Breast MRI in high risk patients

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ISBN: 978-90-902926-7
Lay-out: Ton Everaers, Rotterdam
Fotografie cover: Loek Wijchers, Rotterdam
Ontwerp cover: Nile Graficare , Landsmeer
Kunstenaar bronzen beeld: Abdoulaye Gandema, Burkina Faso
Drukker: Ipskamp Drukkers, Enschede

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MRI ONDERZOEK VAN DE BORST BIJ PATIENTEN MET EEN VERHOOGD RISICO

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
dinsdag 15 december 2015 om 13.30 uur

door

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geboren te Eindhoven

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I

General introduction

In 1986, nearly thirty years ago, Sylvia Heywang was the first to perform contrast-enhanced magnetic resonance imaging (MRI) of the breast (1). She discussed the preliminary results of 20 patients and demonstrated that breast tumors showed stronger contrast-enhancement than normal breast tissue. Already at that time she suggested that MR imaging may be helpful for the evaluation of dense breasts. At present breast MRI is incorporated in daily practice for several indications.

Breast cancer is by far the most prevalent malignancy in women, with a high incidence especially in Europe and North America. The cumulative lifetime risk of breast cancer for Dutch women is approximately 13% (2). A positive family history for breast cancer or a BRCA1 or BRCA2 gene mutation increases the risk of developing breast cancer considerably. The estimated life time risk for BRCA1/2 mutation carriers is 50-85% (3). Options to reduce the risk of breast cancer related death are prophylactic surgery (including prophylactic mastectomy and/or bilateral salpingo-oophorectomy (PBSO)) or chemoprevention. A promising strategy to reduce the risk of breast cancer death is early diagnosis by intensive surveillance.
Women with a strong family history are more likely to develop breast cancer at a young age. Due to higher breast density at younger ages, screening with mammography will be less effective. Based on the consistently high sensitivity of breast MRI in diagnostic settings, with values between 90 and 100% (4-6), the role of contrast-enhanced breast MRI in screening of high-risk women was investigated in previous studies. The outcomes of the first studies were promising: MRI detected cancers still occult at mammography and not yet clinically manifest (7-10). The published results of multiple studies confirmed the effectiveness of MRI in screening of women at high familial risk. In five prospective studies (11-15), a total of 3,571 women were screened with contrast-enhanced MR imaging and mammography. The pooled sensitivity for mammography was 40%, in comparison to 81% for MRI (16). In addition, the first results of the Dutch MRI screening study (MRISC) showed that with MRI the detected breast cancers were smaller and more often node negative in comparison with control groups who were not screened with MRI (11).
At present the role of breast MRI in screening of BRCA1 and BRCA2 mutation carriers is established and most guidelines now recommend MRI screening of these women (17-21), although no consensus exists on the optimal screening protocol for each of the risk groups separately.
Meanwhile, the additional gain of mammography, especially in BRCA1 mutation carriers, has become uncertain. Screening studies showed an extremely low sensitivity (11-13) while at the same time there are raising concerns about the risk of low-dose radiation exposure (22-24). All-in-all the findings raise the question whether mammography is justified if MRI is performed already.

Another unresolved issue is how to screen women with BRCA1/2 mutations once they reach the age of 50 years. MRI greatly increases the costs of screening while the advantages over mammography might be expected to decline with age because of a progressive reduction in breast density and decreased tumor growth rate. Current screening recommendations are not uniform across countries. Annual screening with MRI and mammography are offered for women with a BRCA1/2 mutation with no upper age limit in some countries (17-19), whereas the United Kingdom and the Netherlands, recommend screening with MRI and mammography only until age 50 or 60 years, respectively, after which mammography alone is performed (20,21).

Due to its high sensitivity, breast MRI was and is increasingly added to the work-up of patients with early stage breast cancer. It is thought that the extra information from MRI would contribute to a better surgical plan. As a consequence of more extensive disease detected by MRI, the surgical plan is often changed from lumpectomy to more aggressive surgery (25). Especially the higher rates of mastectomy are worrisome. A remaining question is, whether this more extensive surgery is justified because of lower reoperation rates, lower recurrence rates or a better prognosis.

Breast cancer may present as isolated axillary nodal metastases without any clinically or mammographically detectable breast tumor. The overall incidence of this uncommon presentation of breast cancer is estimated at less than 0.5% of all women with breast cancer (26). When MR imaging can reveal a mammographically and clinically occult breast cancer, optimal local treatment can be given.

AIM OF THIS THESIS

The purpose of this thesis was to investigate the value of breast MRI in screening of women with a family history or a genetic predisposition for breast cancer. In search of the optimal screening strategy for BRCA1 mutation carriers we assessed the radiation-risks as well as the additional value of digital mammography when screening with MRI is already performed. We investigate whether MRI screening is indicated for BRCA1/2 mutation carriers above the age of 50. Secondly, we discuss the use of preoperative MRI, in patients who are planned to undergo breast sparing surgery, an indication still under debate.
Thirdly, we investigated the value of breast MRI when breast cancer presents as isolated axillary nodal metastases without any clinically or mammographically detectable breast tumor.

MRI SCREENING IN WOMEN WITH HIGH FAMILIAL RISK FOR BREAST CANCER

In the MRI Screening study (MRISC), a non-randomized prospective cohort study, we compared the efficacy of mammographic and MRI screening for breast cancer in women with a family history or a genetic predisposition for breast cancer (**chapter 2**). Participants were divided into subgroups: carriers of a BRCA1 or BRCA2 gene mutation (50% to 85% cumulative life-time risk (CLTR)) , and two familial groups with high (30% to 50% CLTR) or moderate risk (15% to 30% CLTR). The objectives of this study were to evaluate screening effects in four different genetic risk groups focusing on (potential) differences between BRCA1 and BRCA2 mutation carriers and to study effects on observed breast cancer mortality.

Despite the excellent contribution of contrast-enhanced MRI in screening of women at high familial risk, MRI depicts not all cancers. In **chapter 3**, we assessed the characteristics of malignancies not detected by MR imaging in the MRISC study and tried to identify possible sources of error.

Cancers missed by screening may present as interval cancers. All other things being equal, the faster the rate of tumor growth, the greater the likelihood that a cancer will present as an interval versus a screen-detected cancer. In three cohorts of women undergoing annual screening with MRI and mammography, seven of the eight reported interval cancers occurred in BRCA1 mutation carriers (11-13). This suggests that one of the hallmarks of BRCA1-associated breast cancers is inherently fast tumor growth.
In **chapter 4** we investigated the influence of age, hereditary risk group, menopause, and breast density on tumor growth rate in high-risk women in three MRI screening studies.

In **chapter 5** we reviewed the images and related reports of a large, recent series of BRCA1 mutation carriers who developed breast cancer. Our evaluation presents results of MR screening with experienced readers, up-to date technology and only digital mammography. The objectives of our study were to determine the efficacy of screening in women with a BRCA1 mutation, to compare the current efficacy to previously published results, and to investigate the additional value of digital mammography over MRI.

Little additional value of mammographic screening over MRI screening in BRCA1 mutation carriers in combination with the risks of low-dose radiation were reasons to weigh the benefits, costs and radiation risks of mammographic screening. In **chapter 6** we evaluated a modified screening strategy

for BRCA1 mutation carriers with MRI from age 25 onwards and postponed mammographic screening until age 40 and compared this new strategy to the current screening strategy of the Dutch guidelines for BRCA mutation carriers. We used a validated computer simulation model (MISCAN (27-30)) to estimate how many breast cancer deaths would be prevented and to perform a cost-effectiveness evaluation comparing the current and the modified strategy. Furthermore, with the most recent exposure-risk models according to the BEIR VII phase 2 report (31), we estimated how many breast cancers and breast cancer deaths would be induced. We combined the results of both models to estimate the net effect of a decade of annual two-view mammographic screening from age 30-39 years, when MRI screening is already performed.

In **chapter 7** we examined the age-related accuracy of MRI alone and MRI combined with mammography relative to mammography alone for screening women with BRCA1/2 mutations, stratified into age groups of $<$ and $\geq$ 50 years, using individual patient data (IPD) from six high-risk screening trials (13, 32-36). We specifically aimed to assess the contribution of MRI for screening BRCA1/2 mutation carriers age $\geq$ 50 years to inform the uncertainty and lack of consensus about the appropriate screening strategy for older BRCA1/2 mutation carriers.

PREOPERATIVE BREAST MRI

In women eligible for breast conserving surgery, we evaluated whether the additional information of preoperative breast MRI would result in a reduction of lumpectomies with tumor-positive resection margins and a reduction of reoperations in comparison with a historical control group **(chapter 8)**. We also determined the percentage of change in the surgical plan as a consequence of the information from the preoperative MRI and whether this change was justified by the pathology results.

BREAST MRI IN MAMMOGRAPHICALLY AND CLINICALLY OCCULT BREAST CANCER

The combined role of breast MRI, sonography, and cytology in patients with axillary metastases as clinical evidence of a possible occult breast cancer was assessed in **chapter 9.**

In **chapter 10** the main findings of this thesis are summarized and discussed.

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BRCA1-associated breast cancers present differently from BRCA2-associated and familial cases: Long-term follow-up of the Dutch MRISC screening study

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ABSTRACT

Purpose
The Dutch MRI Screening Study on early detection of hereditary breast cancer started in 1999. We evaluated the long-term results including separate analyses of BRCA1 and BRCA2 mutation carriers and first results on survival.

Patients and Methods
Women with higher than 15% cumulative lifetime risk (CLTR) of breast cancer were screened with biannual clinical breast examination and annual mammography and magnetic resonance imaging (MRI). Participants were divided into subgroups: carriers of a gene mutation (50% to 85% CLTR) and two familial groups with high (30% to 50% CLTR) or moderate risk (15% to 30% CLTR).

Results
Our update contains 2,157 eligible women including 599 mutation carriers (median follow-up of 4.9 years from entry) with 97 primary breast cancers detected (median follow-up of 5.0 years from diagnosis). MRI sensitivity was superior to that of mammography for invasive cancer (77.4% v 35.5%; $P < .00005$), but not for ductal carcinoma in situ. Results in the BRCA1 group were worse compared to the BRCA2, the high-, and the moderate-risk groups, respectively, for mammography sensitivity (25.0% v 61.5%, 45.5%, 46.7%), tumor size at diagnosis ≤ 1 cm (21.4% v 61.5%, 40.9%, 63.6%), proportion of DCIS (6.5% v 18.8%, 14.8%, 31.3%) and interval cancers (32.3% v 6.3%, 3.7%, 6.3%), and age at diagnosis younger than 30 years (9.7% v 0%). Cumulative distant metastasis-free and overall survival at 6 years in all 42 BRCA1/2 mutation carriers with invasive breast cancer were 83.9% (95% CI, 64.1% to 93.3%) and 92.7% (95% CI, 79.0% to 97.6%), respectively, and 100% in the familial groups ($n = 43$).

Conclusion
Screening results were somewhat worse in BRCA1 mutation carriers, but 6-year survival was high in all risk groups.

INTRODUCTION

Women with a genetic predisposition for breast cancer face a cumulative lifetime risk (CLTR) of breast cancer varying between 15% and 85% (1-4). The risk of breast cancer can be reduced by prophylactic surgery or chemoprevention (5-9). A promising strategy to reduce the risk of breast cancer death is early diagnosis by intensive surveillance. First results of various large prospective studies have shown that magnetic resonance imaging (MRI) appears to be about twice as sensitive as mammography in detecting tumors in women with a susceptibility to breast cancer (10-21). Although most guidelines now recommend MRI screening in BRCA1/2 mutation carriers (22-24), no consensus on the screening protocol exists for all risk groups. Only a few (small) studies investigated screening results in BRCA1 and BRCA2 mutation carriers separately. Furthermore, data on mortality are lacking.
Therefore, based on an extensive update and enlargement of our MRI Screening Study (MRISC), the largest (n = 2,157) in the world to our knowledge, the objectives of our current study were: evaluation of screening effects in four different genetic risk groups focusing on (potential) differences between BRCA1 and BRCA2 mutation carriers and to study, for the first time to our knowledge, effects on observed breast cancer mortality.

PATIENTS AND METHODS

Study Population

The Dutch MRISC study is a nonrandomized prospective cohort study. Between November 1, 1999, and March 1, 2006, 2,275 women with a genetic risk of breast cancer were enrolled by six cancer and/or university centers (Appendix Table A1, online only). The study was approved by the ethics committees of all centers. All women provided written informed consent.
Women (age, 25 to 75 years) with a cumulative lifetime risk (CLTR) of developing breast cancer of ≥ 15% due to a familial or genetic predisposition were eligible for the study (10,25). Women with symptoms or a personal history of breast cancer were excluded. At study entry, participants were divided into subgroups according to their estimated CLTR of breast cancer: carriers of BRCA1, BRCA2, or other mutations (50% to 85% CLTR), a high-risk group (30% to 50% CLTR), and a moderate-risk group (15% to 30% CLTR) without a documented gene mutation. These CLTR categories for breast cancer were based on the modified tables of Claus (4,25).

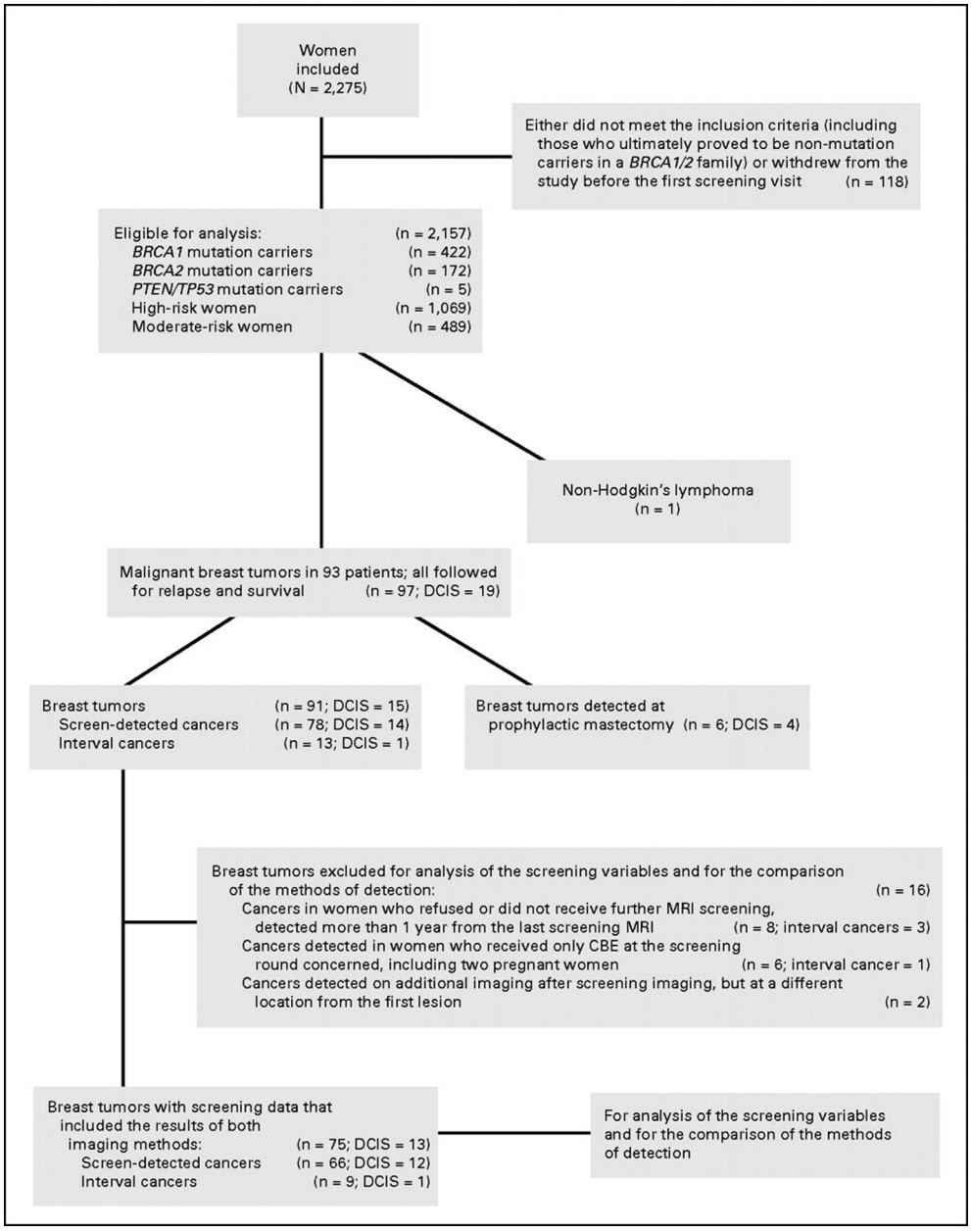

Fig 1. Flow chart describing the number of women and number of breast tumors available for statistical analysis. The numbers of DCIS and interval cancers are included in the total number of breast tumors. DCIS, ductal carcinoma in situ; MRI, magnetic resonance imaging; CBE, clinical breast examination.

Study Protocol

Participating women were screened with biannual clinical breast examination (CBE) and annual (simultaneous) two-view mammography and MRI of the breasts. Through the years, all centers changed from conventional to digital mammography. In all centers, dynamic contrast enhanced MRI was performed on a 1.5 Tesla system (Siemens, Erlangen, Germany). Breast MRI workstations were used to perform time-signal intensity curves. During the study, the MR units were upgraded and scanning protocols improved. The mammography and MRI were scored in a standardized way according to the Breast Imaging Reporting and Data System (BI-RADS) (26,27), and were independently evaluated. We defined as positive a mammography or MRI with BI-RADS score 0, 3, 4, or 5 and a CBE that was classified as uncertain or suspicious, because those were the results that triggered an additional examination. An interval cancer was defined as a carcinoma detected by the woman between two rounds of screening, after initially negative findings on screening. The diagnosis of a malignant tumor was based on the results of histologic examination. Patients were subsequently treated according to standard protocols for local and systemic (adjuvant) treatment. For a more detailed description of the screening protocol (10,25,28) see the online-only Appendix.

The records of all women with breast cancer detected before March 1, 2006, were inspected for the occurrence of a relapse and/or death (using the municipal registry) until January 1, 2009 (Figs 1 and Appendix Fig A1, online only).

Statistical Analysis

Overall breast cancer detection rates were calculated as the total number of breast cancers detected (including ductal carcinoma in situ [DCIS]) per 1,000 woman-years at risk; a Poisson distribution was assumed to calculate the 95% CIs. Detection rates were compared using exact tests (based on the binomial distribution).

For each of the three screening modalities, we calculated sensitivity, specificity, and positive predictive value, including 95% CIs based on the binomial distribution. The differences between sensitivity of screening modalities were tested by a McNemar's test. Sensitivity was compared between the different subgroups with the use of Fisher's exact test. For the analysis of the screening variables and for the comparison of the methods of detection of breast cancer, we used only the screening data that included the results of both imaging methods at the screening rounds (n = 75, Fig 1).

Differences in proportion of interval cancers, age at diagnosis (continuous variable without normal distribution), DCIS or invasive cancer, tumor size

(continuous variable without normal distribution), nodal status, histologic type, histologic grade, estrogen receptor, and progesterone receptor status between subgroups were analyzed by Fisher's exact, Mann-Whitney, or Kruskal-Wallis test. A two-sided P value of lower than .05 was considered statistically significant. The cumulative distant metastasis-free and overall survival were calculated by using the Kaplan-Meier method. Statistical analyses were performed using SPSS (SPSS 16.0 for Windows, SPSS Institute, Chicago, IL) and STATA 11SE (Stata Corp, College Station, TX).

RESULTS

Patients

Of the 2,275 women included in the study, 118 did not meet the various inclusion criteria (Figs 1, A1) (10,25). The 2,157 eligible women included 599 carriers of a pathogenic gene mutation in BRCA1 (n = 422), BRCA2 (n = 172), or PTEN/TP53 (n = 5), 1,069 women in the high-risk and 489 women in the moderate-risk group (Tables 1 and 2). Median follow-up time from entry was 4.9 years (mean, 4.0; range, 0.1 to 6.3 years), with 8,760 woman-years at risk. The mean age at entry was 40.1 years (range, 19 to 75 years) for the total study group, and 38.7, 40.0, 40.8, and 40.0 years for the subgroups of women with a BRCA1 mutation, a BRCA2 mutation, the high-risk, and the moderate-risk group, respectively. In the mutation carriers, high- and moderate-risk group, respectively, 22%, 16%, and 15% had no previous breast cancer screening before study entry.

Breast Cancers

To March 1, 2006, a total of 98 malignant tumors were detected in 94 women (Fig 1). Of the 97 breast cancers, 78 (80%) were invasive and 19 (20%) were DCIS (Table 1); 78 breast cancers were detected by screening (15 in the first and 63 in subsequent screening rounds) and six by chance at prophylactic mastectomy. Ten of 13 interval cancers were found in BRCA1 mutation carriers. Nine of 13 interval cancers were detected within 1 year (median, 8; range, 3 to 10 months; Table 3) and four more than 1 year since last screening by imaging (Fig 1). The median tumor size of all invasive interval cancers was 20 mm (n = 12; range, 12 to 50 mm).

The overall rate of detection was 10.4 per 1,000 woman-years at risk (Table 2), with the highest rate in BRCA2 mutation carriers (39.2 per 1,000), which was due partly to the high incidence of DCIS in this subgroup (7.4 per 1,000).

Table 1. Total number of breast cancers detected, divided into screen-detected cancers and interval cancers, according to risk group.

Risk group	No. of women	No. of cancers detected			No. of screen-detected cancers			No. of interval cancers		
		Total	Invasive	DCIS	Total	Invasive	DCIS	Total	Invasive	DCIS
Mutation carriers										
BRCA1	422	35 (4*)	31 (2)	4 (2*)	21	19	2	10	10	0
BRCA2	172	18 (2*)	13	5 (2*)	15	12	3	1	1	0
PTEN / TP53	5	1	0	1	1	0	1	0	0	0
High-risk group	1069	27	23	4	26	22	4	1	1	0
Moderate-risk group	489	16	11	5	15	11	4	1	0	1
Total	2157	97 (6*)	78 (2*)	19 (4*)	78	64	14	13	12	1

Abbreviations: DCIS, ductal carcinoma in situ; PM, prophylactic mastectomy.
* Indicates No. of cancers detected by PM (in parenthesis). Six breast cancers were detected in a specimen from a PM: four breast cancers (two invasive breast cancers, two DCIS) in BRCA1 mutation carriers, and two breast cancers (two DCIS) in BRCA2 mutation carriers as indicated in parentheses. These cancers are included in the total No. of breast cancers detected, but not included in the No. of interval cancers.

Table 2. Detection of breast cancers (including ductal carcinoma in situ), including screen-detected cancers (n = 78) and interval cancers (n = 13), according to risk group*

			No. of screen-detected and interval cancers		Rate of detection †			
					All cancers		Invasive cancers	
parameter	No. of women	Woman-years at risk	Total	Invasive	Detection rate	95% CI	Detection rate	95% CI
Mutation carriers								
BRCA1	422	1178	31	29	26.3	17.9-37.3	24.6	16.5-35.3
BRCA2	172	408	16	13	39.2	22.4-63.7	31.9	17.0-54.5
PTEN / TP53	5	13	1	0	-		-	
High-risk group	1069	4838	27	23	5.6‡	3.7-8.1	4.8	3.0-7.1
Moderate-risk group	489	2324	16	11	6.9	3.9-11.2	4.7	2.4-8.5
Total	2157	8760	91	76	10.4	8.4-12.8	8.7	6.8-10.9

* The number of cancers and rates of detection are excluding the 6 cancers detected by chance at prophylactic mastectomy. Overall rates of detection (invasive plus in situ), when including the breast cancers detected at prophylactic mastectomy (in total 97 breast cancers, see table 1), are 11.1, 29.7 and 44.1 per 1000 woman-years at risk for the total study group, BRCA1 mutation carriers and BRCA2 mutation carriers, respectively. Rates of detection of invasive cancers, including breast cancers detected at prophylactic mastectomy, are 8.9 and 26.3 per 1000 woman-years at risk for the total study group and BRCA1 mutation carriers, respectively.

† Rates shown are per 1000 woman-years at risk.

‡ Differences in rates of detection between the high- and moderate-risk group for all cancers (P = .50) and invasive cancers (P = 1.0) are not significant.

No clear differences (P = .50) in detection rates between the high- and moderate-risk groups were observed, as discussed before (29).

