second-look ultrasound has been important for guiding the biopsies of large lesions. The main use of MRI-guided biopsy has been for exclusion of cancer in indeterminate lesions, and one might surmise that the benefit to be gained by more access to MRI-guided biopsy would have been fewer repeat CE MRI studies.

We have tested the use of CE MRI in many centres and by many operators. The equipment used had to meet a prescribed technical standard at the start of the study and to be able to run the sequences described in the protocol, but these criteria were met by equipment of two different field strengths and from four manufacturers. These facts indicate the degree of robustness of the technique that would be needed to adopt generalised screening.

Our findings re sensitivity and specificity of CE MRI and mammography concur for the most part with those detailed in two previous prospective screening studies (table 3).[3,4] The MRISC study[4] included women with a much wider age range than ours and hence more postmenopausal women, and had more tested carriers of germline mutations, but the number of cancers in presumed carriers was slightly lower than in our study. The study from Toronto[3] included only known *BRCA1* and *BRCA2* mutation carriers, but 30% of women had a previous diagnosis of cancer, and the study is therefore not directly comparable to ours. Nevertheless, the findings of all three studies indicate lower sensitivities

	Dutch MRISC study, Kriege et al, 2004[5]	Toronto, Canada, Warner et al, 2004[4]	MARIBS
Design	Non-randomised, prospective, multicentre study	Non-randomised, prospective, singlecentre study	Non-randomised, prospective, multicentre study
Number of women	1909	236	649
Number of CE MRI examinations	4169	457	1881
Number of *BRCA1* or *BRCA2* carriers	354 (276 *BRCA1*, 77 *BRCA2*, 1 *BRCA1* and *BRCA2*)	236 (137 *BRCA1*, 99 *BRCA2*)	120 (82 *BRCA1*, 38 *BRCA2*)
Mean age, years (range)	40 (19–72)	46.6 (26–65)	40 (31–55)
Number of eligible cancers	45 (6 DCIS)	22 (6 DCIS)	35 (6 DCIS)
Definition on positive exam	BI-RADS category 3 or above*	BI-RADS category 4 or above	BI-RADS category 3 or above
CE MRI sensitivity (95% CI)	71·1% (55·7–83·6)	77·3% (54·6–92·2)	77% (60–90)
XRM sensitivity	40·0% (25·7–55·7)	36·4% (17·2–59·3)	40% (24–58)
Combined sensitivity	88·9% (75·9–96·3)	86·4% (65·1–97·1)	94% (81–99)
CE MRI specificity	89·8% (88·9–90·7)	95·4% (93·0–97·2)	81% (80–83)
XRM specificity	95·0% (94·3–95·6)	99·8% (98·7–100)	93% (92–95)

XRM=X-ray mammography. *Use of BI-RADS category of 4 or more as the threshold for a positive examination changes the CE MRI sensitivity to 46·7% (31·7–62·1), the XRM sensitivity to 24·4% (12·9–39·5), the CE MRI specificity to 98·9% (98·6–99·2) and the XRM specificity to 99·7% (99·5–99·8).

Table 3: **CE MRI screening for breast cancer in women at raised genetic risk—summary of results from our study and two other prospective studies[4,5]**

than earlier smaller studies, including those from single centres, where sensitivities as high as 100% have been noted.[5,31–33]

Mammography is relatively good at detecting DCIS compared with CE MRI.[34] That the difference in sensitivity between CE MRI and mammography was greater in our study when we restricted the analysis to invasive cancers, is therefore not surprising. This same effect was noted in the MRISC study,[4] but not in the Canadian study[3] or in a report from New York.[35] We decided to compare mammography and CE MRI, and not physical examination or ultrasound, for the diagnosis of breast cancer, since the second two methods are not used in regular surveillance of women in the UK and are hence not supported by our call/recall systems. Furthermore, the published work indicates that physical examination and ultrasound have low sensitivity.[3,36]

Despite the differences in populations and study design, the consistency of the results across these studies strengthens the evidence that the observed difference in sensitivity is real. However, a full assessment of the benefits of CE MRI will depend on some assessment (albeit indirect) of the likely effect on mortality. These findings should also be viewed in the light of the different degree of resource needed to offer CE MRI and mammography screening. Mammography is a fairly cheap investigation in standard use. CE MRI is more sparsely available and needs more personnel and costly facilities and consumables, notably the contrast medium. A full cost-effectiveness analysis linked to this screening study will be published separately. Our results, taken with the two other major prospective studies, do however suggest that CE MRI screening would be of most benefit in carriers of *BRCA1* germline mutations. In *BRCA1* carriers, *BRCA2* carriers, and the full high-risk cohort studied here, combination of CE MRI with mammography provides the most effective screening examination.

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Conflict of interest statement

MOL is a non-executive director of Specialty Magnetics, which is developing a specialised breast MRI system under a Department of Health Medlink award. He has a non-exercised share option. He is also an author of a patent for breast MR image analysis. All other members of the writing committee declare that they have no conflict of interest.

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