Screening Performance

Considering only those 75 breast cancers (including 13 DCIS and nine interval cancers) with results of both imaging methods (Table 3), 32 (43%) were detected only by MRI screening (16 of the 32 in mutation carriers); five of these were also detected by CBE. A total of 19 breast cancers (25%) were detected by both MRI and mammography screening; five also by CBE. Twelve breast cancers (16%) were detected only by mammography screening (including eight DCIS); one also by CBE. Three breast cancers were detected only by CBE screening (4%). Nine (12%) were true interval cancers. Tumor sizes of invasive tumors were largest in the group of interval cancers (median size, 16.5 mm) and smallest in the group of cancers detected by MRI only (median size, 9 mm; P = .002; Table 3). Age at diagnosis tended to be lower (P < .10) in the patient group with interval cancers.

For all 75 breast cancers (invasive plus in situ), the sensitivity was 20.6% for CBE, 41.3% for mammography, and 70.7% for MRI, respectively (Table 4). The difference in sensitivity between mammography and MRI is significant (P = .0016). Including only invasive cancers increased MRI sensitivity to 77.4% but decreased the mammography sensitivity to 35.5% (n = 62; P < .00005). In contrast, for DCIS cancers only, the sensitivity of mammography (69.2%) was much higher than that of MRI sensitivity (38.5%), but, due to small numbers, not significant (n = 13; P = .388). The overall specificity was 97.9% for CBE, 94.6% for mammography, and 89.7% for MRI.

Regarding women younger than 40 years of age at diagnosis, in five of 26 patients, the tumor was only detected by mammography (three patients with DCIS), while in 11 women the tumor was only detected by MRI (one patient with DCIS; Appendix Table A2, online only).

Looking more specifically at mutation carriers, the mammography sensitivity was significantly lower (P = .04) in BRCA1 (25.0%) than in BRCA2 mutation carriers (61.5%). Strikingly, the sensitivity of MRI was much higher than that of mammography in BRCA1 (n = 24; 66.7 v 25.0%; P = .0129) and only slightly higher (n = 13; 69.2 v 61.5%; P = 1.0) in BRCA2 mutation carriers. The sensitivity of CBE was highest in the high- and moderate-risk groups, but overall differences were not significant (P = .22). The specificity of each screening method did not differ much between the risk groups.

Table 3. Comparison of the methods of detection of breast cancer (using only the screening data that included the results of both imaging methods at the screening rounds, n=75).

parameter	MRI screening + Mmg screening - CBEscreening + or –	MRI screening + Mmg screening + CBE screening + or –	MRI screening - Mmg screening + CBE screening + or –	MRI screening - Mmg screening - CBE screening +	Interval cancers	Total number of breast cancers
Mutation carriers						
BRCA1	11	4	2 (2)	1	6	24 (2)
BRCA2	4 (1)	5 (1)	3 (1)	0	1	13 (3)
PTEN	1 (1)	0	0	0	0	1 (1)
High-risk group	9 (1)	8	2 (1)	2	1	22 (2)
Moderate-risk group	7	2	5 (4)	0	1 (1)	15 (5)
Total	32 (3)	19 (1)	12 (8)	3	9 (1)	75 (13)
Median tumor size of						
invasive tumors, mm	9	15	13.5	10.0	16.5	12.0
Range	4-45	4-35	4-20	5-10	12-45	4-45

Invasive tumors ≤ 1 cm, %	62.1	33.3	25.0	100.0	0	45.2
Median age at diagnosis, years	45.5	49.1	41.5	45.7	38.1	45.2
Range	36-53	27-68	31-61	32-49	28-53	27-68

NOTE. Numbers in parenthesis indicate ductal carcinoma in situ. The results have been calculated on the basis of data on 75 of the 97 cancers (Fig 1). A mammographic or MRI study with a BI-RADS score of 3, 0, 4 or 5 and a clinical breast examination that was classified as uncertain or suspicious was defined as positive (+). A mammographic or MRI study with a BI-RADS score of 1 or 2 and a clinical breast examination that was classified as not suspicious was defined as negative (−).
Abbreviations: MRI, magnetic resonance imaging; Mmg, mammography; CBE, clinical breast examination; BI-RADS, Breast Imaging Reporting and Data System.

Patient and Tumor Characteristics

The age at diagnosis (mean 44.4; median, 44.6; range, 27 to 68 years) differed overall significantly (P = .0006) between the different risk groups (Table 5): 58.1% of the BRCA1 mutation carriers had an age at diagnosis of breast cancer younger than 40 years (9.7% younger than 30 years of age), compared with 50.0% in BRCA2 mutation carriers, 18.5% in the high-risk group, and only 6.3% in the moderate-risk group.

Strikingly, DCIS was found in only 6.5% of the BRCA1-associated tumors, in contrast to 18.8% of the BRCA2-associated cases, but differences between risk groups were not significant (Table 5). In BRCA1 mutation carriers, 35.7% of the invasive tumors were larger than 2 cm compared to only 7.7% in BRCA2 mutation carriers. Both in BRCA2 mutation carriers and in women at high and moderate risk, a large proportion of the invasive tumors was smaller than 1 cm (61.5%, 40.9%, and 63.6%, respectively). The tumor sizes differed significantly between the four subgroups (P = .003), and also between BRCA1 and BRCA2 mutation carriers separately (P = .0045).
The distribution of nodal status did not differ between the different risk groups (P = .42). Grade 1 tumors were mostly found in women at high or moderate risk (52.2% and 54.5%, respectively). The women with a BRCA1 mutation had a high proportion of grade 3 tumors (77.8%), in addition to a high percentage of tumors that were negative for steroid receptors.

Disease-Free and Overall Survival

The median follow-up from time of diagnosis of the primary tumors in the 89 surviving patients was 5.0 years (range, 1.7 to 8.4 years).

Table 4. Sensitivity, Specificity, and PPV of CBE, Mammography, and MRI (using only the screening data that included the results of both imaging methods at the screening rounds)*†

Parameter	Sensitivity			Specificity			PPV		
	%	95% CI	No./Total No.	%	95% CI	No./Total No.	%	95% CI	No./Total No.
CBE									
Any breast cancer	20.6	11.7 to 32.1	14/68	97.9	97.5 to 98.2	5,688/5,810	10.3	5.7 to 16.7	14/136
Invasive breast cancer	21.8	11.8 to 32.1	12/55						
DCIS	15.4	1.9 to 45.4	2/13						
Mutation carrier (any breast cancer)									
BRCA1	13.0‡	2.8 to 33.6	3/23	96.9	95.7 to 97.9	982/1,013	8.8	1.8 to 23.7	3/34
BRCA2	7.7	0.2 to 36.0	1/13	98.3	96.4 to 99.4	349/355	14.3	0.4 to 57.9	1/7
Risk group (any breast cancer)									
High	31.6	12.6 to 56.5	6/19	98.2	97.7 to 98.7	3,030/3,085	9.8	3.7 to 20.2	6/61
Moderate	33.3	9.9 to 65.1	4/12	97.8	96.9 to 98.6	1,317/1,346	12.1	3.4 to 28.2	4/33
Mammography									
Any breast cancer	41.3	30.1 to 53.3	31/75	94.6	94.0 to 95.1	5,844/6,178	8.5	5.8 to 11.8	31/365

	Invasive breast cancer	35.5	23.7 to 48.7	22/62						
	DCIS	69.2	38.6 to 90.9	9/13						
	Mutation carrier (any breast cancer)									
	BRCA1	25.0‡	9.8 to 46.7	6/24	94.6	93.0 to 95.9	995/1,052	9.5	3.6 to 19.6	6/63
	BRCA2	61.5	32.6 to 86.1	8/13	93.8	90.9 to 96.0	349/372	25.8	11.9 to 44.6	8/31
	Risk group (any breast cancer)									
	High	45.5	24.4 to 67.8	10/22	94.6	93.8 to 95.3	3,129/3,308	5.3	2.6 to 9.5	10/189
	Moderate	46.7	21.3 to 73.4	7/15	94.8	93.5 to 95.9	1,360/1,435	8.5	3.5 to 16.8	7/82
MRI										
	Any breast cancer	70.7	59.0 to 80.6	53/75	89.7	88.9 to 90.4	5,539/6,178	7.7	5.8 to 9.9	53/692
	Invasive breast cancer	77.4	65.0 to 87.1	48/62						
	DCIS	38.5	13.8 to 68.4	5/13						
	Mutation carrier (any breast cancer)									
	BRCA1	66.7‡	44.7 to 84.4	16/24	91.0	89.1 to 92.6	957/1,052	14.4	8.5 to 22.4	16/111
	BRCA2	69.2	38.6 to 90.9	9/13	91.9	88.7 to 94.5	342/372	23.1	11.1 to 39.3	9/39

Risk group (any breast cancer)									
High	77.3	54.6 to 92.2	17/22	89.1	87.9 to 90.1	2,946/3,308	4.5	2.6 to 7.1	17/379
Moderate	66.7	38.4 to 88.2	10/15	89.5	87.8 to 91.0	1,284/1,435	6.2	3.0 to 11.1	10/161

Abbreviations: PPV, positive predictive value; CBE, clinical breast examination; MRI, magnetic resonance imaging; Bi-RADS, Breast Imaging Reporting and Data System.
* The results have been calculated on the basis of data on 75 of the 97 cancers (Fig 1).
† A mammographic or MRI study with a BI-RADS score of 3, 0, 4 or 5 and a clinical breast examination that was classified as uncertain or suspicious was defined as positive. A mammographic or MRI study with a BI-RADS score of 1 or 2 and a clinical breast examination that was classified as not suspicious was defined as negative.
‡ We compared for all three screening modalities the differences in sensitivity between risk groups overall, and separately between BRCA1 mutation carriers and any other risk group. For CBE and MRI we found no significant differences, while for mammography we only found a significant difference between BRCA1 and BRCA2 mutation carriers (P = .04).

Eleven of 93 patients with breast cancer developed a recurrence: seven of 11 with a gene mutation (Appendix Table A3, online only). All but one were screen-detected tumors. Distant metastasis occurred in five patients (all BRCA1/2 mutation carriers), generally at a young age. The primary tumor sizes were 2, 9, 20, 25, and 40 mm, and only one tumor was node positive. Four patients died (three of 31 = 9.7% of all BRCA1 and one of 16 = 6.3% of all BRCA2 mutation carriers). The cumulative distant-metastasis free and overall survival at 6 years in the 42 BRCA1/2 mutation carriers with invasive cancer were 83.9% (95% CI, 64.1% to 93.3%) and 92.7% (95% CI, 79.0% to 97.6%), respectively (Appendix Fig A2, online only). None of the 43 (non-BRCA1/2) patients in the high- and moderate-risk groups (34 with invasive cancer) developed distant metastasis or died (100% cumulative survival). Four other patients (three with DCIS) developed only a local recurrence or new ipsilateral tumor and two others developed a contralateral breast cancer.

DISCUSSION

In our previous study, we compared tumor characteristics of detected breast cancers with those of age-matched symptomatic controls, concluding that intensive surveillance including MRI can detect breast cancer at an early stage (10). Our pres-

ent data showing comparable results confirm that conclusion. Sensitivity and specificity of MRI screening showed no major differences between the four subgroups studied. In contrast, the sensitivity of mammography was significantly higher in BRCA2 mutation carriers than in BRCA1 mutation carriers (61.5% v 25.0%; P = .04). This can at least partly be explained by the higher proportion of DCIS in BRCA2 than in BRCA1 mutation carriers and the fact that, in our study, mammography had a higher (P = .033) sensitivity in DCIS (69.2%) compared to invasive tumors (35.5%). Based on a review by two experienced radiologists in the context of a quality control side study, a major contributing factor to false-negative MRI diagnoses was non-enhancing DCIS, not visible on the MRIs (even retrospectively) (28). The gain of sensitivity of MRI over mammography was smaller in BRCA2 mutation carriers (69.2% v 61.5%; P = 1.0) than in the other subgroups, including BRCA1 mutation carriers (66.7% v 25.0%; P = .0129). A similar observation was made in a subgroup analysis and in a review of all images of all cancer cases within the MARIBS (Magnetic Resonance Imaging Breast Screening) study (12,20,30). Also in retrospect, only two of their six cases of DCIS were visible on MRI in contrast to all on mammography (30). These results are in contrast to those of Kuhl et al (13,16,31), which showed a high MRI sensitivity for DCIS (as well as for invasive cancer).

Several large prospective MRI screening studies with more than 18 breast cancers detected have been reported (10-21). These studies, including our update, show some variations in results, which might be caused by numerous differences in study populations and methods as recently extensively discussed by Leach (20) and Klijn (21). Nevertheless, all studies concluded that the sensitivity of MRI (range, 68% to 91%) was approximately twice that of mammography (range, 32% to 40%). In contrast, with the exception of one study (13), the specificity of MRI (range, 81% to 97%) was lower than that of mammography (range, 93% to 100%). Combination of MRI and mammography resulted in higher sensitivities (range, 80% to 94%) (17).

In our study, overall 42.7% of the breast cancers were detected only by MRI screening (median, 9 mm; with 62% of tumors ≤ 1 cm, Table 3): 45.8% of the breast cancers in BRCA1 mutation carriers, 30.8% in BRCA2 mutation carriers, 40.9% in high-risk women, and 46.7% in moderate-risk women. These results, in combination with the detection of a favorable tumor stage (particularly in the moderate-risk group), support the recommendation of the American Cancer Society to use annual MRI screening not only for BRCA1/2 mutation carriers, but for all women with an approximately 20% to 25% or greater CLTR of breast cancer due to a familial predisposition (22). However, the cost-effectiveness of MRI screening (29,32-34) should be evaluated for all risk groups separately.

Interestingly, due to our extensive update we were now able to demonstrate differences between BRCA1 and BRCA2 mutation carriers. Apart from lower

Table 5. Characteristics of primary breast cancers detected, including screen-detected cancers (n = 78) and interval cancers (n = 13), according to risk group*†

Characteristic	Risk Group										P	
	BRCA1		BRCA2		High		Moderate		Total			
	No.	%	No.	%	No.	%	No.	%	No.	%	Overall Comparison Between Four Subgroups	Comparison BRCA1 v BRCA2
No. of breast cancers detected	31		16		27		16		91‡			
No. of interval cancers	10	32.3	1	6.3	1	3.7	1	6.3	13	14.3	.01	.07
Age at diagnosis, years												
< 30	3	9.7	0		0		0		3	3.3		
30-39	15	48.4	8	50.0	5	18.5	1	6.3	30‡	33.0		
40-49	9	29.0	6	37.5	10	37.0	10	62.5	35	38.5		
50-59	4	12.9	1	6.3	9	33.3	4	25.0	18	19.8		
≥ 60	0		1	6.3	3	11.1	1	6.3	5	5.5	.0006	.29
Tumor size												
DCIS	2	6.5	3	18.8	4	14.8	5	31.3	15‡	16.5	.16	.32§
Invasive tumors, cm												
≤ 1	6	21.4	8	61.5	9	40.9	7	63.6	30	40.5		
1-2	12	42.9	4	30.8	10	45.5	3	27.3	29	39.2		
> 2	10	35.7	1	7.7	3	13.6	1	9.1	15	20.3	.003	.0045
Nodal status												
Negative	18	64.3	8	66.7	14	66.7	10	90.9	50	69.4		

Positive	10	35.7	4	33.3	7	33.3	1	9.1	22	30.6	.42	1‖
Histologic type												
Ductal	24	85.7	10	76.9	17	73.9	8	72.7	59	78.7		
Lobular	0		1	7.7	3	13.0	2	18.2	6	8.0		
Tubular	1	3.6	0		2	8.7	1	9.1	4	5.3		
Medullary	3	10.7	2	15.4	0		0		5	6.7		
Adenoid cystic	0		0		1	4.3	0		1	1.3	.18	.52
Histologic grade												
1	1	3.7	2	18.2	12	52.2	6	54.5	21	29.2		
2	5	18.5	3	27.3	10	43.5	5	45.5	23	31.9		
3	21	77.8	6	54.5	1	4.3	0		28	38.9	< .001	.15
Estrogen receptor status												
Positive	5	17.9	7	63.6	19	86.4	10	90.9	41	56.9		
Negative	23	82.1	4	36.4	3	13.6	1	9.1	31	43.1	< .001	.02
Progesterone receptor status												
Positive	5	17.9	7	58.3	18	85.7	10	90.9	40	55.6		
Negative	23	82.1	5	41.7	3	14.3	1	9.1	32	44.4	< .001	.02

Abbreviation: DCIS, ductal carcinoma in situ.
* No. of cancers and characteristics of breast cancers detected are excluding six cancers detected at prophylactic mastectomy.
† Percentages are based on the numbers of women with known data; numbers with missing data are not shown.
‡ Including one DCIS in a PTEN mutation carrier.
§ P = .68 for the comparison between BRCA2 mutation carriers and the moderate-risk group.
‖ P = .32 for the comparison between BRCA2 mutation carriers and the moderate-risk group.

mammography sensitivity (25.0% v 61.5%; P = .04), BRCA1 mutation carriers showed a higher proportion of interval cancers (32% v 6%; P = .07), a non-significantly lower proportion of DCIS (6.5% v 18.8%) and a significant greater frequency (P = .0045) of unfavorable tumor size (> 2 cm) at diagnosis (35.7% v 7.7%). These relatively poor results in BRCA1 mutation carriers could be partly explained by different mammographic features (35) and growth pattern (pushing margins) (36), young age, and especially a rapid tumor growth in gene mutation carriers (30,37,38). Moreover, as in other studies (39-42), most of the invasive cancers in BRCA1 mutation carriers were high grade and estrogen receptor and progesterone receptor negative, tumor characteristics which are, in general, also associated with a more rapid tumor growth.

Our study is the first prospective study reporting mortality data to our knowledge. Strikingly all five women developing an incurable stage of disease (i.e. distant metastases) were BRCA1/2 mutation carriers, including four women who died despite a favorable tumor stage (T < 1 cm, N0) in two of them. This observation underscores the need for medical counselors to avoid guaranteeing that all breast cancer deaths can be prevented by early detection of breast cancer as a result of screening. Nevertheless, the low mortality up to 8.4 years from diagnosis (median, 5.0 years) seems promising when compared to previous studies (40,43,44) with an overall survival of 93% at 6 years. Until now, breast cancer mortality reduction was simulated by predictive models based on tumor stage at time of detection (29,32-34,45). The optimal study design for demonstration of reduced mortality by intensive surveillance is a randomized controlled trial. However, in the absence of randomized studies currently and in the future (for ethical reasons), we compared the overall survival of our patients with 26 historical cohorts of patients traced from the literature and from our own institution in exploratory analyses (Appendix Fig A3, online only) (44,46,470. These 26 cohorts comprise totally 1,081 BRCA1/2 (BRCA1: n = 751; BRCA2: n = 330) mutation carriers (median, 42; range, 14 to 170 patients per cohort) and show a median overall survival of 74.5% (range, 50% to 95%). The 5-year cumulative overall survival was higher in our prospective MRISC series of patients (93%; 95% CI, 79% to 98%) than in our institutional historical unselected controls (170 BRCA1, 90 BRCA2) (40,44) as well as in these 26 published series. Furthermore, no distant metastasis and deaths were observed in the high- and moderate-risk groups of our MRISC study. However, in view of the absence of randomization or correction for lead-time or for potential differences in treatment between studies, definite conclusions on survival effects of specific screening strategies cannot yet be made. Furthermore, cross-study comparisons of our observational results with those of historical controls from the literature have strong limitations in view of (possible) differences in populations, study periods, methodology, and breast cancer management.

In conclusion, the update of our study confirms that with a longer follow-up period (≈5 years) the sensitivity of MRI is still strongly superior to that of mammography. In addition, and most strikingly, BRCA1-associated tumors behave completely differently from BRCA2-associated tumors and those from the other risk groups in view of the younger age at diagnosis, lower mammographic sensitivity, the high proportion of interval cancers, the low proportion of DCIS, and unfavorable tumor size at diagnosis. A modification of the screening schedule for BRCA1 mutation carriers (e.g. biannual MRI) or application of specific treatment regimens (48, 49) or preventive measures (5-8) (in view of two deaths in women with very small tumors) may therefore be necessary in order to further improve results on survival, which seem promising with the current screening schedule.

ACKNOWLEDGMENT

We are indebted to the following investigators and data-managers that participated in the MRISC study: Erasmus MC, Rotterdam: P. Bos, C.T.M. Brekelmans, J.M. Collee, A.N. van Geel, A. Jager, W. van Lankeren, M. Menke, D. Urich; Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam: P.E. Besnard, M. Emanuel, K.G. Gilhuijs, M. Piek-den Hartog, H.J. Teertstra, J. Wesseling; Leiden University Medical Center, Leiden: C.J. van Asperen, A.A. van den Berg-Huysmans, H. Janssen, H.M. Zonderland; Radboud University Medical Center, Nijmegen: J.O. Barentsz, L.V.A.M. Beex, H.G. Brunner, M. Hogenkamp, R. Holland, A.L.M. Verbeek, M. Verhoeven, T. Wobbes; VU University Medical Center, Amsterdam: I. Groot, P.A.M. van Leeuwen, F.H. Menko, R.A. Manoliu, A. Taets van Amerongen; Groningen University Medical Center, Groningen: H. Adams, M. Dorrius, L. Jansen, M. Oudkerk, J. de Vries.
Supported Grant No. ZON-MW: 6200.0005 by the Dutch government and the Cancer Genomics Center (C.G.C.), the Netherlands.

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APPENDIX

Inclusion criteria for the MRISC study.

The inclusion criteria for participation in the MRISC study were a cumulative lifetime risk of breast cancer of 15% or more owing to a familial or genetic predisposition, according to modified tables of Claus et al,[4] and an age of 25 to 70 years. Women could be tested at an age younger than 25 years if they had a family history of breast cancer diagnosed before the age of 30 years, since testing began at an age 5 years younger than that at which the youngest family member was found to have breast cancer.

Magnetic resonance imaging.

All patients were investigated in prone position with the breasts pending in a dedicated double breast surface coil. Before scanning, venous access was established in a cubital vein through which a bolus of contrast material (0.1 mmol per kg bodyweight or 15 mL gadolinium chelate) was administered using an automated injector at 2 mL/sec followed by 20 mL saline flush at the same injection rate. Gradient echo T1-weighted series were made before and five times after contrast administration. Subtraction images were obtained with the use of a software subtraction function.
At the start of the study in 1999, a three-dimensional fast, low-angle shot (3D FLASH) was used with the following scan parameters: field of view 320 mm, transversal slices of 1.5 mm thickness, pixel size 1.67 mm × 1.25 mm, scan time 90 seconds, 1 acquisition, return time = 8.1 ms, echo time = 4.0 ms, flip angle 20. During the study, the magnetic resonance units were upgraded and scanning protocols improved. Mainly spatial resolution was improved while maintaining the dynamic series at time intervals of 90 seconds.

Screening parameters.

The (relative) sensitivity of a screening modality was defined as the percentage of cancers with a positive test result (the total number of true-positive test results divided by the total number of cancers). Specificity of a screening modality was defined as the percentage of negative test results in women without a cancer (the total number of true-negative test results divided by the sum of true-negative test results and false-positive test results). The positive predictive value of a screening modality was calculated as the percentage of positive test results that ultimately appeared to be cancer (the total number of true-positive test results divided by the total number of positive test results).

We defined as a positive result a mammography or magnetic resonance imaging with Breast Imaging Reporting and Data System (BI-RADS) score 3 (probably benign [ie, uncertain] finding), 0 (need additional imaging evaluation), 4 (suspicious abnormality), or 5 (highly suggestive of malignancy) and a clinical breast examination (CBE) that was classified as uncertain or suspicious, because in these cases additional examination was indicated (BI-RADS score 3 or 0: ultrasonography with or without fine-needle aspiration, or additional mammography or MRI; BI-RADS score 4 or 5: cytologic or histologic evaluation of a biopsy specimen).

Additional (methodologic) information.

All statistical analyses were performed for the total group of women and for the separate risk and subgroups. Women-years at risk were calculated from the date of the first screening examination to the date of breast cancer detection, bilateral prophylactic mastectomy, or death; the date that a patient stopped surveillance; or the cutoff date for the analysis.

The characteristics of new participating women (mainly BRCA1/2 mutation carriers) since our first analysis at October 1, 2003, were comparable with previous reported results of our study at a median follow-up of 2.9 years.[10]

In the women younger than 40 years of age at diagnosis, we compared the performance of mammography and magnetic resonance imaging only in the 26 women in whom both screening methods were simultaneously used (Appendix Table A2).

For exploratory analyses regarding a comparison with nonscreened or only mammography-screened BRCA1/2 gene mutation carriers, 26 cohorts were collected from articles on overall survival of BRCA1 and/or BRCA2 mutation carriers in comparison with sporadic patients. All individual articles derived from PubMed and three mini-reviews [44,46,47] were checked on concrete survival data of BRCA1/2 mutation carriers. The 5-year survival percentage in our MRISC study was calculated with the Kaplan-Meier method (Appendix Fig A3). The SE and 95% CI of this percentage was calculated with an approach described in Kalbfleisch and Prentice (Kalbfleisch JD, Prentice RL: New York, NY, Wiley, 2002) and implemented in the st command in Stata 10 (Stata Corp, College Station, TX).

Table A1. Participating Centers in the MRI Screening Study, With No. of Included Women

Participating Center	No. of Included Women
Netherlands Cancer Institute, Amsterdam	677
Erasmus Medical Center-Daniel den Hoed Cancer Center, Rotterdam	582
Leiden University Medical Center, Leiden	361
Radboud University Medical Center, Nijmegen	336
VU University Medical Center, Amsterdam	171
Groningen University Medical Center, Groningen	148
Total	2,275

Table A2. Methods of Detection of Breast Cancers in 26 Women < 40 Years of Age at Diagnosis (using only the screening data that included the results of both imaging methods at the screening rounds, n = 75*)

ID	Age at Diagnosis (years)	Risk Group	Mammography Screening	MRI Screening	Invasive/ DCIS	Tumor Size (mm)	Nodal Status
1	36	High	–	+	Invasive cancer	11	–
2	36	BRCA1	–	+	Invasive cancer	18	+
3	35	BRCA2	+	+	Invasive cancer	8	–
4	27	BRCA1	+	+	Invasive cancer	12	–
5	37	BRCA2	+	+	Invasive cancer	7	+
6	33	BRCA1	+	–	DCIS		
7	31	Moderate	+	–	DCIS		
8	32	BRCA1	–	–	Invasive cancer	10	+
9	37	High	–	+	Invasive cancer	12	–
10	36	BRCA1	–	+	Invasive cancer	21	+
11	36	BRCA2	+	–	Invasive cancer	20	+

12	28	BRCA1	–	–	Invasive cancer	45	–
13	37	BRCA2	+	+	Invasive cancer	26	–
14	38	BRCA2	–	–	Invasive cancer	13	–
15	35	BRCA2	+	–	Invasive cancer	4	–
16	39	High	–	+	Invasive cancer	9	–
17	28	BRCA1	+	+	Invasive cancer	18	–
18	36	BRCA1	–	+	Invasive cancer	12	–
19	39	BRCA1	–	+	Invasive cancer	13	–
20	37	PTEN	–	+	DCIS		
21	36	BRCA1	–	+	Invasive cancer	6	–
22	37	High	–	–	Invasive cancer	20	+
23	36	BRCA1	–	+	Invasive cancer	28	–
24	37	BRCA1	–	+	Invasive cancer	9	–
25	31	BRCA1	–	–	Invasive cancer	30	–
26	36	BRCA2	+	–	DCIS		

Abbreviations: MRI, magnetic resonance imaging; DCIS, ductal carcinoma in situ.
* See Fig 1.

Table A3. Patient and primary tumor characteristics with clinical outcome in 11 patients with recurrence, of all 93 patients

ID	Age at Diagnosis (years)	Risk Group	Primary Tumor			Contralateral Breast Cancer	Local Recurrence*	Distant Metastasis	Death	Detection	Cause of Death
			Invasive/ DCIS	Tumor Size (mm)	Nodal Status						
1	58	BRCA1	Invasive cancer	25	N_0	—	—	+	+	Interval cancer	Breast cancer
2	32	BRCA1	Invasive cancer	40	N_0	—	—	+	+	Screen detected	Breast cancer
3	36	BRCA2	Invasive cancer	20	N^+	—	—	+	+	Screen detected	Breast cancer
4	37	BRCA1	Invasive cancer	9	N_0	—	—	+	+	Screen detected	Breast cancer
5	44	BRCA2	Invasive cancer	2	N_0	+	+	+	—	Screen detected	
6	37	PTEN	DCIS	10	N_0	—	+	—	—	Screen detected	
7	52	High	Invasive cancer	16	N^+	—	+	—	—	Screen detected	
8	52	High	DCIS (+LCIS)	15	N_0	—	+	—	—	Screen detected	
9	31	Moderate	DCIS	17	N_0	—	+	—	—	Screen detected	
10	33	High	Invasive cancer	21	N_0	+	—	—	—	Screen detected	
11	36	BRCA1	Invasive cancer	6	N_0	+	—	—	—	Screen detected	

Abbreviations: DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ.
* Local recurrence or second ipsilateral primary breast cancer.

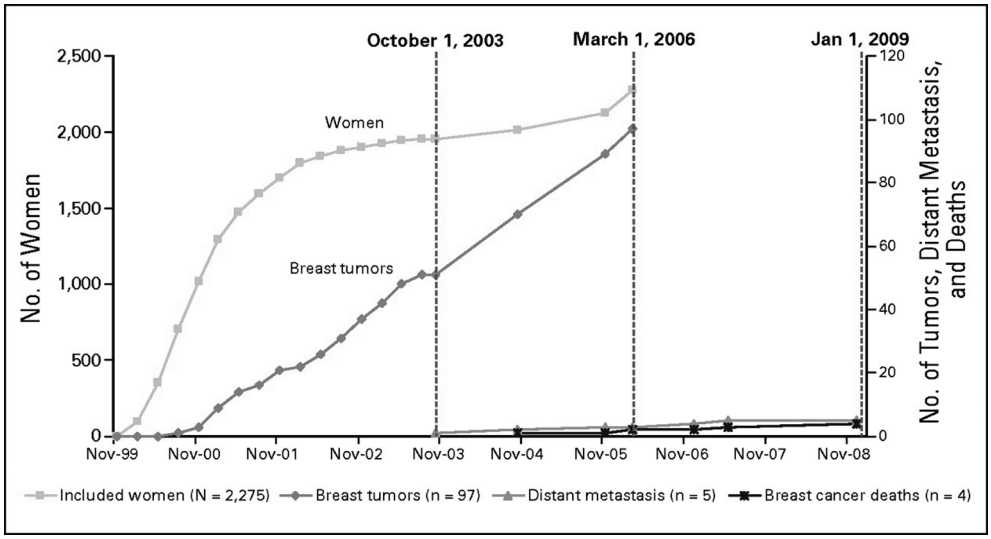

Fig A1. Women at increased risk for breast cancer enrolled, malignant tumors detected, number of distant metastasis, and number of breast cancer deaths. October 1, 2003, cutoff date for first analysis;[10] March 1, 2006, cutoff date for second analysis of screening variables; January 1, 2009, cutoff date for analysis of relapse and mortality in the cohort of 93 patients with 97 breast cancers detected before March 1, 2006.

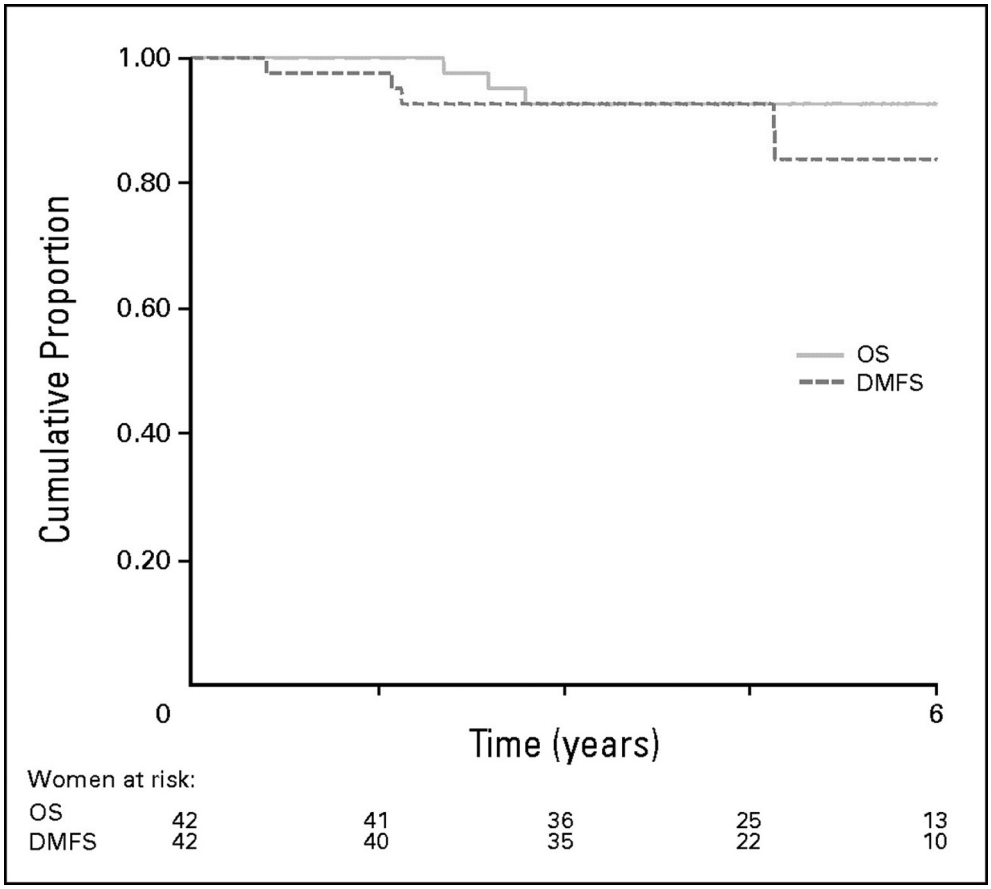

Fig A2. Cumulative distant-metastasis free survival (DMFS) and overall survival (OS) at 6 years from diagnosis of the primary tumor in all 42 BRCA1/2 mutation carriers with an invasive breast cancer (median follow-up, 4.9; range, 2.9 to 8.1 years). For (Dutch) control groups, see Appendix Figure A3.

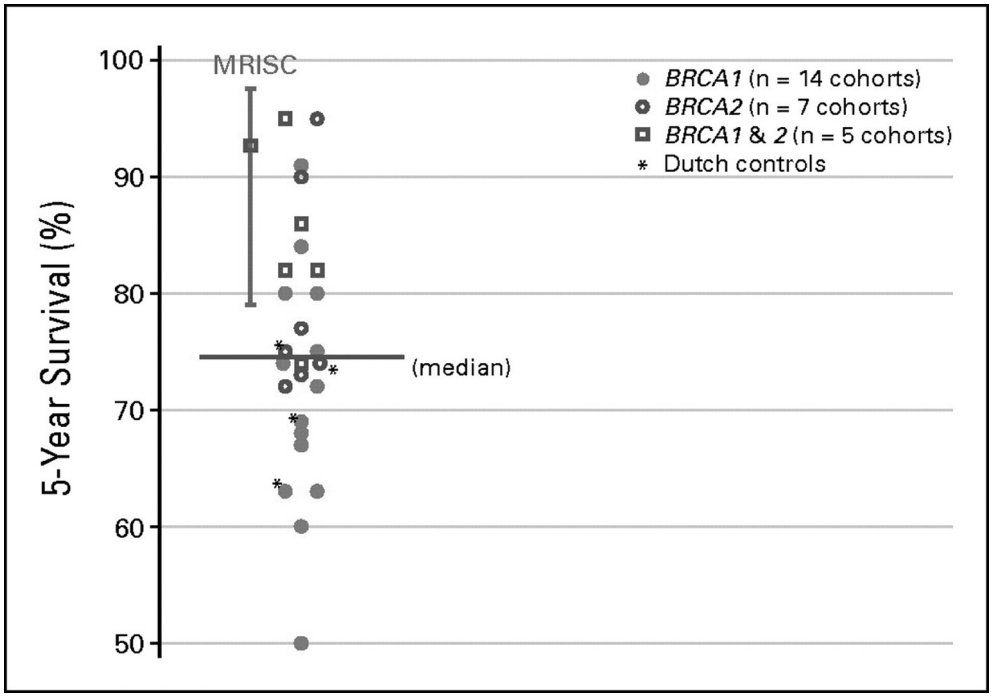

Fig A3. Five-year overall survival (OS) percentages for MRI Screening Study data on 42 BRCA1/2 mutation carriers with invasive breast cancer (92.7% combined with a 95% CI, 79% to 98%) and those for all 26 cohorts of patients with BRCA1/2-associated invasive breast cancer traced from the literature (shown as a dot plot). These 26 cohorts comprise a total of 1,081 BRCA1/2 (BRCA1: n = 751; BRCA2: n = 330) mutation carriers. Points are distinguished according to BRCA type. The horizontal line indicates the median OS (74.5%) of all 26 cohorts. (*) The Dutch reported control series of BRCA1 and BRCA2 mutation carriers.

3

Assessment of false-negative cases of breast MR imaging in women with a familial or genetic predisposition

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Breast Cancer Research and Treatment 2010;119(2):399-407

ABSTRACT

In order to assess the characteristics of malignant breast lesions those were not detected during screening by MR imaging. In the Dutch MRI screening study (MRISC), a non-randomized prospective multicenter study, women with high familial risk or a genetic predisposition for breast cancer were screened once a year by mammography and MRI and every 6 months with a clinical breast examination (CBE). The false-negative MR examinations were subject of this study and were retrospectively reviewed by two experienced radiologists. From November 1999 until March 2006, 2,157 women were eligible for study analyses. Ninety-seven malignant breast tumors were detected, including 19 DCIS (20%). In 22 patients with a malignant lesion, the MRI was assessed as BI-RADS 1 or 2. One patient was excluded because the examinations were not available for review. Forty-three percent (9/21) of the false-negative MR cases concerned pure ductal carcinoma in situ (DCIS) or DCIS with invasive foci, in eight of them no enhancement was seen at the review. In six patients the features of malignancy were missed or misinterpreted. Small lesion size (n = 3), extensive diffuse contrast enhancement of the breast parenchyma (n = 2), and a technically inadequate examination (n = 1) were other causes of the missed diagnosis. A major part of the false-negative MR diagnoses concerned non-enhancing DCIS, underlining the necessity of screening not only with MRI but also with mammography. Improvement of MRI scanning protocols may increase the detection rate of DCIS. The missed and misinterpreted cases are reflecting the learning curve of a multicenter study.

INTRODUCTION

Breast cancer is by far the most prevalent malignancy in women, with a high incidence especially in Europe and North America. The cumulative lifetime risk of breast cancer for Dutch women is approximately 13% (1). A positive family history for breast cancer or a germ line BRCA1 or BRCA2 mutation increases the risk of developing breast cancer considerably. The estimated life time risk for BRCA1/2 mutation carriers is 50–85% (2). Options to reduce the risk of breast cancer related death are prophylactic surgery (including prophylactic mastectomy and/or bilateral salpingo-oophorectomy (PBSO)), chemoprevention, or intensive surveillance.

Women with a strong family history are more likely to develop breast cancer at young age. Because of higher breast density at younger ages, screening with mammography will be less effective. Mammographic sensitivity for breast cancer declines significantly with increasing breast density (in the large study of Kolb et al.(3) from 98 to 48% for the densest breasts). Apart from a higher breast density it appeared that, especially in BRCA1/2 mutation carriers, also a higher growth rate and aspecific mammographic characteristics of the tumors contribute to a lower sensitivity (4-7). Because of the consistently high sensitivity of MRI of the breast in diagnostic settings, with values between 90 and 100% (8-10), the role of contrast-enhanced MRI of the breast in screening of high-risk women was investigated. The first results of screening high-risk women with MRI were promising: MRI detected cancers still occult at mammography and not yet clinical manifest (11-14).

The published results of multiple studies confirm the effectiveness of MRI in screening of women at high familial risk. In five prospective studies (15-19), 3,571 women were screened with contrast-enhanced MR imaging and mammography, and with ultrasound in three of five studies. The pooled sensitivity for mammography was 40%, in comparison to 81% for MRI (20). The detected cancers in 168 patients were small: 49% ≤ 10 mm diameter, and only 19% of invasive cancers were associated with lymph node involvement [20]. Similar figures were found in the review of Warner et al. (21) who evaluated 11 prospective non-randomized studies in which MRI and mammography were used to screen women at very high risk for breast cancer (not only women with high familial risk). In their meta-analysis, the sensitivity of mammography and MRI was 39 and 77%, respectively (at a cut-off value of BI-RADS ≥ 3).

Despite the excellent contribution of contrast-enhanced MRI in screening of women at high familial risk, MRI depicts not all cancers. In the present study, we assess the characteristics of malignancies not detected by MR imaging in the Dutch MRI screening study (MRISC study) and try to identify possible sources of error.

METHODS

In the Dutch MRISC study, a non-randomized prospective multicenter study, women with high familial risk or a genetic predisposition for breast cancer were screened once a year by mammography and MRI and every 6 months with a clinical breast examination (15).
The women were recruited from six centers with familial breast cancer clinics. At the start of the MRISC study in 1999, in five of the six centers there was experience with breast MR imaging in a diagnostic population and variable experience in a screening setting. In one center breast MR imaging started short time before beginning of the study. This center was coached intensively.
In all six centers dynamic contrast-enhanced MRI was performed on a 1.5 Tesla system. The MR units were, in five of the six centers, purchased from Siemens Medical Solutions (Erlangen, Germany) and in one center from Philips Medical Systems (Best, The Netherlands). All patients were investigated in prone position with the breasts pending in a dedicated double breast surface coil. Premenopausal women were scanned on the day 5–15 of the menstrual cycle. Before scanning venous access was established in a cubital vein through which a bolus of contrast material (0.1 mmol per kg bodyweight or 15 ml gadolinium chelate) was administered using an automated injector at 2 ml/s followed by 20 ml saline flush at the same injection rate. Gradient echo T1-weighted series were made before and five times after contrast administration. Subtraction images were obtained with the use of a software subtraction function. All MRI examinations were evaluated on a dedicated breast MRI workstation.
At the start of the study in 1999, a three dimensional fast low-angle shot (FLASH 3D) was used before and five times after contrast administration. The parameters of the dynamic series were: FOV 320 mm, transversal slices of 1.5 mm thickness, pixel size 1.67 mm × 1.25 mm, scan time 90 s, 1 acquisition, TR = 8.1 ms, TE = 4.0 ms, flip angle 20°. During the study, the MR units were upgraded and scanning protocols improved. Mainly spatial resolution was improved while maintaining the dynamic series at time intervals of 90 s. At the beginning of the study all centers, except one, performed mammography on conventional units. Through the years the other five centers also proceeded to digital mammography. Standard oblique and craniocaudal projections were obtained with additional views if necessary.
Mammography and MR examination were scored according to the Breast Imaging Reporting and Data System (BI-RADS) (22) with independent readings. An imaging test with BI-RADS score 3 ("probably benign finding"), O ("need additional imaging evaluation"), 4 ("suspicious abnormality"), and 5 ("highly suggestive of malignancy") was defined as positive, because in these cases additional examination was indicated. A BI-RADS score of 1 ("negative") and 2 ("benign finding") were defined as negative.

Participants were divided into three subgroups according to their estimated cumulative lifetime risk (CLTR) of developing breast cancer: carriers of the BRCA1 or BRCA 2 or other mutations (50–85% CLTR), a high-risk group (30–50% CLTR) and a moderate-risk group (15–30% CLTR).
A screen-detected malignancy was found during a screening round by MR imaging, mammography, or CBE or any combination of these methods. For mammography and MRI, we calculated the sensitivity defined as the percentage of malignancies with a positive test result. The overall results of the main analysis of the MRSIC study (to be published separately) may show slightly different numbers due to minor differences in patient groups. Cancers detected in specimens from prophylactic mastectomy were excluded from analysis. An interval carcinoma was defined as a malignancy detected between two screening rounds. A false-negative MRI case was defined as a biopsy proven malignancy while the MRI examination, performed within 1 year prior to detection, was evaluated as negative (BI-RADS 1 or 2). The false-negative MR cases were subject of this study and were retrospectively evaluated. Review of the false-negative MRI examinations was done by two experienced radiologists reaching consensus. In the MRISC study, the MR examinations were evaluated blinded to the information of mammography. This review was done with all clinical and diagnostic information about location, size, and histology of the malignancy available to the two radiologists (IMO and CB or CL).
In case there was no lesion or suspicious enhancement visible in retrospect, the diagnostic quality of the MR examination was assessed as possible cause of a false-negative diagnosis. The radiologists assessed the diagnostic quality of the MRI by evaluating motion artefacts, inadequate infusion and timing of contrast material, and the degree of background enhancement.
In case malignancy could be identified in retrospect, it was scored as missed or misinterpreted. The lesion (an enhancing mass or non-mass like enhancement) at the MRI was evaluated on a dedicated MRI workstation. The reviewing radiologists performed assessment of lesion size, morphology, and enhancement kinetics.

RESULTS

From November 1999 to March 2006, 2,157 women were eligible for study analyses, including 599 proven carriers of a BRCA1 (n = 422) or BRCA2 (n = 172) mutation or PTEN/TP53 (n = 5), 1,069 women in the high-risk group and 489 in the moderate-risk group.
Ninety-seven malignant breast tumors were detected in 93 patients, including 19 DCIS (20%). Seventy-eight cancers were screen detected, 13 were inter-

val cancers and six malignancies were found at prophylactic mastectomy. The latter six malignancies were excluded for analysis of sensitivity. The 93 patients however, did not all have a complete screening round previous to the detection of the malignancy. Clinical examination, MRI and/or mammography were not always all performed. Eighty-one of the 93 patients underwent mammography before the detection of breast cancer. In 36 cases, mammography demonstrated the malignancy: sensitivity 44% (36/81).
Seventy-six patients underwent a screening round with MRI examination before the detection of a malignancy. In 22 of the 76 patients, the MRI was assessed as BI-RADS 1 or 2. The overall sensitivity of MRI was 71% (54/76). The sensitivity for invasive carcinoma was 78% (49/63), for pure DCIS 39% (5/13). One patient was excluded from the review because the MR examinations were not available anymore. This concerned a small invasive focus with DCIS. Therefore, 21 patients from the MRISC study with a biopsy proven malignancy and a MR examination scored as BI-RADS 1 or 2, were included in this study.

Clinical and radiological data of malignancies occult on MRI, also at the review

Also in retrospect, no enhancing mass or non-mass like enhancement could be identified in 12 of the 21 MRI examinations (Table 1). Except for one inadequate examination (Table 1, case 12), the BI-RADS classification remained 1, also at the review. Eight of these cases, in which no explanation for the false-negative diagnosis was found, were non-palpable mammographically detected DCIS. Seven of them were pure DCIS, and one concerned DCIS with an invasive focus of 4 mm. Mean tumor size was 20 mm (range 7–50 mm) (Table 1, case 1–8).
The ninth case (Table 1, case 9) in which no explanation was found for not showing the lesion at the screening, concerned an interval carcinoma in a BRCA1 carrier, which became evident 10 months after imaging. It was a 12-mm invasive ductal adenocarcinoma, grade 3, probably with a high growth rate.
In one patient (Table 1, case 10) small size and extensive diffuse contrast enhancement of the breast parenchyma were probably reasons for false negativity. This woman underwent lumpectomy because of mastopathic complaints. In the lumpectomy specimen, accidentally a 5-mm grade 1 invasive ductal carcinoma was discovered at histological examination.
In a 36-year-old women with a CLTR of 30–50%, who presented with a palpable mass 10 months after screening, intensive diffuse enhancement of the breast parenchyma prevented the detection of the malignancy (Table 1, case

Table 1. Clinical and radiological data of 12 malignancies occult on MRI, also at the review

	Risk category	Age at diagnosis	Histology	Tumor size PA	Palpable	XM review BIRADS	MR review: reason of FN diagnosis
1	CLTR 30–50%	45	DCIS grade 1	18 mm	No	0 → 4	None
2	CLTR 15–30%	48	DCIS grade 2	10 mm	No	0 → 4	None
3	CLTR 15–30%	60	DCIS grade 3	8 mm	No	4 → 4	None
4	CLTR 15–30%	31	DCIS grade 2	17 mm	No	4 → 4	None
5	BRCA1	42	DCIS grade 1	50 mm	No	4 → 4	None
6	BRCA2	36	DCIS grade 3	7 mm	No	4 → 4	None
7	BRCA1	32	DCIS grade 3	20 mm	No	4 → 4	None
8	BRCA2	35	Foci of IDC and DCIS grade 3	4 mm, and 28 mm	No	4 → 4	None
9	BRCA1	53	IDC, grade 3	12 mm	Yes, interval 10 months after screening	1 → 1	None
10	CLTR 30–50%	49	IDC, grade 1	5 mm	No, found with lumpectomy performed for mastopathy	2 → 2	Small size, intensive enhancement
11	CLTR 30–50%	36	IDC, grade 2	15 mm	Yes, interval 10 months after screening	na	Intensive enhancement
12	BRCA2	36	Two lesions IDC and DCIS grade 3	20 mm and 10 mm, size DCIS na	No	4 → 4	Inadequate examination BI-RADS 1 → 0

FN false negative, XM mammography, PA pathology, DCIS ductal carcinoma in situ, IDC invasive ductal adenocarcinoma, na not available, CLTR cumulative life time risk, → change of BI-RADS category from study to review

Table 2. Clinical and radiological data of 9 malignancies, evaluated on MRI as normal in the study, but visible at the review

	Risk Category	Age at diagnosis	Histology	Tumor size PA (mm)	Palpable	XM review BIRADS	MR review Morphology	Enhancement	MR review BIRADS	Reason FN MR diagnosis
1	BRCA1	40	IDC, grade 3	15	Yes interval 4 mths after screening.	1 → 3	Lesion: mass margin: smooth shape: round size: 4 mm	Homogeneous curve: type 3	1 → 3	Small size
2	BRCA1	44	IDC, grade 3	12	Yes interval 8 mths after screening	1 → 1	Lesion: mass margin: smooth shape: round size: 4 mm	Homogeneous curve: type 2	1 → 3	Small size
3	CLTR 30–50%	37	Two lesions IDC, grade 3, DCIS	13 and 7, na	Yes interval 3 mths after screening	2 → 3	Lesion: mass margin: smooth shape: round size: 5 mm	Homogeneous curve: type 3	1 → 3	Small size
4	CLTR 15–30%	39	DCIS grade 2 and 3	50	No	3 → 3	Lesion: non mass-like, segmental size: 50 mm	Heterogeneous curve: type 1	2 → 4	Misinterpreted as benign enhancement
5	CLTR 30–50%	45	IDC, grade 1	8	No	3 → 3	Lesion: mass margin: irregular shape: lobulated size 11 mm	Rim Curve: type 3	2 → 5	Misinterpreted as lymph node
6	CLTR 30–50%	53	IDC, grade 1	15	No	4 → 4	Lesion: mass margin: smooth shape: round size: 15 mm	Heterogeneous curve: type 2	1 → 3	Misinterpreted as normal tissue
7	BRCA1	27	IDC grade 3	45	Yes, interval pregnancy 5 mths after screening	1 → 1	Lesion: mass margin: smooth shape: round size: 9 mm	Rim Curve: type 3	1 → 5	Missed

8	BRCA1	31	IDC, grade na	30	Yes interval 7 mths after screening	na	Lesion: mass margin: irregular shape: irregular size: 15 mm	Heterogeneous curve: type 3	1 → 5	Missed
9	CLTR 15–30%	45	IDC, grade 2, extensive DCIS grade 2	12	No	3 → 4	Lesion: mass margin: smooth shape: lobulated size: 10 mm	Rim Curve: type 3	1 → 5	Mass missed; DCIS occult on MR

FN false negative, XM mammography, IDC invasive ductal carcinoma, DCIS ductal carcinoma in situ, na not available, CLTR cumulative life time risk, PA pathology → change of BIRADS category from study to review, Curve type 1 cumulative enhancement, Type 2 = plateau, Type 3 = washout

11). At the review no mass or suspicious contrast enhancing areas could be distinguished. Also, the mammography was re-evaluated as normal. A 15-mm invasive ductal carcinoma grade 2 was found.

In case 12 (Table 1), a multifocal invasive carcinoma with surrounding DCIS was not detected on the MR examination with serious motion artefacts. This inadequate MR examination should have been repeated. Mammography and ultrasound only revealed the largest invasive lesion. The additional surrounding DCIS was not visible on the mammogram.

Clinical and radiological data of malignancies visible at the review

In 9 of the 21 reviewed cases an abnormality was observed in retrospect, which changed the BI-RADS classification of the MRI (Table 2). Four times it was changed to BIRADS 3, once to BIRADS 4 and also four times into BI-RADS 5. Retrospectively in 8 cases, a mass was seen and in one case a non mass-like segmental enhancement.

In three of these nine cases (Table 2, case 1–3) small round lesions, 4 or 5 mm diameter, with type 2 or 3 time–intensity curves could be distinguished. At the review, the BI-RADS classification changed from 1 to 3. In these three patients the lesions became clinically evident as interval carcinoma. Two of the three patients were BRCA1 mutation carriers.

In three patients (Table 2, case 4–6) an enhancing mass or area was described but incorrectly interpreted as benign lesions or benign enhancing breast tissue. At the review, the BI-RADS classification became 3, 4, and 5, respectively.

In three other patients, a suspicious abnormality was missed (Table 2, case 7–9). The MR

examination of one of them, a BRCA1 mutation carrier, showed a 9-mm round, well defined lesion however with rim enhancement and wash-out on the time–intensity curves. This lesion was classified as BI-RADS 5 at the review and became palpable during pregnancy as a 45-mm invasive ductal carcinoma, grade 3. The screening mammogram was again evaluated as normal (Table 2, case 7). Another BRCA1 mutation carrier presented 7 months after screening with an interval carcinoma. On her MR examination, a 15-mm BI-RADS 5 lesion was missed. The screening mammogram was not available for review (Table 2, case 8). The third missed lesion (Table 2, case 9) was a 10-mm lobulated mass with rim enhancement. Time–intensity curves showed a type 3 curve. The mass was evaluated as BI-RADS 5. It proved to be a 12-mm invasive ductal adenocarcinoma grade 2 with extensive DCIS, grade 2. The DCIS was occult on MR but visible on mammography.

DISCUSSION

Conform to our previous results and the results from other prospective studies (15-19), the sensitivity of contrast-enhanced MR imaging for breast cancer screening in women with a familial or genetic predisposition is significantly higher compared to the sensitivity of mammography. However, MRI demonstrated not all malignancies.

We reviewed the examinations of 21 of the 97 cancers in the MRISC study who were not detected with MRI. Eight of these 21 undetected cancers were pure DCIS. All but one were also at the review classified as BI-RADS 1 while no enhancing masses or foci or non-mass like enhancement could be discriminated on the MR examination. Also, one case of DCIS with an invasive focus was occult on MRI, in the study as well at the review. In the mid-term analysis of the MRISC study, the sensitivity for the detection of pure DCIS is 39% (5/13) for MR imaging and 73% (11/15) for mammography. Four of the five intraductal cases visualized by MR were mammographically occult. In our study, mammography and MRI were complimentary for the detection of DCIS, with a higher sensitivity for mammography. Pooling together the 40 cases of DCIS detected in the mid-term analysis of the MRISC study and of the Canadian, English, German, and Italian screening studies (16-19), MRI has a sensitivity of 60% (23/38) (two patients with DCIS did not underwent MR). The sensitivity of mammography for DCIS is 60% (24/40) while 10 of the 40 (25%) cases were detected only by mammography. In our opinion, therefore, it is too early to leave out mammography from ongoing screening programs and current guidelines for women at increased familial breast cancer risk. The MRI sensitivity for DCIS in the present study is conform to

the MARIBS study (17), where two of the six DCIS were diagnosed with MR (sensitivity 33%), but lower than reported in the other screening studies. Warner et al. (16) detected four out of six DCIS with MRI (sensitivity 67%), while Kuhl et al. (18) diagnosed eight out of nine intraductal cancers with MRI (sensitivity 89%). In the study of Sardanelli et al. (19) all four cases of DCIS were diagnosed with MRI (sensitivity 100%). Remarkable results are obtained in a prospective observational study of Kuhl et al. (23) in which 92% of DCIS cases were diagnosed by MRI, and only 56% by mammography. The above mentioned study of Kuhl et al. has, however, a totally different study population: in the Dutch MRISC study only asymptomatic women with a familial risk of breast cancer (with 28% BRCA1/2 mutation carriers) were included while in the study of Kuhl et al. only eight (5%) women underwent MR as a screening examination for familial breast cancer. In contrast with the MRISC study, patients with an abnormal mammogram as well as patients with clinical symptoms or a history of previous breast cancer were included. Furthermore, the study was conducted in a single center, with a high level of expertise in performing and reading breast MR examinations. These factors might have influenced the finding of a high sensitivity of MRI for DCIS. Schouten van der Velden et al. (24) evaluated the literature from 1995 till 2008 on this subject and found that in these 30 studies the detection rate of DCIS by MRI ranged from 38 to 100%. Consistent with the results of Kuhl et al. (23) also other studies achieved high sensitivities for the detection of DCIS with MRI (25-28). However, also in these studies most of the patients underwent MR for evaluation of known or suspected breast cancer, sometimes clinically evident. In some studies also cases of DCIS with microinvasion were included. Although the improvement of MR technique through the years with emphasis on high spatial resolution will have improved the detection of DCIS, the results of these studies certainly reflect a patient selection.

The detection of DCIS on MRI depends on three factors: tumor neovascularization, scanning technique, and MR presentation and recognition. The growth of a solid tumor above a diameter of a few millimeters is dependent of formation of new vascular structures. This neovascularization, with an increased permeability of the microvessels and high vascular density, is the prerequisite for contrast agent pooling in and around malignant lesions. Also, DCIS is capable of inducing neovascularization. The process of angiogenesis is stimulated by growth factors such as vascular endothelial growth factor (VEGF) and platelet-derived endothelial growth factor/thymidine phosphorylase (PD-ECGF/TD) released into the stroma by tumor and immune cells (29-30). Vogl et al. (29) found PD-ECGF/TP to be present in all cases of DCIS, without a significant correlation with the DCIS subtype. In the study of Guidi et al. (30), in 84% of the cases of DCIS microvessel density was more prominent than in benign tissue. The degree of angiogenesis was variable and

strongly related to the degree of vascular endothelial growth factor (VEGF) expression. High grade DCIS was more often associated with a strong VEGF expression than low grade lesions, which was also observed by Vogl et al. (29). However, these differences in VEGF expression between low grade and high grade lesions were not statistically significant. The variable degree of angiogenesis in DCIS will explain partly why not all cases will be visible on MR. In our series the seven cases pure DCIS without enhancement concerned high grade as well as low grade lesions. Also, Santamaria et al. (31) observed that the nuclear grade of DCIS was not significantly related to the degree of enhancement or the time–intensity curve. Facius et al. ([27), on the contrary, who evaluated retrospectively the MR characteristics of 74 cases of pure DCIS, found contrast enhancement similar to glandular tissue only in low grade DCIS. This is in concordance with the results of Kuhl et al. (230 who found that the sensitivity of MRI increased with higher nuclear grade, detecting 98% of high grade DCIS and 85% of low and intermediate grade DCIS.
The detection of DCIS requires a high spatial resolution scanning technique, ideally with a submillimeter pixel size in each in-plane direction and a slice

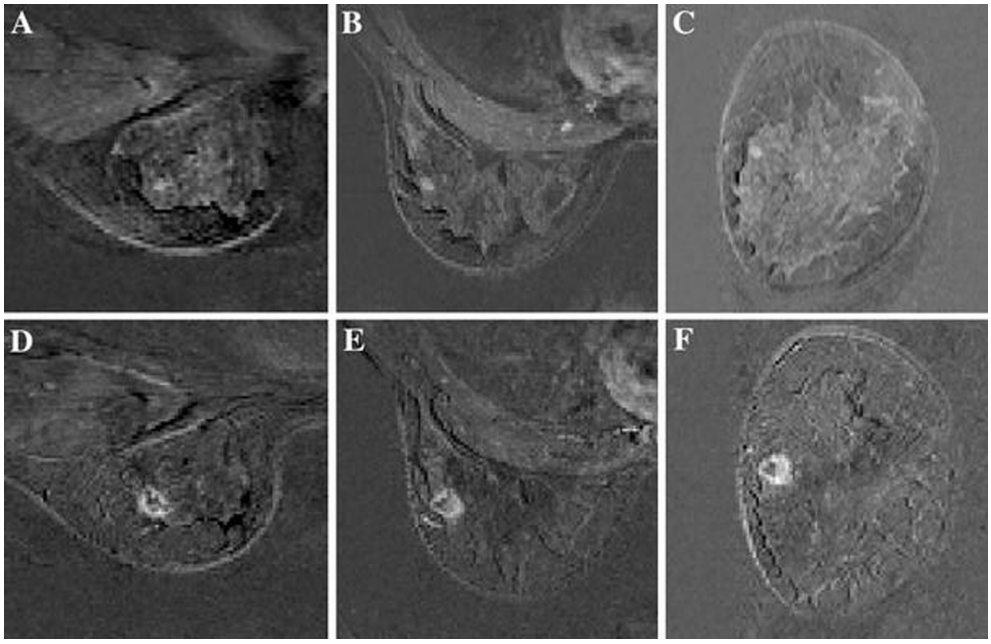

Fig. 1 a–f Example of missed malignancy in a 40-year old BRCA1 gene carrier due to small size at time of screening but visible at review. Shown are subtracted MR images of initial enhancement in sagital (a, d), axial (b, e) and coronal (c, f) planes at time of screening (upper row a-c) and at time of diagnosis (lower row d-f). Four months after screening there is palpable malignancy of 15 mm showing as a irregular mass with rim-enhancement (d, e, f). Retrospectively a small (4 mm) mass with wash out is seen at the screening MRI (a, b, c)

thickness of 1–3 mm (32,33). DCIS is confined to the ducts and the ducts are surrounded by normal tissue. Image voxels represent an average intensity of the components including the voxels. When larger voxels are used the "partial volume averaging effect" may prevent reliable detection the often smaller structures of DCIS. Most of the non-enhancing DCIS cases of the MRISC study concerned MRI examinations made in the beginning years of the study. Insufficient spatial resolution might have been an important factor of not depicting DCIS.

Could false-negative diagnoses have been avoided?
A technically inadequate examination prevented the right diagnosis in one patient (Table 1, case 12), which could have been avoided by repeating the examination.
Although the MR examinations were planned preferably between day 5 and 15 of the menstrual cycle, intensive back ground contrast enhancement was seen regularly. By repeating the examination of all premenopausal patients with intensive contrast enhancement in accordance with the menstrual cycle, the chance of detecting the malignancy would have been higher (Table 1, case 10,11), although this will not be achievable.
Three false-negative MR diagnoses concerned small lesions with a type 2 or 3 curve in young high-risk patients (Table 2, case 1–3) who presented later with an interval carcinoma. These cases indicate that small lesions with a type 2 or 3 curve in young high-risk patients and especially in BRCA1 mutation carriers, with more rapidly growing tumors (34), cannot be neglected (Fig. 1). Short-interval follow-up consisting of second look ultrasound and/or MR examination has to be considered. However, this will negatively influence the false positive fraction and consequently increase additional work-up and number of biopsies.

Contrary to the MRISC study, in the MARIBS study (17) all MR as well as the mammographic examinations were double red. The effect of double reading of the MR examinations was evaluated in a population of screening examinations mixed with symptomatic cases (35). The double reading policy achieved a higher sensitivity: 84% with single reading and 91% with double reading, but at costs of higher recall and biopsy rate. In our study, double reading probably could have prevented that five malignancies, evaluated at the review as BI-RADS 4 and 5 lesions, were not detected (Table 2, cases 4, 5, 7, 8, 9). An alternative to double reading would be computer-aided diagnosis (CAD). During this period of the MRISC study CAD was available in only one center. In contrast with single center studies with only a few readers, the MRISC study is a multicenter study with a group of radiologists with varying levels of experience. The misinterpretation of the MR examination in three malignan-

cies (Table 2, cases 4–6) as well as the three missed carcinomas (Table 2, case 7–9) reflect the learning curve of a multi-center study.

CONCLUSION

More than 40% of the false-negative MR diagnoses involved pure DCIS and DCIS with invasive foci without enhancement and therefore a correct false-negative MR diagnosis, indicating a lower sensitivity of MRI for DCIS. In the MRISC study, mammography and MRI were complementary for the detection of DCIS, underlining the necessity of screening not only with MRI but also with mammography.
Other causes of a false-negative MR diagnosis were inadequate examination, small lesion size and extensive background enhancement (about 30%). In young high-risk patients, and especially in BRCA1 mutation carriers, short-term follow-up has to be considered for small lesions. The missed or misinterpreted cases, in about 30% the reason of a false-negative diagnosis, are reflecting the learning curve of a multicenter study

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BRCA1 mutation and young age predict fast breast cancer growth in the Dutch, United Kingdom, and Canadian magnetic resonance imaging screening trials

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Clinical Cancer Research 2007; 13(24);7357-62

ABSTRACT

Purpose
Magnetic resonance imaging (MRI) screening enables early detection of breast cancers in women with an inherited predisposition. Interval cancers occurred in women with a BRCA1 mutation, possibly due to fast tumor growth. We investigated the effect of a BRCA1 or BRCA2 mutation and age on the growth rate of breast cancers, as this may influence the optimal screening frequency.

Patients and Methods
We reviewed the invasive cancers from the United Kingdom, Dutch, and Canadian MRI screening trials for women at hereditary risk, measuring tumor size at diagnosis and on preceding MRI and/or mammography. We could assess tumor volume doubling time (DT) in 100 cancers.

Results
Tumor DT was estimated for 43 women with a BRCA1 mutation, 16 women with a BRCA2 mutation, and 41 women at high risk without an identified mutation. Growth rate slowed continuously with increasing age ($P = 0.004$). Growth was twice as fast in BRCA1 ($P = 0.003$) or BRCA2 ($P = 0.03$) patients as in high-risk patients of the same age. The mean DT for women with BRCA1/2 mutations diagnosed at ages ≤40, 41 to 50, and >50 years was 28, 68, and 81 days, respectively, and 83, 121, and 173 days, respectively, in the high-risk group. Pathologic tumor size decreased with increasing age ($P = 0.001$). Median size was 15 mm for patients ages ≤40 years compared with 9 mm in older patients ($P = 0.003$); tumors were largest in young women with BRCA1 mutations.

Conclusion
Tumors grow quickly in women with BRCA1 mutations and in young women. Age and risk group should be taken into account in screening protocols.

INTRODUCTION

Women with a family history of breast cancer or with a mutation in BRCA1 or BRCA2 are at elevated risk of developing breast cancer. Cancers often occur at a very young age in women with mutations. By age 50 years, the estimated cumulative breast cancer risk is 40% for women with BRCA1 mutations and 16% for BRCA2 (1). In women without a BRCA1 or BRCA2 mutation with increased risk based on family history, the estimated cumulative breast cancer risk by age 50 is 5% to 10%, which is two to four times the population risk (2). Several studies have reported that breast cancers in premenopausal high-risk women can often be detected at a favorable stage by annual screening with magnetic resonance imaging (MRI) and mammography (3-7). The purpose of a screening program is to identify breast cancer at an early stage before metastatic spread. The survival of women diagnosed with breast cancers <1 cm and with negative lymph nodes is excellent. In BRCA mutation carriers and in familial high-risk patients, tumor size at detection is a key predictor of survival (8,9) and mortality risk may be reduced by early tumor detection (10).

Cancers that are missed by screening may present as interval cancers. All other things being equal, the faster the rate of tumor growth, the greater the likelihood that a cancer will present as an interval versus a screen-detected cancer. In three cohorts of women undergoing annual screening with MRI and mammography, seven of the eight reported interval cancers occurred in BRCA1 mutation carriers (3-5,11). This raises the possibility that one of the hallmarks of BRCA1-associated breast cancers is inherently fast tumor growth. Tumors were shown to grow more rapidly in the younger compared with the older age groups both in mutation carriers and in women at high risk in a recent Dutch study (12), but tumors occur more commonly at a young age in women with BRCA1 and, to a lesser extent, BRCA2 mutations. Tumor growth rate and screening frequency can influence the effectiveness of screening and may be important factors when considering a surveillance strategy in a particular age group (13-15).

Breast cancers are more often high grade in women with BRCA1 mutations than in other high-risk women both before age 50 (84% grade 3 versus 17%) and after age 50 (47% versus 23%; (16)). This may suggest faster growth of tumors in women with BRCA1 mutation. The pathologic characteristics of BRCA2-related cancers are more similar to those in high-risk and sporadic cases (17,18). Tumor growth rates may therefore differ between women with BRCA1 versus BRCA2 mutations but could only be assessed in five women with BRCA2 mutations in the previously reported Dutch study (12). Induced menopause by bilateral preventive salpingo-oophorectomy halves breast cancer risk in women with BRCA1/2 mutations (19). It may be that

menopause and bilateral preventive salpingo-oophorectomy slow the growth rate of hereditary breast cancer.
Beside family history and age, high breast density at mammography is one of the longest known and best documented risk factors for breast cancer (20-23). The stroma of the breast, containing collagen and blood vessels, is known to influence tumor growth in human breast cancer cell cultures (24,25). We speculated that dense breast tissue might influence tumor growth rate.
We investigated the influence of age, hereditary risk group, menopause, and breast density on tumor growth rate in three MRI screening studies in high-risk women with annual imaging, complete registration of DNA testing, and follow-up.

PATIENTS AND METHODS

Invasive tumors found during screening in patients of the Dutch Erasmus screening group and 6-center MRISC study, the 22-center United Kingdom MARIBS study, and the Canadian single-center study were included in this analysis. All studies had been given institutional ethical approval and all women had given informed consent. The eligibility criteria for each study were previously published (3-5,12). All three studies included women with BRCA1/2 gene mutations and women at 20% to 40% lifetime risk of developing breast cancer (high risk). Patients were included in this analysis if the MRI and/or mammogram from the diagnostic screen were available for review together with the previous screening examinations. The Dutch images were reviewed by I-M. Obdeijn, the United Kingdom images were reviewed by R.M.L. Warren and F.J. Gilbert, and the Canadian images were reviewed by P.A. Causer.

Patients

(*a*) In the Dutch MRISC study, we could evaluate the size of 22 invasive tumors detected between July 1, 2003 and January 1, 2006, which had been imaged at least 1 year previously with the same radiological technique, either MRI or mammography. These results were added to the previously described results of 26 invasive tumors detected in the MRISC study before July 2003 (3,12) and the Erasmus University Medical Centre group of 9 invasive tumors detected at high-risk screening with yearly MRI, mammography, and clinical examination and 12 tumors detected at surveillance with annual mammography and clinical examination (12).

(*b*) Tumor size could be evaluated in 14 cancers detected within the MARIBS study between August 1997 and May 2004 (4). This study included women ages 35 to 50 years. All patients with BRCA1 or BRCA2 mutations had been tested before the study or were anonymously DNA tested within the study. (*c*) The size of 17 cancers detected between November 1997 and September 2005 in the Canadian high-risk MRI screening study could be evaluated (5). The study included women ages 25 to 60 years with or without a previous history of breast or ovarian cancer. In total, tumor volume doubling time (DT) could be assessed in 100 invasive tumors.

Breast density was assessed visually at diagnostic mammography using a semiquantitative four-point scale (<25% of dense breast tissue = 1; 25-50% = 2; 50-75% = 3; and >75% = 4) in the Dutch and Canadian patients. The MARIBS study used a three-point scale: fatty, mixed, or dense. These were reclassified as 1, 2.5, and 4. Women were regarded as postmenopausal if menstruation had spontaneously ceased more than 12 months earlier.

Measurements and calculation of tumor growth rates

The MRI and mammography methods have been described (3-5).

The method of taking the measurements and the DT and growth rate (1/DT) calculations has been described (12,26) In short, if the tumor could be clearly identified at the diagnostic MRI and previous MRI was available, three mutu-

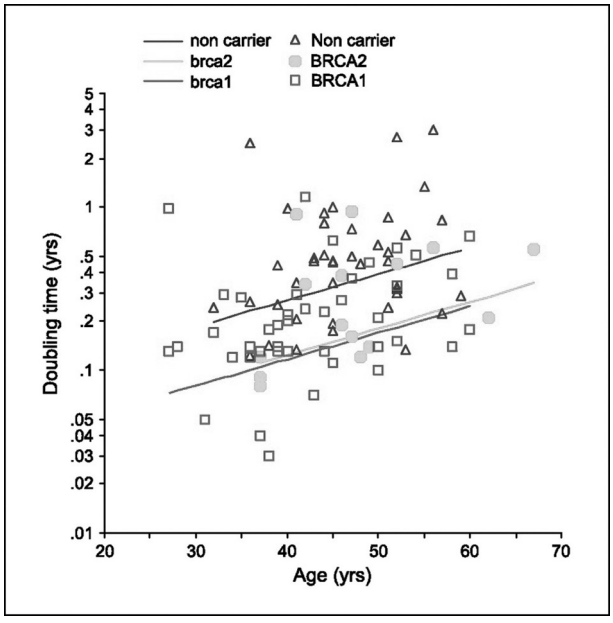

Fig. 1. Correlation between DTs of the 100 invasive tumors and age in the three risk groups. Each red square indicates the measurements for a BRCA1 mutation carrier, each green dot indicates the measurements of a BRCA2 carrier, and each blue triangle indicates the measurements of a non carrier. The corresponding lines connect the geometric mean values for the risk group.

ally perpendicular measurements, including the single largest diameter (SLD = *a*) of the tumor, were made. For all cancers positively identified at diagnostic mammography with a previous mammogram available, the largest diameter (*a* = SLD) was measured together with a second maximum diameter perpendicular to the first (*b*) on both the oblique and craniocaudal views. For tumors measurable in both views, the largest, the smallest, and the mean of the other two sizes (*c*) were used to calculate tumor volume. The volume of the tumor was estimated using the following formula for obloid spheroids: $V = 4/3\varpi \times 1/2a \times 1/2b \times 1/2c$.

Tumors were assumed to have exponential growth (i.e., growth with a constant volume DT) as this is usually assumed to be the best approximation for the range of tumor sizes in our study (4-42 mm; (27,28)).

For cancers with a measurable tumor at two or more previous MRI and/or mammography evaluations, and where a previous image showed no visible tumor, only the measurable sizes were used for the calculation of individual DTs (Fig. 1).

The group with no visible tumor at the previous examination was included so that the potentially fastest growing tumors were counted for the estimation of growth rate.

In the previous study, tumor size at "no visible tumor" was set to be <0.004 cm^3 corresponding to a diameter of <2 mm. Taking into account the smallest measurements at MRI and mammography and the extrapolated tumor size from the tumors with two or more real measurements and no visible tumor at a previous image, we set the tumor size for no visible tumor at MRI as <2 mm and at mammography as <4 mm (assumed lower detection limit).

The slope of the straight line connecting the two log-transformed volume measurements was calculated using least-squares regression for three or more real volume measurements.

Tumor volume DTs were calculated using the following formula: $DT = 1/\beta$, where β is the slope of the regression line of the logarithm (base 2) of the tumor volume versus time. The assumed lower detection limit may result in an underestimation of the true slope, and consequently, the tumor DT may be overestimated (i.e., a left-censored observation of the DT).

Statistical methods

Differences in patient and tumor characteristics between the three risk groups were tested with the use of the Kruskal-Wallis test in case for continuous variables and with the χ^2 test for categorical variables. To determine the correlation between tumor size at mammography/MRI and at histopathologic

examination, we calculated Pearson's correlation coefficient (*r*). To provide an approximate normal distribution of volume DTs, these were logarithmically transformed for all analyses. Therefore, all reported mean DTs represent geometric means. Comparison of the transformed DT between risk groups was done using ANOVA. Multiple regression was used to evaluate simultaneously the effects of age, risk group, and breast density. STATA software (CNREG) was used in these calculations to allow for the presence of left-censored volume DTs in 40 cases. A two-sided *P* value of <0.05 was considered to indicate statistical significance.

RESULTS

Patients and tumor characteristics

Tumor size could be assessed at diagnosis and on previous imaging in 100 patients with invasive tumors: 43 who had a BRCA1 mutation, 16 who had a BRCA2 mutation, and 41 high-risk women. The characteristics of the patients

Table 1. Patient characteristics in the United Kingdom, Canadian, and Dutch studies

	United Kingdom	Canadian	Dutch	Total
Total no.	14	17	69	100
BRCA1	5	8	30	43
BRCA2	4	7	5	16
High risk	5	2	34	41

	United Kingdom	Canadian	Dutch	*P*
Mean age, y (range)				
BRCA1	40 (34-45)	50 (38-60)	41 (27-60)	0.06
BRCA2	47 (41-52)	54 (46-67)	40 (37-46)	0.01
High risk	43 (36-47)	44 (39-48)	47 (32-59)	0.4
Total	42 (31-52)	50 (38-67)	44 (27-61)	0.02
Mean density at mammography	2.8	2.3	2.4	0.4
Median size at pathology, mm (range)	13 (6-31)	8 (4-20)	12 (4-42)	0.045

in the three centers are given in Table 1. Patients were on average significantly younger in the United Kingdom and Dutch groups than in the Canadian group ($P = 0.009$ and 0.004, respectively; average age: 42, 44, and 50 years, respectively). Median tumor size was 8 mm in the Canadian study compared with 12 mm in the Dutch study ($P = 0.02$) and 13 mm in the United Kingdom study ($P = 0.03$).

Table 2. Patient and tumor characteristics in the three risk groups

	Total (*N* =100)	BRCA1 (*n* =43)	BRCA2 (*n* =16)	High risk (*n* =41)	*P*
Mean age, y (range)	45 (27-67)	43 (27-60)	48 (37-67)	46 (32-59)	0.04
Menopausal status					
Premenopause	67	29 (67%)	10 (63%)	28 (69%)	
Postmenopause (BPSO)	10	8 (19%)	1 (6%)	1 (2%)	0.07
Postmenopause (natural)	23	6 (14%)	5 (31%)	12 (29%)	
Mean density at mammography	2.4	2.3	2.7	2.4	0.5
Cancers by age (y)					
≤40	31	20 (46%)	3 (19%)	8 (20%)	0.02
>40	69	23 (54%)	13 (81%)	33 (80%)	
Cancer detection					
Interval	11	9 (21%)	0	2 (5%)	0.03
Screening	89	34 (79%)	16 (100%)	39 (95%)	
Median size at pathology, mm (range)					
In the total group	11 (4-42)	13 (4-40)	8 (4-15)	11 (4-42)	<0.001
≤40 y	15 (4-40)	18 (4-40)	11 (7-15)	12 (4-20)	0.003*
>40 y	9 (4-42)	12 (4-35)	7 (4-10)	10 (5-42)	
Grade					
1	11 (12%)	1 (3%)	1 (7%)	9 (24%)	
2	38 (43%)	12 (32%)	9 (60%)	17 (46%)	<0.001
3	40 (45%)	24 (65%)	5 (33%)	11 (30%)	

NOTE: Data are number of patients (%) unless otherwise indicated.
Abbreviation: BPSO, bilateral preventive salpingo-oophorectomy.
* P value for difference in tumor size ≤40 and >40 y in the total group.

Ten cancers in the Dutch study were detected between screens [3 in the MRISC study before July 2003 and 2 in the Erasmus screening group (12)] and 1 in the Canadian study. The tumor was visible in retrospect in five interval cases (four on the MRI and one on the mammogram). Five of the interval cancers were in patients ages ≤40 years (range, 31-58 years). Only one of the interval cancers was diagnosed within 6 months of the previous imaging. Patient and tumor characteristics in the three hereditary risk groups are given in Table 2. The average age was significantly lower for patients with BRCA1 mutations than for BRCA2 and high-risk patients. Forty-six percent of the BRCA1 patients were ages ≤40 years. The median tumor size was larger in the women who were ages ≤40 years than in the older women ($P = 0.003$) and was largest in the women with BRCA1 mutations who were ages ≤40 years. The median size of the tumors differed between BRCA1-related, BRCA2-related, and high-risk cases (13 versus 8 versus 11 mm, respectively; $P < 0.001$). Invasive tumor size decreased continuously with increasing age ($P = 0.001$) at univariate analysis. There was no significant difference in mammographic breast density between the groups. Significantly more cancers were detected in the interval between screens in the BRCA1 group (9 of 43) than in the BRCA2 (0 of 16; $P = 0.045$) or the high-risk group (2 of 41; $P = 0.049$). The median tumor size at pathology was 18 mm in interval cancers versus 13 mm in screen-detected cancers ($P = 0.1$).

Tumor measurements and DTs of the 100 invasive tumors

Calculations of tumor volume DTs were done using two or more real measurements at MRI or mammography for 60 tumors (uncensored group) and one real measurement at diagnosis with a previous examination showing no

Table 3. Number and modality of the measurements used for DT calculations according to risk group
Number and modality of the measurements used for DT calculations according to risk group

	MRI ≥2	Mx ≥2	MRI 1 + n.v.t.	Mx 1 + n.v.t.	Total ≥2	Total 1 + n.v.t.	P*
Total no.	35	25	27	13	60	40	
BRCA1	14	9	15	5	23	20	
BRCA2	6	2	7	1	8	8	0.2
High risk	15	14	5	7	29	12	

NOTE: ≥2, two or more real measurements.
Abbreviations: Mx, mammography; n.v.t., no visible tumor.
* P value for the difference between the three risk groups in number of DT calculated with uncensored (≥2) versus censored (1 + no visible tumor) measurements.

visible tumor for 40 (censored group) as shown in table 3. There was no significant difference between the uncensored and censored group with regard to tumor size at pathology, median size (12 versus 10 mm, respectively; P = 0.7), and grade distribution (P = 0.7). The difference in age tended toward significance (mean age, 46 versus 43 years, respectively; P = 0.06).
Tumor size at pathology correlated well with the measured size at diagnostic MRI (r = 0.7) and moderately well with size at mammography (r = 0.6; (28)). Including the patients who received neoadjuvant chemotherapy, the mean time between last imaging and pathology size measurement was 2 months (72 days). The mean DT for the total cohort was 71 days and 46, 52, and 129 days for the BRCA1, BRCA2, and high-risk cases, respectively. The mean DT was 28 days for all patients ages ≤40 years and 103 days for the older group. The mean DT was 37 days for all interval cancers versus 74 days for the screen-detected cancers (P = 0.25).

Growth rates of the 100 cancers by age, risk group, and breast density

At univariate analysis, tumor volume DT correlated significantly with age (P = 0.003). With each 10-year increase in age, the mean DT increased by a factor of 1.6 (95% confidence interval, 1.2-2.1). This factor applies to all three risk groups (difference between risk groups: P = 0.71).
Menopause did not correlate significantly with DT either in univariate analysis (P = 0.1) or after adjustment for age (P = 0.5). Adjusted for age, no significant correlation was found between DT and Bloom-Richardson grade.
A significantly shorter average DT was seen in BRCA1-related cancers (P = 0.003) and in BRCA2-related cancers (P = 0.03) compared with high-risk patients adjusted for age and center (Table 4). The average DTs of BRCA1/2-related cancers were half that of the high-risk cases of the same age (Fig. 1).

Table 4. Multivariate analysis of tumor volume DT in 100 invasive tumors in relation to age and risk group (with adjustment for center)

Factor	DT ratio	95% CI of DT ratio	*P*
Age	1.6*	1.2-2.1	0.004
BRCA1	0.5†	0.3-0.8	0.003
BRCA2	0.5†	0.2-0.9	0.03

Abbreviation: 95% CI, 95% confidence interval.
* Effect of an increase of age with 10 y.
† Versus high risk.

DT did not correlate significantly with breast density at mammography (P = 0.3) at univariate analysis. A trend was seen for slower growth at higher density adjusting for age and risk group (P = 0.07).

Results per age cohort

Growth rate (P = 0.003) and tumor size (P = 0.001) decreased with age without a natural cutoff point. When comparing the absolute DT and tumor sizes of the BRCA1, BRCA2, and high-risk patients by age cohort, growth rate and tumor size decreased significantly with increasing age in the total group and in mutation carriers. In the group ages ≤40 years at diagnosis, the mean DT for BRCA1, BRCA2, and high-risk patients was 28, 26, and 83 days, respectively; for ages 41 to 50 years, the mean DT was 69, 65, and 121 days; and for patients ages >50 years, DT was 77, 112, and 173 days. As the results for the BRCA1- and BRCA2-related tumors were so similar and there were so few tumors in the BRCA2 group ages ≤40 years (n = 3) and >50 years (n = 4), their DT results are combined with those of the BRCA1 group in Table 5.

Table 5. Numbers of patients, mean DT, average breast density, and tumor pathology size of the 100 cancers per age and risk group

	≤40 y (n = 31)	41-50 y (n = 42)	>50 y (n = 27)	P*
No. BRCA1/2	23	24	12	
No. high risk	8	18	15	
Mean DT days (95% reference)				
BRCA1/2	28 (4-222)	68 (9-553)	81 (10-653)	0.004
High risk	83 (12-593)	121 (17-850)	173 (25-1,202)	0.06
Mean density				
Total group	2.6	2.5	2.0	0.03
Median pathology size, mm (range)				
In the total group	15 (4-40)	10 (4-42)	9 (4-27)	0.009
BRCA1/2	15 (4-40)	9.5 (4-35)	8.5 (4-25)	0.016
High risk	11.5 (4-20)	10 (6-42)	9 (5-27)	0.45

* P for the difference in mean DT between the three age groups (adjusted for study center).

Mammographic density did not differ significantly between patients ages ≤40 years and those ages 41 to 50 years (P = 0.4), but density was significantly lower in the women ages >50 years (P = 0.04). Multiple regression showed

that pathologic tumor size at diagnosis decreased significantly in older cohorts ($P < 0.001$) but did not correlate with density ($P = 0.3$).

Subgroup analyses

Testing for effect modification, the effect of age on DT did not differ between the three centers ($P = 0.92$). In addition, the independent influence of a BRCA1/2 mutation on DT (adjusted for age) was consistent in the three centers ($P = 0.6$). These results remained similar when using only the 60 tumors with two or more real measurements for the analyses. In addition, comparing measurements obtained with MRI and mammography, no influence of modality was found ($P = 0.81$).

When the limit of detection at MRI was set at <0.01 cm^3 instead of <0.004 cm^3, reanalysis showed little change in the independent effects of age and risk group on DT. When recalculated with the adapted threshold, the mean DTs in the BRCA1/2 group in the ≤40, 41 to 50, and >50 age groups were 30, 73, and 98 days, respectively. In the high-risk group, they were 89, 123, and 175 days, respectively.

DISCUSSION

A finding unique to our study is that, at the same age, the average growth rate of the tumors of women with a BRCA1 or BRCA2 mutation was twice as fast as that of high-risk patients (DT ratio, 0.5). This mutation effect on tumor growth was consistent in the three countries. The mean tumor DT of 46 days in the BRCA1 group and 52 days in the BRCA2 group in this multinational study is very similar to the 45 days in the 30 women with a BRCA mutation reported in the previous Dutch-only study (12). With twice as many carriers in the current analysis, this finding seems robust. We could not show a difference between BRCA1 and BRCA2 mutations in effect on tumor growth rate. Tumors in women with either BRCA1 or BRCA2 mutations tend to appear at a younger age than sporadic cancers and are more often high grade (8,16-18). Clear differences between BRCA1- and BRCA2-related cancers have been described in hormonal receptor status. BRCA1-related tumors are commonly estrogen receptor negative and progesterone receptor negative (often her2neu negative, basal type). BRCA2-related tumors are usually estrogen receptor positive and progesterone receptor positive, similar to sporadic or high-risk patients (16-18). The significantly faster tumor growth in both mutation groups compared with high-risk women makes it highly unlikely that

growth rate is associated with the estrogen receptor or progesterone receptor status. Despite pooling the multinational data of the three largest MRI high-risk screening studies, only three tumors detected before age 40 in women with BRCA2 mutations could be assessed. And although the faster growth in women with BRCA1 mutations below the age of 40 was reflected by their larger tumor size at detection and the occurrence of interval cancers, BRCA2-related tumors were small and no interval cancers occurred. To confirm DTs in tumors with BRCA2 mutations, a larger study would therefore be desirable. The decreasing growth rate of breast cancers with increasing age was confirmed in both women with BRCA1/2 mutations and in high-risk patients in this combined study. On average, invasive tumors doubled in volume in 1 month in mutation carriers diagnosed up to age 40 compared with 2 months for carriers ages 41 to 50 and 3 months for carriers diagnosed after age 50. The corresponding DTs in high-risk patients in these three age categories were 3, 4, and 6 months, respectively. When a tumor doubles its volume four times, tumor size at imaging will increase from 2 to 5 mm or from 4 to 10 mm. This is a detectable change, and although in studies the rate of distant metastases increased much faster with increasing tumor size in high-grade cancers (as often seen in BRCA1/2-related tumors) than in low grade cancers, as long as the tumor was detected in the 2- to 10-mm size range the prognosis was excellent (8-10,18). In our BRCA1 group under age 40, however, mean tumor pathology size was 18 mm, a size at which the risk of metastases is relatively high for these usually high-grade cancers (29,30).

We cannot compare the growth rates in our study directly to the growth rate of tumors of women in the average-risk population as screening is not offered below age 40 years. Peer et al. (26) calculated a median tumor volume DT of 80 days in patients ages <50 years not selected for risk and a DT of 160 days for women ages >50 years, very similar to our finding of 183 days for high-risk women ages >50 years. Large-scale population mammography screening studies have also shown that the sojourn time (the time interval during which a tumor can be detected at imaging, but not yet clinically) is longer for women ages >50 years than for women ages between 40 and 50 years (13-15,30-32).

Dense breast tissue was not associated with enhanced growth rate and did not explain the larger tumor size in our younger age groups at multivariate analysis. Therefore, dense breast tissue does not seem a valid reason to increase screening frequency. This is consistent with the findings by White et al. (32). We could not show an influence of tumor grade or menopausal status on tumor growth rate independent of age.

We can recognize some limitations to our study as a consequence of the combination of material from three different national trials. The inclusion criteria were similar but not identical, resulting in different contributions to the

three risk groups and the older age profile of the Canadian participants. The image review processes were undertaken separately by the three national groups, and although methods were precisely described and discussed, one cannot be sure that these were exactly comparable. The gain from combining the material to give greater statistical power for the subset analysis, however, outweighs these limitations. In tumors measurable only at detection, but not at previous imaging, tumor size was estimated to be below the limit of detection. Varying this threshold in a sensitivity analysis generated very similar DTs, however. Our study is to our knowledge the first breast cancer growth rate study with results that are partly based on three-dimensional imaging of tumor volume at MRI. These measurements may be more accurate than the calculated volume from two-dimensional studies such as mammography. Our results, however, did not show a difference between the two modalities.
Our data suggest that, in women ages <40 years with a BRCA1 mutation, breast tumors are relatively common, grow quickly, and are often high grade. Moreover, with annual screening, these tumors are larger at diagnosis and interval cancers may be more common than in other high-risk women. When screening very young women, however, the false-positive rate may be higher and this could reduce the cost-effectiveness. This study has shown that age and mutation status should be considered together with other factors when developing recommendations for screening high-risk women.

ACKNOWLEDGMENTS

We thank all the participating women of the three national studies for their trust; the clinical contributors, radiologists, nurses, physicists, engineers, and data managers, whose dedication and skill were vital to the three studies and for the Dutch study, especially Miret Emanuel, Claudette Loo, and Carla Boetes; and Professor S.W. Duffy for his helpful advice.

Footnote

Grant support: Dutch Health Insurance Council grant OG 98-03 (Dutch study), UK Medical Research Council grant G9600413 (MARIBS study), and Canadian Breast Cancer Research Alliance (Canadian study). The cost of UK MRI studies is paid for from subvention funding for research from the UK National Health Service. The protocol is based in part on developments supported by Cancer Research UK and the Yorkshire Cancer Research Campaign.

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5

Should we screen BRCA1 mutation carriers only with MRI? A multicenter study

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Breast Cancer Research and Treatment 2014;144:557-582

ABSTRACT

BRCA1 mutation carriers are offered screening with MRI and mammography. Aim of the study was to investigate the additional value of digital mammography over MRI screening.

BRCA1 mutation carriers, who developed breast cancer since the introduction of digital mammography between January 2003 and March 2013, were included. The images and reports were reviewed in order to assess whether the breast cancers were screen-detected or interval cancers and whether they were visible on mammography and MRI, using the Breast Imaging and Data System (BI-RADS) classification allocated at the time of diagnosis. In 93 BRCA1 mutation carriers who underwent screening with MRI and mammography, 82 invasive breast cancers and 12 ductal carcinomas in situ (DCIS) were found. Screening sensitivity was 95.7% (90/94). MRI detected 88 of 94 breast cancers (sensitivity 93.6%) and mammography 48 (sensitivity 51.1%) (two-sided $p<0.001$). Forty-two malignancies were detected only by MRI (42/94=44.7%). Two DCIS were detected only with mammography (2/94=2.1%) concerning a grade 3 in a 50-year-old patient and a grade 2 in 67-year-old. Four interval cancers occurred (4/94=4.3%), all grade 3 triple negative invasive ductal carcinomas.

In conclusion, digital mammography added only 2% to the breast cancer detection in BRCA1 patients. There was no benefit of additional mammography in women below age 40. Given the potential risk of radiation induced breast cancer in young mutation carriers, we propose to screen BRCA1 mutation carriers yearly with MRI from age 25 onwards and to start with mammographic screening not earlier than age 40.

INTRODUCTION

The BRCA1 and BRCA2 gene mutations were discovered in 1994 and 1995 (1,2), exposing women with these mutations to a six to eightfold risk of developing breast cancer compared to the average female population. In the decade thereafter prospective screening studies were initiated (3-8) investigating the role of magnetic resonance imaging (MRI) of the breast as an adjunct to mammography in screening of high risk women. By then, mammography was the accepted method for early diagnosis of breast cancer and MRI the new promising technique. The outcomes were remarkably consistent across studies and showed that MRI has a much higher sensitivity than mammography. Several studies showed that with MRI the detection of breast cancers occurred at an earlier stage with a more favorable prognosis (6,9).
At present the role of MRI of the breast in screening of BRCA1 and 2 mutation carriers is established. Meanwhile, the additional gain of mammography, especially in BRCA1 mutation carriers, has become uncertain. Screening studies showed an extremely low sensitivity of mammography in BRCA1 mutation carriers (3,4,7) while at the same time there are raising concerns about the risk of radiation exposure (10-12). All in all the findings raise the question whether mammography is justified if MRI is performed already.
The published results, however, were mainly for conventional film-screen mammography. The current standard, digital mammography is significantly more sensitive in young women and in women with dense breast tissue (13). Furthermore the published screening results date from the beginning period of MR screening when limited experience was available while nowadays more radiologists are experienced MR readers and at the same time MR technology and protocols are further developed and improved. We, therefore, assessed the sensitivity of MRI and mammography in BRCA1 breast cancer cases. Our study presents results of MR screening with experienced readers, up-to date technology and only digital mammography.
The objectives of our study were to determine the efficacy of screening in women with a BRCA1 mutation, to compare the current efficacy to previously published results, and to investigate the additional value of digital mammography over MRI.

PATIENTS AND METHODS

Patients

For this retrospective study we included a consecutive series of BRCA1 mutation carriers who developed breast cancer since the introduction of digital

mammography. Our study group consists of BRCA1 mutation carriers with breast cancer detected during surveillance. Also BRCA1 mutation carriers with a prior history of breast cancer were included. All cases were provided by the databases of the family breast cancer clinics of the Erasmus Medical Center Rotterdam, the Antoni van Leeuwenhoek Hospital in Amsterdam and of the University Medical Center in Nijmegen .
According to the protocols approved by the Medical Ethical Committees of the participating centers, all included women provided written informed consent. The women were under surveillance in or referred to the Erasmus Medical Center in Rotterdam, the Antoni van Leeuwenhoek Hospital in Amsterdam or the University Medical Center in Nijmegen. According to the Dutch guidelines (14), women with a proven BRCA1 mutation were offered annual clinical breast examination, screening with MRI from age 25 and mammography from age 30 onwards. High-resolution breast MRI was performed in each of the three centers conform, local protocol. In all three centers, extensive experience exists with screening of women with familial or genetic predisposition for breast cancer.
The inclusion period started after introduction of digital mammography in each of the participating hospitals (range from January 2003 to September 2005) and ended in March 2013.
To compare tumor stages we described symptomatic women in whom a BRCA1 mutation was identified after tumor detection (the symptomatic group).

Outcome assessment

The images and related reports of all patients at the time of diagnosis were reviewed by one of the three dedicated breast radiologists (IMO, GWW, RM) in order to assess whether the breast cancers were screen-detected or interval cancers and whether the cancers were visible on mammography and MRI. One radiologist (IMO) reviewed nearly all cases. In the three centers mammograms and MRI examinations were already scored according to the Breast Imaging and Data System (BI-RADS) classification (15). The BI-RADS classification allocated at the time of diagnosis was used for evaluation. BI-RADS classification 3, 4 and 5 were defined as positive findings because additional work-up was indicated. BI-RADS 0 was not considered as a final assessment.
A screen-detected breast cancer was defined as a breast cancer found during a screening round by MRI and /or mammography. If a breast cancer was identified clinically (became palpable or caused other symptoms) in between two screening rounds it was considered an interval cancer. Patients with

breast cancer detected in specimens from prophylactic mastectomy were excluded from analysis as were patients screened with either MRI or mammography.
The pathology reports were scored for tumor characteristics. The largest diameter of the tumor as mentioned in the pathology report was recorded to indicate size. In case of multifocal or multicentric disease the size of the largest cancer was registered and counted as one malignancy. In patients treated with neo-adjuvant chemotherapy the largest diameter measured on MRI was recorded as the size of the breast cancer.

Statistical methods

For the comparison of the two screening modalities, MRI and mammography, we used the data of patients for who results were available of both imaging methods. The differences in sensitivity between MRI and mammography were tested by a McNemar's test for paired proportions.
Differences in proportion of tumor stage and node negativity between screen-detected and symptomatic cancers were analyzed by Fisher's exact test. A two-sided P-value of lower than .05 was considered statistically significant. Statistical analyses were performed using SPSS (IBM SPSS Statistics 20).

RESULTS

From January 2003 to March 2013, 128 BRCA1 mutation carriers were diagnosed with breast cancer in one of the three participating centers. In eight patients, breast cancer was found at prophylactic mastectomy and these patients were excluded from analysis. Ten patients with screened with either MRI (n=9) or mammography (n=1) were also excluded.
The study group consists of 93 BRCA1 mutation carriers with 94 breast cancers detected under screening with both MRI and mammography available. One of these patients experienced metachronous contralateral breast cancer. The remaining 18 patients are unscreened symptomatic patients in whom BRCA1 mutation carriership was determined later. They form the symptomatic group. One patient with a palpable as well as a screen-detected contralateral breast cancer was allocated to both groups (Fig 1).
In the 93 patients of the study group the screening performance of MRI and mammography, and of the modalities separately, was determined (Fig. 1). The mean age was 44.2 years (range (24-72) with 32 women below 40 (34%) at time of the diagnosis. Seventeen patients had a previous diagnosis of breast

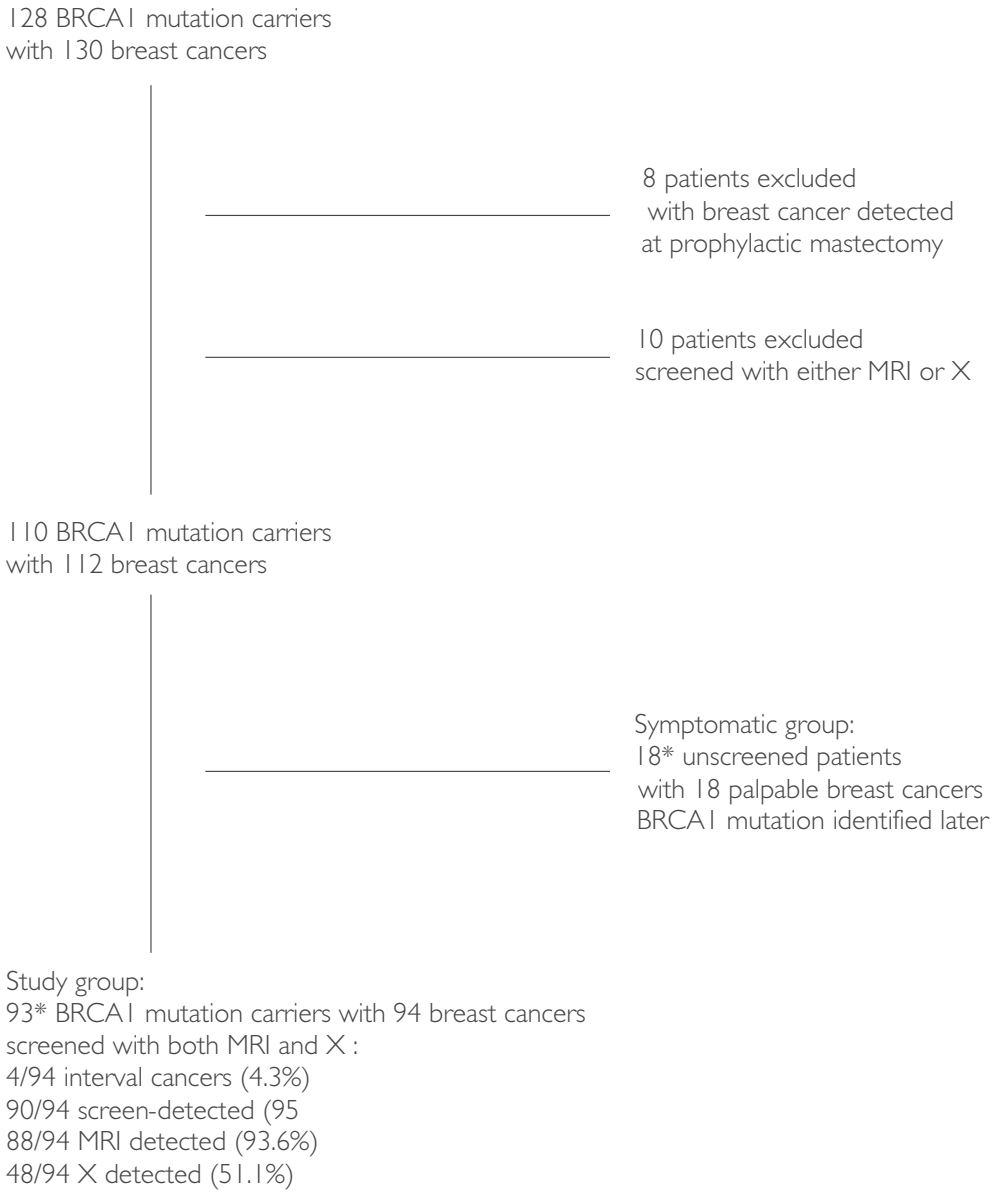

Fig. 1. Flow chart describing the number of BRCA1breast cancer cases available for analysis
X: mammography, MRI: magnetic resonance imaging. *One patient with a palpable and a contralateral screen-detected breast cancer is counted in both groups

Table 1. Tumor stages of breast cancers detected in screened and in unscreened symptomatic BRCA1 carriers in the present study, and in screened BRCA1 mutation carriers in a meta-analysis of earlier studies

	DCIS		Invasive breast cancer			N	
	n	n	size ≤10 mm	size 11-20 mm	size >20 mm	pos	neg
Cancers in the study group n=94	12.8%	87.2%	47.9%	25.5%	13.8%	17%	83%
	(12/94)	(82/94)	(45/94)	(24/94)	(13/94)	(16/94)	(78/94)
Cancers in the symptomatic group n=18	0%	100%	16.7%	27.8%	55.5%	44.4%	55.6%
	-	(18/18)	(3/18)	(5/18)	(10/18)	(8/18)	(10/18)
Cancers in screened BRCA1 mutation carriers in meta-analysis of earlier studies (16) n=67	11.9%	88.1%	37.3%	31.4%	19.4%	19.1%	80.9%
	(8/67)	(59/67)	(25/67)	(21/67)	(13/67)	(12/63*)	(51/63*)

DCIS: ductal carcinoma in situ, 16: Heijnsdijk et al. and personal communication with E. Heijnsdijk, N: nodal status, * nodal status unknown in 4 patients

cancer. Prophylactic bilateral salpingo-oophorectomy (PBSO) had been performed in 31 patients at least one year before breast cancer diagnosis.

Eighty-two invasive breast cancers with a mean size of 12.2 mm (range 1-47) and 12 DCIS with a mean size of 17.5 mm (range 5-50) were found (Table 1). With 90 breast cancers screen-detected the sensitivity of screening was 95.7% (90/94). MRI detected 88 of 94 breast cancers (93.6%) and mammography 48 (51.1%), a significant difference in sensitivity (two-sided $p<0.001$). Forty-two malignancies were detected only by MR (42/94=44.7%) and 2 DCIS only with mammography (2/94=2.1%). These 2 DCIS detected with mammography concerned a grade 3 DCIS of 40 mm in a patient of 50 years and a grade 2 DCIS of 5 mm in a patient aged 67. All 12 DCIS were screen-detected of which MR diagnosed 10 (83.3%) and mammography 6 (50.0%), due to small numbers this difference was not statistically significant (two-sided $p=0.29$). Six DCIS were detected only by MRI (50%) and 2 only with mammography (16.7%).

Four interval cancers (4/94=4.3%) occurred in pa-

tients aged 35, 45, 46 and 49 years. In all 4 patients it concerned grade 3 invasive ductal carcinomas (IDC), estrogen receptor (ER), progesterone receptor (PR) and HER-2 negative, with diameters of 10, 12, 18 and 47 mm.
Also in retrospect the lesions were not visible, neither on MRI nor on mammography. The breast cancers detected in the study group were significantly more often detected in the favorable Tis and T1a/b stage (60.6% (57/94)) than the cancers in the symptomatic group (16.7% (3/18)) (two-sided p=0.001) and more often node negative (83% (78/94) versus 55.6%(10/18)) (two-sided p=0.023) (Table 1).
If we had excluded BI-RADS 3 as a positive finding 7 breast cancers would have been missed decreasing the sensitivity of screening to 88.3% (83/94). The sensitivity of MRI would have been 83% (78/94) and the sensitivity of mammography 36.2% (34/94).

DISCUSSION

Our evaluation of screening results in BRCA1 breast cancer cases showed that more than 60% of breast cancers was detected as DCIS or small invasive lesions (≤ 10 mm). This is significantly better than the 17% of early stage breast cancer in the unscreened symptomatic group, stressing the necessity of screening. It also means an improvement in comparison with the screening results in BRCA1 mutation carriers from a meta-analysis of previous studies as presented by Heijnsdijk et al. (16). In that study nearly 50 % of breast cancers in BRCA1 was detected as DCIS or invasive breast cancer of 10 mm or less (Table 1). This improvement in outcome is in line with the higher sensitivity of MRI in the present study (93.6% (88/94)) in comparison with the pooled sensitivity of MRI in previous studies (77.6 % (52/67)) (3-5,7) (Note that in 2 studies (8,9) it was not possible to determine the sensitivities in BRCA1 mutation carriers separately). This higher sensitivity is most likely explained by a learning effect of the screening radiologists, but may also be influenced by improvement in MRI scanners, sequences and post-processing algorithms. The relatively high sensitivity of mammography (51.1% (48/94)) in comparison with previous results (29.2% (14/48) (3,4,7) indicates the better performance of digital mammography in comparison to conventional film-screen mammography (13). Nevertheless, the added value of mammography in young patients already screened with MRI may be questioned. The Italian HIBCRIT study already showed that in a population of high risk women the addition of mammography to MRI screening only yields no more than a minimal increase in sensitivity (8). Strikingly, in our study, mammography detected only 6 of 12 DCIS while MRI detected 10. The 2 DCIS not visible

on MR occurred in two patients aged 50 and 67 years old and were were the only cancers detected solely with mammography which is 2.1% (2/94) of the group under screening. By omitting mammography from the screening regimen, a grade 3 DCIS of 40 mm and a grade 2 DCIS of 5 mm would have been missed. However, with a screening policy of yearly MRI and digital mammography from age 40 onwards no additional breast cancer or DCIS would have been missed (apart from the 4 interval carcinomas which would have occurred with either protocol). This is in line with Heijnsdijk (16) who calculated natural history models of other screening protocols for BRCA1 based on the combined results of three screening studies. The predicted effectiveness of screening with MRI was only slightly lower than the predicted effectiveness of screening with MRI and mammography.

If mammography does not contribute sufficiently to early detection, it may, especially in BRCA1/2 mutation carriers, do harm because they are more sensitive to the DNA damaging effect of ionizing radiation and have a higher risk of breast cancer induction through radiation. This applies not only to high doses used for radiotherapy but also to low dose diagnostic radiation exposure (10,11), although not all studies confirmed this relationship. For instance in the large case control study of Narod et al.(17), no association was found between ever having mammography and risk of breast cancer. Pierce et al.(18) investigated the effect of radiotherapy after breast conserving therapy in BRCA1 and 2 mutation carriers and noticed no significant difference in rate of recurrences at 5 years between BRCA1 /2 mutation carriers and sporadic controls. Though, it is important to realize that the effect of exposure to radiation has a latency time of 10 to 15 years. In both studies the mean follow-uptime of 8.5 and 7.5 years respectively was possibly too short to observe any effect.

Andrieu et al. (10) analyzed the risk of breast cancer from exposure to chest X-rays and found an increased breast cancer risk at any exposure. They confirmed a higher risk in younger women exposed before age 40 and in women who are exposed more frequently. Mammographic screening of carriers at young ages meets both conditions. A large retrospective cohort study (12) of 1993 BRCA1/2 mutation carriers showed that any exposure to diagnostic radiation in BRCA1/2 mutation carriers before the age of 30 was associated with an increased risk of breast cancer. They observed an almost twofold significant risk increase for exposure to more than four radiographs before age 30. At ages 30-39 the same risk increase was observed, although not significant probably because only a few cases were included in the latter category. We only studied BRCA1 mutation carriers, because in these women the association between exposure and breast cancer risk is well documented. Although women with a BRCA2 mutation are likely also more prone to radiation induced breast cancers, numbers are relatively low and the associa-

tion between radiation at young age and the development of breast cancer is therefore less clear (12). Secondly, the mammographic sensitivity in BRCA1 mutation carriers is much lower and the added benefit over MRI is poorer. In the MARIBS and the MRISC study (4,7) the additional value of mammography over MRI was 0% and 11 % respectively in BRCA1 mutation carriers while in BRCA2 mutation carriers 38% and 23% of lesions were detected by mammography only. Thirdly, the results of the current screening strategy in BRCA2 mutation carriers appear beneficial. In the study of Heijnsdijk (16) 80% of the BRCA2 mutation carriers was detected in stage T1a/b or DCIS, compared to nearly 50% of the BRCA1 carriers. This may be explained by the important histologic differences between BRCA1 and BRCA2 associated breast cancer as demonstrated in many studies (19,20). The typical tumor characteristics such as ER, PR and HER-2 negativity and the high histologic grade differentiate BRCA1 associated breast cancer from BRCA2 associated and sporadic breast cancer. These characteristics are associated with more rapid tumor growth and are reflected in screening results as a low percentage of ductal carcinoma in situ, a higher proportion of invasive breast cancer with an unfavorable tumor size and more interval cancers (7, 21). It remains to be evaluated whether the addition of mammography to MRI screening in BRCA 2 patients at younger age is another reason for the more favorable cancer stage in this population or whether it should also be omitted.

The main limitation of this study is its retrospective study design. However, it is important to mention that to avoid information bias the original allocated BIRADS classification was used. Ideally, the next step following this study would be a prospective randomized study. However, even with an international multicenter study it would still very difficult to guarantee sufficient numbers within a reasonable time period. A decision model and computer simulation would be an alternative method to give helpful insights into the decision. Another limitation is that no information can be provided about the specificity of the screening modalities as we evaluated only breast cancers cases and not a complete screened cohort. A third limitation is that although we present a large cohort of BRCA1 mutation carriers with breast cancer, the sample size is small to compare mammography and MRI. As a consequence we cannot rule out that mammography has some additional value for detection of DCIS in older women.

CONCLUSION

Our evaluation of the screening results in BRCA1 mutation carriers showed improvement of MRI as well as mammography performance in comparison with former studies. The additional value of digital mammography over MRI was nevertheless very limited, only (2%) and only in patients older than 40 years. In this series there was no benefit of mammographic screening in women below 40. Especially in women younger than 40 years the possible benefit of mammographic screening could be reduced due to risk of radiation-induced breast cancer. As a consequence we propose to screen BRCA1 mutation carriers yearly with MRI from age 25 onwards and to start with mammographic screening not earlier than age 40.

Acknowledgements
The authors thank Eveline Heijnsdijk and Sepideh Saadatmand for their efforts.

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6

Mammographic screening in BRCA1 mutation carriers postponed until age 40: Benefits, costs and radiation risks

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Submitted

ABSTRACT

Purpose
BRCA1 mutation carriers are offered screening with MRI and mammography. Aim of this study was to weigh the benefits and risks of postponing mammographic screening until age 40.

Patients and methods
With the MISCAN microsimulation model two screening protocols were evaluated: 1) the current Dutch guidelines: annual MRI from age 25-30, annual MRI and mammography from age 30-60, and biennial mammography in the nationwide program from age 60-74, and 2) the modified protocol: postponing annual mammography until age 40. A cost-effectiveness analysis comparing both protocols was performed.
The risks of radiation-induced breast cancer and breast cancer mortality were estimated with absolute and relative exposure-risk models of the 7th Biological Effects of Ionizing Radiation Committee (BEIR-VII).

Results
Current screening guidelines prevent 13,139 breast cancer deaths per 100,000 BRCA1 mutation carriers. Postponing mammography until age 40 would increase breast cancer deaths by 23 (0.17%), but would also reduce radiation-induced breast cancer deaths by 15 or 105 breast cancer deaths using the absolute and relative risk model respectively per 100,000 women screened. The estimated net effect is an increase of 8 or a reduction of 82 breast cancer deaths per 100,000 women screened (depending on the risk model used). The incremental cost-effectiveness comparing the current versus the modified protocol is at least €272,900 per life year gained.

Conclusions
Screening according to the modified protocol is only slightly less effective or may even be better than the current guidelines. The high cost-savings justify a possible small loss of effectiveness. We therefore advise to screen BRCA1 mutation carriers annually with MRI from age 25 onwards and to postpone mammographic screening until age 40.

INTRODUCTION

Women with a BRCA1 mutation have a strongly elevated risk of developing breast cancer compared to the general female population (1) and the risk increase starts early in life. Based on the outcome of prospective screening studies (2-6) these women are recommended to undergo annual screening with MRI and mammography, starting at the ages of 25 and 30 years respectively (7,8). In studies investigating efficacy of screening in BRCA1 and 2 mutation carriers and women with high familial risk, the pooled sensitivity of MRI (81%) was twice as high as that of mammography (41%) (9). When focusing on BRCA1 mutation carriers the mammographic sensitivity was even lower (29% (14/48)) (2,3,5). In these studies mainly film-screen mammography was used.

We previously investigated the efficacy of screening in BRCA1 mutation carriers with MRI performed with up-to-date technology and read by experienced radiologists, and with digital instead of film-screen mammography. In comparison with earlier studies we found a higher sensitivity for MRI (94%) as well as for mammography (51%) (10). However, the additional value of mammographic screening over MRI was only 2% while at the same time there are increasing concerns about the risk of low-dose radiation exposure, especially in young BRCA mutation carriers, because of their impaired ability to repair the radiation induced double-strands DNA breaks (11-13). Little mammographic contribution to early breast cancer detection in BRCA1 mutation carriers was also found in the combined screening results of the MRISC, the MARIBS and the Canadian studies (14). Based on these findings it seems worthwhile to assess a modified screening strategy for BRCA1 mutation carriers. The purpose of the present study was to evaluate a modified screening strategy for BRCA1 mutation carriers with MRI from age 25 onwards and postponed mammographic screening until age 40 and to compare it with the current screening strategy of the Dutch guidelines for BRCA mutation carriers. We used a validated computer simulation model (MISCAN (15-18)) to estimate how many breast cancer deaths would be prevented and to perform a cost-effectiveness evaluation comparing the current and the modified strategy. Furthermore, with the most recent exposure-risk models according to the BEIR VII phase 2 report (19), we estimated how many breast cancers and breast cancer deaths would be induced. We combined the results of both models to estimate the net effect of a decade of annual two-view mammographic screening from age 30-39 years, when MRI screening is already performed.

METHODS

Data

The data consisted of screening results of a consecutive series of BRCA1 mutation carriers who developed breast cancer since the introduction of digital mammography while under surveillance in or referred to the familial breast cancer clinics of the Erasmus Medical Center Rotterdam, the Antoni van Leeuwenhoek Hospital in Amsterdam or the University Medical Center in Nijmegen (10). In accordance with the Dutch guidelines (7) women with a proven BRCA1 mutation were offered annual clinical breast examination, screening with MRI from age 25 and mammography from age 30 onwards. High resolution breast MRI was performed in each of the three centers conform local protocol. The inclusion period started after introduction of digital mammography in each of the participating hospitals (range from January 2003 to September 2005) and ended in March 2013.
From January 2003 to March 2013 94 breast cancers were found in 93 BRCA1 mutation carriers: 82 invasive breast cancers and 12 ductal carcinomas in situ (DCIS). Screening sensitivity was 95.7% (90/94). The mean age was 44.2 years (range (24-72) with 32 women below 40 (34%) at time of diagnosis. MRI detected 88 of 94 breast cancers (sensitivity 93.6%) and mammography 48 (sensitivity 51.1%) (two-sided $p<0.001$). Forty-two malignancies were detected only by MRI (42/94=44.7%). Two DCIS were detected only with mammography (2/94=2.1%) which were a grade 3 in a 50-year-old patient and a grade 2 in a 67-year-old. Four interval cancers (4/94=4.3%), all grade 3 triple negative invasive ductal carcinomas, occurred in women aged 35, 45, 46 and 49 years respectively.

We used the MISCAN microsimulation model to evaluate the performance and the cost-effectiveness of different screening strategies. Separately we used the BEIR VII radiation-risk models to calculate the effect of radiation.

Microsimulation model

MISCAN is a well-validated microsimulation model used to evaluate various screening programs (15-18). In MISCAN the natural history of breast cancer is modeled as the onset of breast cancer, the progression through five possible preclinical disease stages: DCIS and 4 preclinical invasive stages with increasing tumor diameters (T1a, T1b, T1c or >T2) and the transition of one of the preclinical stages into a clinically diagnosed stage until the women die from breast cancer or from other causes (see Figure 1). From each preclinical stage a tumor may either be clinically diagnosed or may progress to the

next preclinical stage. Breast cancer screening is introduced as an intervention in the natural history. By applying screening the tumor may be detected by screening in an earlier (preclinical) stage.
In the model for the general population, onset rate, transition probabilities between various tumor stages, stage duration, probability of screen detection, survival after clinical diagnosis or screen detection are based on data of the Dutch nationwide screening program (20). The improvement of prognosis after detection by screening is based on the long-term effects of the Swedish trials (21-23). The model has previously been adapted to BRCA1 mutation carriers, by calibrating the onset probability, age of onset of the disease, and transition probabilities and durations of the stages to data of the BRCA1 mutation carriers of the three large screening projects in the Netherlands (MRISC), Canada, and United Kingdom (MARIBS) (14).

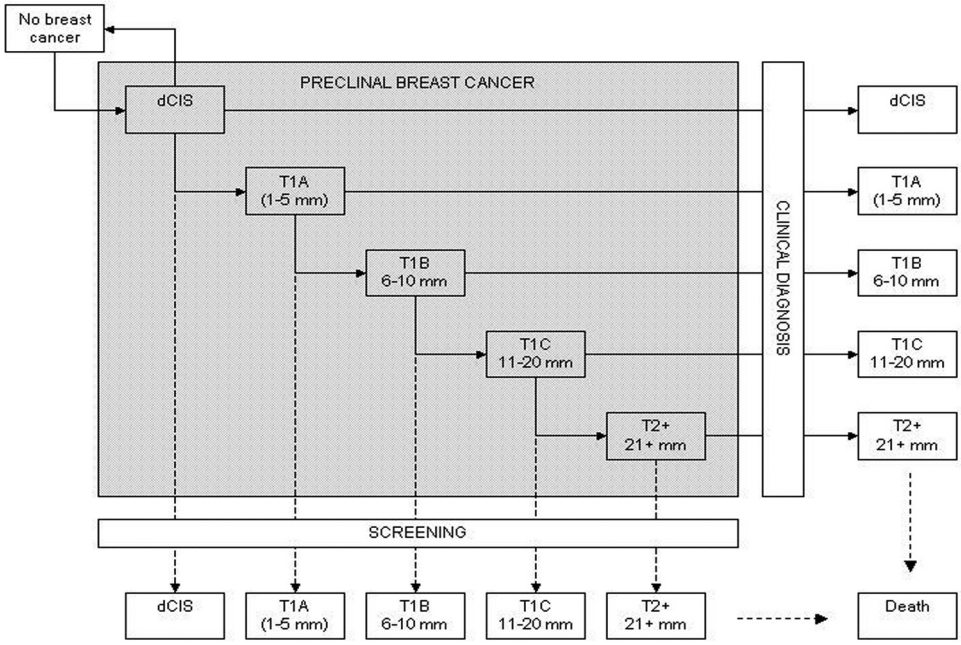

Figure 1. Transitions in the MISCAN model. From each pre-clinical stage, a tumor may be clinically diagnosed or may grow into the next pre-clinical stage. By applying screening, the tumor may be detected by screening.

Calibration and application of the model

To account for the improved sensitivity of both MRI and digital mammography compared to the sensitivity of MRI and (mainly) film-screen mammography in the above mentioned screening trails (14), we calibrated the test sensitivities in the BRCA1 mutation carrier model to the stage distribution and number of cancers missed by MRI or mammography in the dataset described above (10). These test sensitivities depend on age, stage and screening method. The resulting sensitivities were used as input in the model (Appendix 1, online only).

The screening protocols were run in the model for a simulated cohort of 10 million BRCA1 mutation carriers born in 1980. The results are expressed per 100,000 BRCA1 mutation carriers. A 90% attendance rate at each screen was assumed conform in the MRISC study (5). Two screening protocols were evaluated: 1) the current guidelines for BRCA1 mutation carriers: annual MRI from age 25-30, annual MRI and mammography from age 30-60 and biennial mammography in the nationwide program from age 60-74, and 2) the modified protocol: annually MRI from age 25-40, annually MRI and mammography from age 40-60 and biennial mammography in the nationwide program from age 60-74.

Cost-effectiveness

The cost-effectiveness analysis was performed from the healthcare payer perspective (24,25). We used a life time follow-up to predict the number of invitations, number of screens, number of screen detected and interval cancers by stage, breast cancers deaths and life years (LY) gained. Costs of screening and treatment by stage were determined previously, based on hospital prices provided by hospitals, the national breast cancer screening program and national guidelines in 2012 (26). The costs of diagnoses were based on the frequencies of additional diagnostic tests for BRCA1 mutation carriers in the MRISC trial, including ultrasonography with or without fine-needle aspiration, histologic biopsy and repeated mammography and MRI conducted because of uncertain or suspicious screening tests (5), combined with the unit costs of the different diagnostic procedures (26). In total the diagnostic costs were € 4626 per breast cancer detected in the trial (Appendix 2, online only). A discount rate of 3.5% was used for costs as well as effects. All costs are presented in both Euro's and US Dollars. Euro's were converted to US dollars by using the purchasing power parity for health of 1.72 (27).

Risk of radiation induced breast cancer

The radiation risk models of the 7th Biological Effects of Ionizing Radiation Committee (BEIR-VII) (19) were used to estimate the additional breast cancers and breast cancer deaths due to screening exposure. Historically, epidemiological data concerning health risks from exposure to low levels of ionizing radiation have been analyzed with 2 dose response models: Excess Absolute risk (EAR) and Excess Relative Risk (ERR).

The EAR assumes that the risk caused by the exposure is independent of the baseline risk and is proportional to the dose. Risk from the exposure is added to the baseline risk (additive model).

The simplest formula for the EAR model is: $R = a + bD$

(R=total risk, a= baseline risk and b=risk coefficient, D=dose) (28). The model is described in Appendix 3 (online only).

Repeated exposure to low doses such as with mammographic screening are considered to be less harmful than the high doses whereat atomic bomb survivors were exposed or than the high doses used in radiation therapy. Therefore, the BEIR VII committee suggested that the predicted number of induced breast cancer and breast cancer deaths due to mammographic screening should be divided by a correction factor of 1.5, the Dose/Dose Rate Effectiveness Factor (DDREF). The risk of radiation induced breast cancer increases with younger age at exposure and higher attained age. After age 50, the risk increases less steeply. A dose-response coefficient of 148 before age 50 and 94 after age 50 was used (18). The EAR model has been used before to evaluate the benefits and risks of mammography screening before age 50 (18).

The ERR model assumes that the risk caused by the exposure is proportional to the baseline risk as well as to the dose. The risk from exposure is a product of the baseline risk and the dose (multiplicative model).

The simplest formula for the ERR model is: $R = a + abD$

(R=total risk, a= baseline risk and b=risk coefficient, D=dose) (28). The model is described in Appendix 3 (online only).

In the present study we used the EAR as well as the ERR model to explore breast cancer risks due to a decade of annual mammography in BRCA1 mutation carriers.

We evaluated the used glandular doses in all BRCA1 and BRCA2 mutation carriers and first degree relatives aged 30-39 years who had mammography in our clinic during a one year period (from April 2013 till April 2014). For our risk analyses we calculated the used mean glandular dose of a two-view mammogram performed with a digital mammography unit (Selenia, Hologic).

Table 1A. Effects (without discounting) of two screening programs per 100,000 BRCA1 mutation carriers

	Current protocol BRCA1	Modified protocol BRCA1	Difference modified vs current protocol
Effects			
Invitations	2,726,806	2,733,180	6,374
Visits	2,453,445	2,458,985	5,540
Cancers	63,737	63,538	-199
Breast cancer deaths	12,346	12,369	23
Breast cancer deaths prevented by screening	13,139	13,116	-23
Life years	5,284,230	5,283,540	-690
Life years per person	52,8423	52,8354	-0.0069

Table 1B. Effects and costs*,** (with 3.5% discount)# and cost-effectiveness of two screening programs per 100,000 BRCA1 mutation carriers

	Current protocol BRCA1	Modified protocol BRCA1	Difference modified vs current protocol
Effects			
Invitations	1,582,056	1,584,728	2,672
Visits	1,423,850	1,426,169	2,319
Breast cancers detected	30,717	30,572	-145
Breast cancer deaths	5,502	5,513	11
Life years	2,270,960	2,270,760	-200
Life years per person	22,7096	22,7076	-0.002
Costs (* 1000 euro)			
Invitations	3,164	3,170	6
Visits	610,604	556,944	-53,660
Diagnoses	142,095	141,428	-667
Treatment	266,099	265,652	-447
Breast cancer mortality	99,038	99,227	189
Total	1,121,001	1,066,421	-54,580

ICER * (cost/life year gained)			272,900
Costs (** 1000 dollar)			
Invitations	5,442	5,452	9
Visits	1050,239	957,944	-93,296
Diagnoses	244,404	243,256	-1,148
Treatment	457,691	456,922	-769
Breast cancer mortality	170,345	170,671	326
Total	1,928,122	1,834,244	-93,878
ICER ** (cost/life year gained)			469,388

*costs in Euro's, ** costs in US dollars (2015), #according to UK recommendations
ICER: Incremental cost-effectiveness ratio

Life years gained by screening vs lost by radiation-induced breast cancer deaths

In a final analysis we calculated the net life years gained by screening minus life years lost by radiation-induced breast cancer deaths. Life years gained by screening were obtained from the MISCAN model. Life years lost due to radiation-induced breast cancer were estimated. As a consequence of the latency time, the years lost due to radiation-induced breast cancers deaths are less than in non-radiation-induced breast cancers deaths. In order to make an estimation of the life years lost due to radiation-induced breast cancer deaths we assumed a latency time of 10 years.

RESULTS

Calibration results

After calibration, the MISCAN model reproduced the stage distribution of the cancers found during the study reasonable well (Figure 2). The predicted proportion of tumors

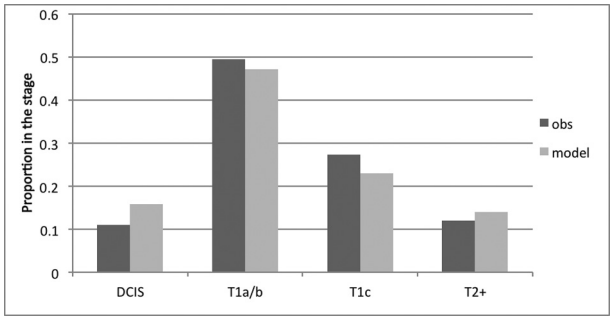

Figure 2. The predicted stage distribution compared to the observed stage distribution in the dataset.
Obs = observed stage distribution in the BRCA1 data set. Model = stage distribution predicted by the calibrated BRCA1 model

missed by mammography and MRI are 41% and 17%, respectively, compared to 49% and 6% found in the database.

Breast cancer mortality prevented by screening and cost-effectiveness

Table 1A, B presents the results and cost-effectiveness of the two screening protocols. These results are without the estimated risks of radiation-induced breast cancer and radiation-induced breast cancer deaths. All results are presented per 100,000 women born in 1980. Screening with MRI and mammography according to the current protocol for BRCA1 mutation carriers resulted in 63,737 breast cancers detected, 13,139 breast cancer deaths prevented by screening and 12,346 breast cancer deaths. Omitting mammography before age 40 resulted in 23 (0.17%) breast cancer deaths prevented less, 199 screen-detected breast cancers less and 690 life years lost per 100,000 BRCA1 mutation carriers (Table 1A).
Including all breast cancer care costs (screening, diagnoses and treatment, the current screening protocol cost in total 1,121,001 Euro's (1,928,122 US Dollars) whereas screening with mammography postponed to age 40 cost 1,066,421 Euro's (1,834,244 US Dollars) (Table 1B). The incremental cost-effectiveness ratio (ICER) of the current versus the modified protocol is 272,900 Euro's (469,388 US Dollars) per life year gained.

The risk of radiation-induced breast cancer and radiation-induced breast cancers deaths

The average glandular dose of a two-view digital mammogram used in 100 BRCA1/2 mutation carriers and untested first-degree relatives who visited our breast clinic for mammographic screening in a period of one year was 4.4 mGy (range 1.7- 7.1). In all our calibrations we used the dose of 4.4 mGy per two-view mammography.

Mammographic screening according to the Dutch guidelines for BRCA1 mutation carriers would induce 189 or 1,582 extra breast cancers per 100,000 women screened, using the EAR and the ERR risk models respectively. These numbers would be reduced to 90 and 771 respectively for the EAR and ERR risk models when annual mammography starts at age 40 (Table 2).
Mammographic screening according to the Dutch guidelines would induce 28 or 208 breast cancer deaths using the EAR and the ERR model respectively. Starting mammographic screening at age 40 these numbers would be reduced to 13 or 103 breast cancer deaths respectively for the EAR and the ERR model.

Table 2. Estimates of radiation-induced breast cancer incidence and mortality versus life years gained and breast cancer mortality prevented by screening per 100,000 screened BRCA1 mutation carriers

	Radiation-induced incidence		Radiation-induced mortality		Mortality prevented by screening	Net effect of screening: prevented minus induced mortality		Life years gained by screening	Net effect of screening on life years gained	
	EAR model	ERR model	EAR model	ERR model		EAR model	ERR model		EAR model	ERR model
Annual mammography from age 30*&	189	1,582	28	208	13,139	13,111	12,931	337,840	337,280	333,680
Annual mammography from age 40*&	90	771	13	103	13,116	13,103	13,013	337,150	336,890	335,090
Net effect of postponing mammography& to age 40	-99	-811	-15	-105	-23	+8	-82	-690	-390	+1410

* In both screening scenarios annual MRI was performed from age 25-60 and biennial mammography from age 60-74.
& In the calibrations the observed average glandular dose of 4.4 mGy per two-view mammography was used.
Mortality prevented by screening and life years gained by screening were calculated with the MISCAN model.
Net effect of screening on mortality equals mortality prevented by screening minus radiation-induced mortality.
Net effect of screening on life years gained equals life years gained by screening minus life years lost by radiation-induced mortality (not separately mentioned in the table).
Life years lost by radiation-induced mortality was calculated using a latency-time of 10 years implying that 20 years are lost per radiation-induced breast cancer.

The net effect of prevented mortality by screening and induced mortality by radiation in case of postponing mammography until age 40 would be an increase of 8 breast cancer deaths or a decrease of 82 breast cancer deaths, using the EAR and the ERR model respectively.

Life years gained by screening and lost by radiation-induced breast cancer deaths

Without the estimated risks of radiation-induced breast cancer deaths, postponing mammography till age 40 resulted in 23 breast cancer deaths prevented less and 690 life years lost. This means that per breast cancer death, 30 life years are lost. For radiation-induced breast cancer we assumed a latency time of 10 years and therefore 20 life years are lost for one radiation-induced breast cancer death. (table 2). By postponing mammography to age 40 the net breast cancer deaths prevented would be 8 less or 82 more and the net years gained by screening would be 390 years lost or 1410 years gained, using he EAR and ERR models respectively. Since the calculated net effect is more in favor of postponing mammography than the results in Table 1, the discounted ICER is at least 272,900 Euro's (469,388 US Dollars) per life year gained.

DISCUSSION

In this analysis we present for the first time the cost-effectiveness of mammographic screening in BRCA1 mutation carriers combined with the effect of radiation-induced breast cancer. Using the models we estimate that when BRCA1 mutation carriers are screened according to the current protocol only 23 (0.17%) breast cancer deaths are prevented more per 100,000 BRCA1 mutation carriers screened than when a mammography is postponed until age 40 (Table 2). However, taking into account the risks of radiation-induced breast cancer deaths our estimates show that this small positive effect of ten year mammographic screening will be nearly nullified to 8 (0.06%) per 100,000 BRCA1 mutation carriers screened using the EAR model (Table 2). Applying the ERR model, postponing mammography will even result in a net decrease of breast cancer deaths of 82 (0.6%) per 100,000 BRCA1 mutation carriers screened (Table 2). On the one hand, by omitting a decade of yearly mammography,199 cancers will not be detected. On the other hand the radiation- induced breast cancer incidence is reduced by 50% meaning that 99 respectively 811 radiation-induced breast cancers will be prevented per 100,000 BRCA1 mutation carriers screened (Table 2).

As mentioned above, the risk outcomes depend on whether the EAR or the ERR model is used. So the question is, which model provides for BRCA1 mutation carriers the best information of the excess risks? The Biological Effects of Ionizing Radiation (BEIR) VII-phase-2, published in 2006 is an extensive report and an update of our current knowledge of health risks from exposure to low levels of ionizing radiation (19). The used models for estimating breast cancer incidence and mortality are those developed by Preston and colleagues (29) and are based on large pooled analyses of eight cohort studies. These studies are characterized by relatively large populations of exposed women (ranging from 600 to 23,000), comparable groups of unexposed women, long follow-up, and a broad range of individual dose estimates derived from detailed dosimetry. The included women are from cohorts in Asia, Europe and North America who received single high doses, fractionated high-dose-rate exposures and protracted low-dose-rate exposures with ages at exposure ranging from infancy to post menopause. The largest population are the atomic bomb survivors; the other populations in these studies were exposed to radiation for medical reasons. The authors (29) conclude that low dose radiation exposure increases breast cancer risks at any age according a no-threshold linear dose response but that the risk tends to decrease with age at exposure. Regardless of the age at exposure, risks continue to be elevated throughout the remainder of a women's life, with the largest excess rates late in life. Although they suggest the use of an EAR model as the basis for breast cancer risk estimation in general exposed populations, the authors stress that there is no simple unified model that describes the risks for all different populations. BRCA mutation carriers, however, differ from the general population. The difference is not only due to their elevated breast cancer risk but also because of evidence of their reduced ability to repair radiation induced DNA damage (30-31) suggesting that there may be an interaction between the two risk factors, mutation and radiation. So for BRCA1 mutation carriers the ERR model probably estimates breast cancer risks due to radiation better than the EAR model. Therefore we decided to use both models. According the EAR model the risk from exposure is added to the baseline risk while according to the ERR model the risk from exposure is multiplied by the baseline risk, which explains the differences in outcome. Nevertheless both outcomes indicate that the net effect of 10 year mammographic screening is disappointing.

Few investigators have calculated breast cancer risks estimates due to mammography at young age. Only Berrington the González (32) also estimated the breast cancer mortality risk due to a decade of mammographic screening from age 30 till 39 for BRCA1/2 mutation carriers using a ERR model and found a comparable mortality risk (330 per 100,000 women screened).

There are some limitations in this study. We used two separate models to calculate the cost-effectiveness and the effects of radiation and estimated the

net effects by combining the undiscounted effectiveness result. Our model structure did not allow for combining the effects with discounting. Nevertheless, since the calculated net effect in the combined analysis was more in favor of postponing mammography than the results from the cost-effectiveness analysis excluding radiation risk, we can safely conclude that the discounted ICER is at least 272,900 Euro's (469,388 US Dollar) per life year gained.
Another limitation is that the MISCAN model uses the test sensitivities without considering a correlation between the tests. However, we found a strong correlation with low additional value for mammographic screening above MRI screening (10,14). Therefore, the gain of ten year mammography screening may in practice be even smaller.
For this analysis we used a recent dataset of a large cohort of BRCA1 mutation carriers with breast cancer diagnosed with digital mammography and up-to-date MRI evaluated by experienced radiologists. It has previously been suggested that there is little additional value of mammographic screening in BRCA mutation carriers. By calculating not only the prevented mortality and cost-effectiveness but also the radiation risks of mammographic screening we provide strong arguments to indeed postpone mammographic screening until age 40.

CONCLUSION

Our estimates suggest that for BRCA1 mutation carriers the net benefit of mammographic screening from age 30 till 39 will be very small (0.06%) (8 breast cancer death prevented per 100,000 women screened) or even negative (0.6%) (82 extra breast cancer deaths per 100,000 women screened). This result depends on whether the EAR or the ERR radiation risk model is used. The high incremental cost-effectiveness ratio of €272,900 per life year gained justifies a possible small loss of effectiveness. We therefore advise to screen BRCA1 mutation carriers yearly with MRI from age 25 onwards and to postpone mammographic screening till age 40.

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APPENDIX 1.

Test sensitivities by age and stage used as input in the calibrated model. Between age 50 and age 55 the test sensitivities are interpolated linearly.

	Mammography below age 50	Mammography above age 55	MRI below age 50	MRI above age 55
DCIS	0.360	0.720	0.449	0.471
T1A	0.101	0.407	0.947	0.980
T1B	0.140	0.620	0.980	0.990
T1C	0.450	0.900	0.99	0.990
T2+	0.515	0.980	0.99	0.990

APPENDIX 2

Costs of diagnoses of 20 breast cancers in BRCA1 mutation carriers

	Costs*	Number	Total costs
Visits	69,05	217	14984
Mammographic examinations	103,23	31	3200
MRI examinations	367,59	117	43008
Ultrasound examinations	77,08	217	16726
Fine needle biopsies	141,73	46	6520
Core and vacuum biopsies	175,86	46	8090
Cancers		20	92528
Per cancer			4626*
			7957**

*costs in Euro's, ** costs in US Dollars (2015)

APPENDIX 3

EAR and ERR breast cancer risk models according to the BEIR VII phase 2 report (19)

EAR model:

The risk of developing breast cancer due to screening exposure was estimated using the excess absolute rate (EAR) model by the BEIR-VII committee, who adapted and reparameterised the pooled analysis EAR model by Preston

(2002). The model is described as follows:
$\lambda(t, d, E) = \lambda(t, 0) + \Sigma_i\, \varepsilon(t, d_i, E_i)$
and
$\varepsilon(t, d, E) = d * 148 * \exp(-0.05\ (E - 30) + 3.5 \ln (t/60))$ if $t < 50$
$\varepsilon(t, d, E) = d * 94 * \exp(-0.05\ (E - 30) + \ln (t/60))$ if $t \geq 50$
The incidence $\lambda(t, d, E)$ per 1000 women years is equal to the predicted baseline incidence without radiation $\lambda(t, 0)$ plus the sum of all induced breast cancers due to radiation $\Sigma_i\, \varepsilon(t, d_i, E_i)$ at each screening round. d is the glandular dose (4.4 mGy), E is the exposure age and t is the attained age. We assumed a 10 year lag time for the induction of cancer.
The lifetime risk of breast cancer in a situation with mammography screening was calculated by multiplying the incidence at a given age with the survival at that age and cumulating the products over de years (18):
$I_d = \Sigma_t \lambda\ (t, d_1, d_2, \ldots., E_1, E_2, \ldots) * S(t)$
The lifetime risk of induced breast cancer mortality was calculated by multiplying the breast cancer incidence at a given age with the survival and case fatality (p(t)) at that age, and cumulating the products for all ages:
$M_d = \Sigma_t \lambda\ (t, d_1, d_2, \ldots., E_1, E_2, \ldots) * p(t) * S(t)$
Age-specific case fatality was obtained from MISCAN. Survival was calculated using a recent life table for Dutch females. We assumed that cancers that were induced by radiation could become screen detected at a similar rate as non-induced breast cancers, and therefore could benefit from screening in a similar way.

6

ERR model:
The model that was used is an excess relative risk model for the risk of radiation-induced breast cancer incidence (R_j) at attained age j, where λ_j is the underlying breast cancer incidence rate in the BRCA1 population at the attained age j (Berrington de Gonzalez, 2005).
$R_j = \lambda_j 0.74(age_j/50)^{-2}\ \Sigma d_k$
D_k is the radiation dose at age k and the doses are summed up to 10 years prior to the attained age j to allow for the lag period for the induction of breast cancer. The underlying breast cancer incidence rate in the BRCA1 population by age was obtained from MISCAN.
The lifetime risk of breast cancer and the induced breast cancer mortality were calculated in a similar way as for the EAR model.

7

Magnetic resonance imaging improves breast screening sensitivity in BRCA mutation carriers age ≥ 50 years: Evidence from an individual patient data meta-analysis

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Journal of Clinical Oncology 2015;33(4): 349-356

ABSTRACT

Purpose

There is no consensus on whether magnetic resonance imaging (MRI) should be included in breast screening protocols for women with *BRCA1/2* mutations age ≥ 50 years. Therefore, we investigated the evidence on age-related screening accuracy in women with BRCA1/2 mutations using individual patient data (IPD) meta-analysis.

Patients and Methods

IPD were pooled from six high-risk screening trials including women with BRCA1/2 mutations who had completed at least one screening round with both MRI and mammography. A generalized linear mixed model with repeated measurements and a random effect of studies estimated sensitivity and specificity of MRI, mammography, and the combination in all women and specifically in those age ≥ 50 years.

Results

Pooled analysis showed that in women age ≥ 50 years, screening sensitivity was not different from that in women age < 50 years, whereas screening specificity was. In women age ≥ 50 years, combining MRI and mammography significantly increased screening sensitivity compared with mammography alone (94.1%; 95% CI, 77.7% to 98.7% v 38.1%; 95% CI, 22.4% to 56.7%;P .001). The combination was not significantly more sensitive than MRI alone (94.1%; 95% CI, 77.7% to 98.7% v 84.4%; 95% CI, 61.8% to 94.8%; P .28). Combining MRI and mammography in women age ≥ 50 years resulted in sensitivity similar to that in women age < 50 years (94.1%; 95% CI, 77.7% to 98.7% v 93.2%; 95% CI, 79.3% to 98%; P= .79).

Conclusion

Addition of MRI to mammography for screening BRCA1/2 mutation carriers age ≥ 50 years improves screening sensitivity by a magnitude similar to that observed in younger women. Limiting screening MRI in BRCA1/2 carriers age ≥ 50 years should be reconsidered.

INTRODUCTION

Women with BRCA1 or BRCA2 mutations are estimated to have a 5x to 7x higher cumulative risk of developing breast cancer by age 70 years (57% to 65% for BRCA1 and 45% to 78.3% for BRCA2 mutation carriers) than the general population (1,2). These women are likely to develop breast cancer at an earlier age (mean age, 42.5 and 46.8 years for BRCA1- and BRCA2-related cancers, respectively) (3). In addition, both young age and BRCA mutations are associated with fast tumor-doubling time (4-6). Therefore, it is recommended that screening for these women compared with women from the general population commence earlier (at age 25 to 30 years), occur more frequently (ie, annually), and include magnetic resonance imaging (MRI) because of the low sensitivity of mammography in this population (sensitivity, 32% to 39%) and the much higher sensitivity of MRI (68% to 100%) (7,8).

MRI has some drawbacks: a range of reported sensitivities for ductal carcinoma in situ (DCIS) (9-12), the inability to visualize nonenhancing DCIS (even retrospectively) (13), lower specificity (7,14) higher cost, the need for an intravenous contrast agent, and potential to cause more distress for the patient (15). Thus, there is consensus that women at high risk for hereditary breast cancer should be screened with a combination of MRI and mammography (16-19).

However, current recommendations are limited by the paucity of age-specific evidence and are therefore not uniform for screening women with BRCA1/2 mutations once they reach the age of 50 years. The advantages of MRI over mammography might be expected to decline with age because of a progressive reduction in breast density and decreased tumor growth rate (20). Because the use of MRI greatly increases cost and reduces specificity, the argument for screening high-risk women age ≥ 50 years with MRI, in the absence of clear data demonstrating its effectiveness, has been less compelling. Conversely, some studies have shown that MRI is significantly more sensitive than mammography in BRCA1/2 mutation carriers age ≥ 50 years (9,21).

Consequently, annual screening MRI and mammography are offered for women with a BRCA mutation with no upper age limit in some countries (16,22,23), whereas other countries, such as the United Kingdom and the Netherlands, recommend screening MRI and mammography only until age 50 or 60 years, respectively, after which mammography alone is performed (17,18). Two study-level meta- analyses reported the screening accuracy of MRI and mammography in high-risk women of all ages but could not adequately address the age-specific contribution of MRI, given the heterogeneity across studies and the limitations of study-level analyses (7,14).

We examined the age-related accuracy of MRI alone and MRI combined with mammography relative to mammography alone for screening women with

BRCA1/2 mutations, stratified into age groups of < and ≥ 50 years, using an individual patient data (IPD) meta- analysis. We specifically aimed to assess the contribution of MRI for screening BRCA1/2 mutation carriers age ≥ 50 years to inform the uncertainty and lack of consensus about the appropriate screening strategy for older BRCA1/2 mutation carriers.

PATIENTS AND METHODS

Study Design

An IDP meta-analysis was conducted, including data from 2,033 women.

Literature Search and Data Acquisition

A search was performed in the Medline database in August 2010 and repeated in April 2013 (Appendix Fig A1, online only). Titles, abstracts, and full text were read to check for eligible studies independently by two investigators (N.H., G.H.d.B.). The references of selected articles were also screened for other potentially eligible studies. Results from the two reviewers were compared, and differences were resolved by discussion and consensus.

Eligible studies had to meet the following criteria: prospective cohort study of women with BRCA1/2 mutations or a family history of breast or ovarian cancer compatible with an underlying genetic susceptibility; comparison of mammography and MRI for breast screening; and reported participant demographics, disease stage, and sensitivity and specificity of screening, with at least 1 year of follow-up after the last screening round to confirm absence of disease. For our meta-analysis, only women with BRCA1/2 mutations were included.

Data requirement and collection

Principal investigators of eligible studies were formally contacted to participate in the IPD meta-analysis and to provide deidentified data. Those who agreed to participate were requested to provide data in a predefined format to ensure standard classification of variables.

Data handling and assembly

All received data were validated by comparing to the results reported in the original publication; any discrepancies were discussed with the original investigators for clarification. A common database was assembled that included all data for subjects with a BRCA1 or BRCA2 mutation who had both MRI and mammography in the same surveillance round. In the our analysis, we considered sonly creening rounds with at least one year of follow-up.

Quality assessment

The quality of the included studies was assessed by an investigator (X.-A.P.) using the QUADAS-2 checklist (24). The QUADAS-2 checklist is a tool to evaluate the risk of bias and applicability of primary accuracy studies, comprising four domains: patient selection, index test, reference standard, and flow and timing. An additional item was whether MRI and mammography imaging results were read independently.

Primary outcome and definitions

The primary outcome was the sensitivity and specificity of the test (Appendix, online only). An imaging result of Breast Imaging Reporting and Data System (BIRADS) 0, 3, 4, 5 was considered to be a positive screening result and BI-RADS 1, 2 was considered to be a negative screening result. This threshold was chosen because one of the included studies classified imaging results as positive or negative using this threshold (11) and because this approach allowed us to pool data from all studies using a standardised classification. A patient was classified as having cancer (DCIS or invasive cancer) based on the pathological confirmation of breast malignancy. A patient was classified as not having an interval cancer when there was no evidence of cancer in the follow-up period (up to the next screening round). Breast cancer detected within 1 year of follow-up period in a patient who and had negative imaging result, was considered an interval cancer. In case of > one tumour found in the same woman in one screening round, the largest tumour was reported. Tumours found by chance during risk-reducing mastectomy were not considered in the analysis if reported > 1 year after the last screening (9,10). When combining MRI and mammography, a positive test result was when at least one of the tests produced a positive result.

Table 1. Overview of included studies

Study	Time frame	Study design/ reading policy	Women with BRCA1/2 mutation			Positive test (BIRADS)
			No.	Median age (years)	Range (years)	
Toronto, Ontario, Canada[9]	November 1997 to June 2009	Single-centre study; single reading	491	44	25-66	0,3,4,5
Italy (HIBCRIT 1 Study)[21]	June 2000 to January 2007	Multicentre study/ single reading	343	45	22-79	4,5
United Kingdom (MARIBS)[11]	August 1997 to May 2004	Multicentre study/ double reading	194	39	33-55	0,3,4,5
Austria[30]	January 1999 to July 2006	Single centre study/ single reading	162	39	21-79	4,5
The Netherlands (MRISC)[10]	November 1999 to March 2006	Multicentre study/ single reading	709	37	20-75	0,3,4,5
Montreal, Quebec, Canada[33]	August 2003 to May 2007	Single centre study/ single reading	134	45	21-75	4,5

Abbreviations: BIRADS, Breast Imaging Reporting and Data System; CBE, clinical breast examination; HIBCRIT 1, High Breast Cancer Risk Italian 1; MARIBS, Magnetic Resonance Imaging for Breast Screening; MRI, magnetic resonance imaging; MRISC, Magnetic Resonance Imaging Screening. * These estimates are based on the data as provided by the authors and represent a crude proportion as these are not adjusted for repeated screening in the same woman.

Statistical analysis

A generalized linear mixed model was used to estimate and compare sensitivity and specificity between screening modalities for the two different age groups (≥ 50 v <50 years) (Appendix, online only). Sensitivity and specificity were analyzed simultaneously, since these measures are correlated. Age group, screening modalities and their interactions were introduced in the

Follow-up and Intermediate tests	Completed Screening Rounds Breast Cancer	Sensitivity (%)* MRI	Mammography	Specificity (%)* MRI	Mammography
Positive test: biopsy; If MRI is positive but no other tests are, MRI is repeated within 1 month. Intermediate test: (BIRADS 3) 6-,12- and 24-month follow-up	1334 53	87.0 24.1		81.6 94.8	
Positive test: Biopsy Negative test: 12-month follow-up Intermediate test: (BIRADS 3) 4-month follow-up.	604 29	96.6 37.9		88.0 96.5	
Positive test: Biopsy Negative test: 12-month follow-up No intermediate test	356 27	74.1 44.4		81.2 90.3	
Positive test: Biopsy Negative test: follow-up till the last round Intermediate test: (BIRADS 3) 6-month follow-up.	348 18	94.4 61.1		88.2 97.3	
Positive test: Biopsy Negative test: if imaging test was negative and CBE was suspect, additional test was required. Intermediate test: (BIRADS 0,3) US +/- fine needle aspiration or imaging test	1,405 48	45.0 32.5		91.0 94.4	
Positive test: Biopsy Negative test: follow-up till the last round Intermediate test: (BIRADS 3) 6-month follow-up	132 9	88.9 55.6		70.7 78.0	

model as fixed effects for both sensitivity and specificity. Heterogeneity in sensitivity and specificity was modelled separately, by adding a bivariate random effect for studies. Heterogeneity was quantified by an intraclass correlation coefficient. All analyses were performed with SAS software (version 9.3; SAS Institute, Cary, NC).

Table 2. Characteristic of breast cancers stratified by detection models (n=184)

		Detection model			
	Total patients	MRI only (n=90)	Mammography only (n=16)	MRI and mammography (n=55)	Interval cancers (n=23)
Women aged <50	141	66	13	43	19
Type of cancer					
DCIS	29	9	6	7	7
Invasive cancer	112	57	7	36	12
Tumour size, cm					
<1	31	20	1	8	2
≥1	65	32	5	20	8
Not available	16	5	1	8	2
Grade					
1	8	6	0	1	1
2-3	96	47	6	34	9
Not available	8	4	1	1	2
Nodal status					
Negative	73	39	3	25	6
Positive	25	13	3	5	4
Not available	14	5	1	6	2
Women aged ≥ 50	43	24	3	12	4
Type of cancer					
DCIS	8	6	1	1	0
Invasive cancer	35	18	2	11	4
Tumour size, cm					
<1	12	8	1	1	2
≥1	18	8	0	8	2
Not available	5	2	1	2	0
Grade					
1	4	1	0	1	2
2-3	28	16	1	9	2
Not available	3	2	1	1	0
Nodal status					
Negative	23	14	1	5	3
Positive	7	1	0	5	1
Not available	5	3	1	1	0

Abbreviations: DCIS, ductal carcinoma in situ; MRI, magnetic resonance imaging.

RESULTS

The literature search yielded 254 publications for abstract reading; 23 publications on 15 studies (several publication were from the same study population) fulfilled the inclusion criteria, and their study authors were contacted (9-11,21,25-35). On close review, three studies were not eligible: one study did not have any breast cancer data (31); one study had a large overlap in study population with another study (32); one single-center study was part of a multi-center study which was included (35). Ultimately, investigators from six of twelve studies agreed to contribute data (table 1). In all six studies, MRI and mammography were obtained annually. Both screening modalities were performed on the same day when possible or within one to two months of each other. Different test thresholds and follow-up procedures were implemented by different research teams (Table 1). All studies were considered to be of good quality (Appendix Table A1, online only). In the original studies, study-specific MRI sensitivity ranged from 45% to 96.6% and mammography sensitivity from 24.1% to 61.1% (Table 1).

Table 3 Characteristic of women with BRCA1/2 mutations

	Total group (N=1,951)		Women diagnosed with breast cancer (N=183*)	
Characteristics	No.	%	No.	3%
Age at study entry, years				
Median	41		45	
IQR	34-49		38-51	
<40	864	44.3	70	38.3
40-49	650	33.3	70	38.3
50-59	329	16.9	33	18.0
≥60	108	5.5	10	5.4
Gene mutation				
BRCA1	1,219	62.5	112	61.2
BRCA2	732	37.5	71	39.0
Prior breast cancer or ovarian cancer	345	17.7	46	25.0
Previous breast cancer screening	1086	55.7	99	54.1
Hormonal contraception therapy	795	40.7	81	44.3
Hormonal replacement therapy use	130	6.7	13	7.1

* One women was diagnosed with two breast cancers at different screening rounds

Study population and screening program

A total of 1,951 of 2,033 women with BRCA1/2 mutations (median age 41 years, interquartile range [IQR]: 34-49) had both MRI and mammography results in the same screening round and were included in our models. The median follow-up time of those women (excluding incomplete screening rounds) was three years (IQR: 1 to 4 years). Among 5,816 completed screening rounds, cancer status from 1,637 rounds was not confirmed by either biopsy or follow-up, hence 4,179 screens had confirmed outcomes. There were 3,241 screens among 1514 women aged <50 and 938 screens in 437 women aged ≥50.

Breast cancers

There were 184 breast cancers in 183 women including 23 interval cancers (one woman had breast cancer diagnosed in two different screening rounds; Table 2). The median age of women at cancer diagnosis was 45 years (IQR: 38 to 51 years; Table 3). There were 141 breast cancers detected in women aged <50 years with 4,786 women-years of follow-up, and 43 breast cancers detected in women aged ≥50 years with 1,345 women-years of follow-up. The breast cancer incidence was 29.5 cases per 1000 women-years at risk (95%CI, 25 to 34.5) for women aged < 50 years, and 32 cases per 1000 women-years at risk (95%CI, 23.8 to 42.2) for women aged ≥50 years (P=0.66). There were 19 interval cancers in women aged < 50 years (DCIS, n=7; invasive ductal carcinoma, n=9; and other type of tumours, n=3) and four interval cancers in women aged ≥ 50 years (invasive ductal carcinoma, n=2; invasive lobular carcinoma, n=1, and unspecified invasive tumour, n=1).

Sensitivity and specificity of mammography and MRI

All ages.

Overall, MRI detected 145 (78.8%) of 184 breast cancers and mammography detected 71 (38.6%) of 184 tumours. Combining both tests diagnosed 163 (88.6%) of 184 tumours and increased the estimated (modelled) screening sensitivity significantly compared to mammography alone (93.4% v 39.6%, P< .001), whereas the specificity was significantly reduced (80.3% v 93.6%, P= .0016) (Table 4). Had mammography not been performed, screening sensitivity and specificity would not have been statistically significantly changed (Table 4). However, without mammography, 16 tumours would have been missed (DCIS, n=7; invasive tumours <1cm, n=2; Table 2). Forty eight percent (90 of 184) of the breast cancers were only detected by MRI, among them 47.8% (43/of 90) of the early stage cancers (DCIS, n=15; and small invasive tumours [ie, <1cm], n=28; Table 2).

Women age < 50.
The contribution of MRI in screening is reflected by the increased sensitivity of the combination compared with mammography alone (93.2% v 40%, P< .001), although at the price of a significantly reduced specificity (78.7% v 93%, P< .001; Table 4). The sensitivity and the specificity of the combination was not statistically significantly different from that of MRI alone (93.2% v 85.7%; P= .32, 78.7% v 83.5%, P= .28, respectively; Table 4). Without mammography, 13 (9.2%) of 141 cancers would have been missed (DCIS, n=6; invasive tumour < 1 cm, n=1; Table 2). Without MRI at least 46.8% (66 of 141) of cancers in this age-group would have been missed (DCIS, n=9; invasive tumours <1cm, n=20; Table 2).

Women aged ≥ 50 years.
The sensitivity of mammography was relatively low (38.1%; 95%CI, 22.4% to 56.7%) and no higher than the sensitivity in women age < 50 years. MRI alone and the combination of mammography with MRI had significantly higher sensitivities than mammography alone (84.4%; P= .0027 and 94.1%; P < .001, respectively; Table 4). Mammography alone remained the most specific method (95.9%) compared to MRI alone (88.5%; P= .0079) or both tests combined (85.3%; P= .001; Table 4). The sensitivity and specificity of combined mammography and MRI (94.1% and 85.3%, respectively) were not significantly different from that of MRI alone (84.4%, P= .28 and 88.5%, P= .37, respectively). In this age-group, had mammography not been applied, at least three (7%) of 43 cancers would have been missed (DCIS, n=1; invasive tumour < 1 cm, n=1; Table 2). Without MRI at least 24 (55.8%) of 43 cancers would have been missed (DCIS, n=6; invasive tumours <1cm, n=8; Table 2).
In the 108 women aged ≥ 60 years, 10 breast cancers (interval invasive lobular carcinoma, n=1) were diagnosed. In this group, MRI detected nine of 10 cancers. Mammography detected three of 10 cancers and these three cancers were also detected by MRI.

Differences in sensitivity and specificity between women aged < 50 and ≥ 50 years.
No statistically significant difference was observed in sensitivity of either mammography or MRI when stratified by age. The specificity of both mammography and MRI significantly improved in women aged ≥ 50 years compared to women aged < 50 years (by 2.9% and 5% respectively; Table 4).

Heterogeneity across studies (Intraclass correlation coefficient).
There was relatively little heterogeneity across studies and it differed for specificity and sensitivity of each method. The intraclass correlation coefficient for specificity of MRI, mammography and the combination were 5.5%,

Table 4. Sensitivity and specificity of mammography and MRI in women with BRCA1/2 mutations

Age (years)	Mammography		MRI		MRI plus Mammography	
	Sensitivity (%) (95%CI)	Specificity (%) (95%CI)	Sensitivity (%) (95%CI)	Specificity (%) (95%CI)	Sensitivity (%) (95%CI)	Specificity (%) (95%CI)
All ages	39.6 (30.1-49.9)	93.6 (88.8-96.5)	85.3[a] (69.1-93.8)	84.7[b] (79-89.1)	93.4[a] (80.2-98)	80.3[c] (72.5-86.2)
<50 (n=1514)	40 (30.5-50.3)	93.0 (87.8-96)	85.7[a] (69.4-94.1)	83.5[d] (77.6-88.1)	93.2[a] (79.3-98)	78.7[a] (70.6-85)
≥50 (n=437)	38.1 (22.4-56.7)	95.9[e] (92.1-97.9)	84.4[f] (61.8-94.8)	88.5[gh] (83.5-92.2)	94.1[a] (77.7-98.7)	85.3[ij] (78.5-90.2)

Abbreviation: MRI, magnetic resonance Imaging
[a]Compared with mammography (P < .001)
[b]Compared with mammography (P= .0101)
[c]Compared with mammography (P= .0016
[d]Compared with mammography (P= .0089)
[e]Specificity of mammography in women age ≥ 50 years compared with that in women < 50 years (P= .005)
[f]Compared with mammography (P=0.0027)
[g]Compared with mammography (P=0.0079)
[h]Specificity of MRI in women age ≥ 50 years compared with that in women < 50 years (P < .001)
[i]Compared with mammography (P= .001)
[j]Specificity of combination in women age ≥ 50 years compared with that in women < 50 years (P= .005)

13.3% and 7.2%, respectively. The intraclass correlation coefficient for sensitivity of MRI, mammography and the combination were 20.1%, 2.2% and 25.1%, respectively.

DISCUSSION

Pooled analysis using IPD in women with BRCA1/2 mutations from six studies showed that in BRCA1/2 mutation carriers age ≥ 50 years, combining MRI and mammography resulted in the highest sensitivity compared with mammography alone (94.1%; 95% CI, 77.7% to 98.7% v 38.1%; 95% CI, 22.4% to 56.7%; P <.001) and MRI alone (94.1%; 95% CI, 77.7% to 98.7% v 84.4%; 95% CI, 61.8% to 94.8%; P= .28). Combining MRI and mammography in women age ≥ 50 years resulted in similar sensitivity to— but higher specificity than— that for younger women. Somewhat surprisingly, mammographic sensitivity was no higher in women age ≥ 50 years than in younger women. Assuming that justification for adjunct MRI screening in younger women with BRCA1/2 mutations is based on the additional breast cancer detection from MRI, it would be equally justifiable, on the basis of this meta-analysis, to offer such women adjunct MRI screening beyond age 50 years.

The argument for screening women with BRCA1/2 mutations at age ≥ 50 years with only mammography is partly that mammography is generally considered to be effective in women beyond age 50 years, and it is expected that increasing age would lead to decreasing breast density, which in turn would improve mammography sensitivity (20,36). However, the latter was not observed in our analysis. In the Toronto study included in this meta-analysis, an inverse correlation between age and density was observed in BRCA1/2 mutation carriers (37). Although mammography sensitivity for invasive cancers was greater in women with low compared with high breast density (sensitivity, 40% v 10%), absolute values were low for both groups, and the difference not significant (37). In the Netherlands cohort of BRCA1/2 mutation carriers, also included in our work, MRI sensitivity was superior to that of mammography, especially in women with low breast density, and breast density did not significantly affect mammography sensitivity (38). One possible explanation is that a high proportion of women had a negative mammogram before entering the study, and the cancers that had not been detected by mammography were subsequently diagnosed by MRI. In addition, small size tumors that had been detected early by MRI could also be potentially detected by mammography later, if MRI had not been used at all. However, it is likely that later detection may not have resulted in an equivalent prognosis.

The IPD meta-analysis suggests that women with BRCA1/2 mutations may

still benefit from MRI screening after reaching age 50 years. Previous publications of screening in BRCA mutation carriers showed that MRI continued to find cancers missed by mammography in women age ≥ 50 years; however, the numbers were too small to make definitive conclusions (9,21,39,40). In a recent cost-effectiveness simulation study using a threshold of ≤ €20,000 additional cost per life-year gain, the Dutch screening regimen for BRCA mutations carriers, in which MRI is combined with mammography from age 30 until 60 years, was found to be more cost effective than the British screening recommendations (screening with MRI and mammography only until age 50 years) or the US strategy (screening with MRI and mammography from age 25 years onward) (41). Our study extends this information through IPD meta-analysis. Furthermore, although it remains debatable whether the costs of screening with MRI and mammography beyond the age of 60 years actually outweigh the benefits from a socioeconomic point of view, our results suggest that from a cancer detection perspective, a patient benefit beyond age 60 years seems likely. In fact, although the numbers were much smaller, the incremental increase in sensitivity of adding MRI to mammography in women age ≥ 60 years was similar to what has been observed in younger women.

In this IPD meta-analysis, MRI consistently resulted in much higher sensitivity and lower specificity than mammography alone for all ages. This pattern was also noted in the individual primary studies and systematic reviews conducted thus far focusing on women at high risk of breast cancer because of gene mutation or family history (7,14). In our data, we observed a high proportion of small tumors detected by MRI that were not detected on mammography. In addition, the contribution of mammography was mostly gained through detecting DCIS (half of tumors detected by mammography alone were DCISs). Although some previous studies with relatively smaller numbers of DCIS showed higher sensitivity of mammography than MRI in detecting DCIS (10,11), MRI was more sensitive for detecting DCIS in our IPD meta-analysis, which is consistent with some recent publications (9,42).

An inherent limitation of the IPD methodology is that it depends on the availability of IPD from original studies 43, and we did not have data from all studies. Nonetheless, in our meta-analysis, we had a sample size of 2,033 women, representing the largest-ever analysis to our knowledge of women with BRCA1/2 mutations from high-risk screening trials. Although investigators of six studies declined our invitation to contribute IPD, this only resulted in approximately 716 women with BRCA1/2 mutations not being included, with the number of breast cancers ranging from three to 21 per study (25-29,34). Because the results from noncontributing studies were generally within the range of our meta-analysis estimates, we would not expect their noninclusion to have had a substantial impact on our estimates. Our IPD meta-analysis population is likely to be representative of women with BRCA1/2

mutations; hence, the findings on screening accuracy are likely to be broadly generalizable to women with BRCA1/2 mutations. It should be kept in mind that because most of our data concerned women between ages 30 and 70 years, our estimates are most applicable in this age bracket.

Heterogeneity across the original studies limited previous reviews and study-level meta-analyses from analyzing age-related screening accuracy specifically in women with BRCA mutations. Through the literature search, it was apparent that few of the high-risk studies included only women with BRCA1/2 mutations (9,25). In addition, only five studies reported sensitivity and specificity of MRI and mammography for subgroups with BRCA1/2 mutations (9-11,25,27), and only two studies stratified results by age (9,21). Four studies reported the comparison between MRI alone and the combination of MRI and mammography (21,27,28); however, these used variable thresholds for classifying test results (cutoff point of BIRADS 3 or 4). Therefore, what particularly distinguishes our work is that we were able to pool IPD from contributing studies using a consistent categorization of data and hence to perform meta-analyses stratified by age groups from the largest collective data set of women with BRCA1/2 mutations screened to date, to our knowledge. Because our IPD meta-analysis included studies started when the technique was not routine practice,[43] improvements in interpretation might be expected over time. However, exploring the data in the study, sensitivity and specificity fluctuated without any clear pattern over the years of screening (Appendix Fig A2, online only).

The optimal conceptual model for our IPD meta-analysis would have been a model with a random effect for both participants and studies, assuming that the heterogeneity of sensitivity and specificity were explained by the variation among women as well as studies. Because this model did not converge, we summarized the longitudinal data of each woman to multiple binomials and addressed only heterogeneity across studies. The strength of this model is that it can be easily compared with study-level meta-analyses, although the model has the advantage of using IPD. Furthermore, we were able to model the sensitivity and specificity for three screening regimens simultaneously, while taking into account negative correlation between sensitivity and specificity measures.

In conclusion, evidence from our IPD meta-analysis indicates that screening BRCA1/2 mutation carriers with both MRI and mammography improves screening sensitivity, relative to mammography alone, in women age < 50 as well as ≥ 50 years. Given the evidence from this meta-analysis, it would be reasonable to offer breast MRI screening to women with BRCA1/2 mutations beyond age 50 years and also to reassess any existing recommendations that MRI screening for BRCA1/2 mutation carriers be discontinued at age 50 years.

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APPENDIX

The primary outcome

The primary outcome was sensitivity and specificity of each screening modality. Sensitivity of a screening modality was defined as the number of true positive breast cancers out of the total number of breast cancers. Specificity of a screening modality was defined as the number of true negative cases out of the total number of negative screening visits.

A true-positive breast cancer was defined when there was a positive screening result (BI-RADS 0,3,4,5) which was followed by a pathology proven breast cancer. A false- positive was defined when there was a positive screening result and there was no breast cancer proven by pathology; a positive screen (with no pathology performed) and but a negative imaging test on a short follow-up or up to the next screening round; or no interval cancer detected within one year of follow-up.

A true-negative case was defined as a negative screening result and also a negative screening result at 1-year follow-up by at least one of the screening modalities and no interval cancer. A false-negative patient case was defined as a negative screening result and a breast cancer proven by a pathology test within 1-year of follow-up.

Sensitivity and specificity were estimated by the mixed model in which they were defined by a binomial distribution of having a number of true-positive or negative in a sequence of the total number of screening visits with or without breast cancer.

Generalized Linear Mixed Model

We analysed data at the study level with a random effect for the study and ignored the variance between women. The reason for this was that although we had individual-level outcomes, we were not able to fit a model including random effects for both studies and patients. The repeated measurements were taken care of by summarizing the repeated measurements of each women. The data were summarized to form binomial counts for each woman. The response for a patient was the number of true-positive and true-negative imaging results (ie, counts) and the total number of screening visits with and without a breast cancer detected based on the standard reference. For each women, there were six records according to three modalities and true cancer status. We modelled the counts with a binomial distribution conditionally on the random effects for studies. The fixed effects include: patient age at baseline, true cancer status, screening modality and their interactions. Sensitivity and specificity for each screening modality was modelled separately.

For each study, we had (Y_{i0k}, Y_{i1k}) as the number of true negatives and true positives for women **i** screened with modality **k**. Formally written: Conditionally on the random study effects (U_{0k}, Y_{1k}), the counts (Y_{i0k}, Y_{i1k}) were assumed independently distributed
with

$$Y_{ijk}|U_{jk} \quad u \sim \text{Bin}(n_{ij}, p_{ijk}(u)) \qquad\qquad j = 0,1$$

with logit $P_{ijk}(u) = ß_{0jk} + ß_{1jk} * age_i + u$
i: Subject ith
j: True cancer status (yes *v* no)
k: Screening modalities (MRI, mammography, or combination)
nij: Number of visits for woman i true cancer status **j**
$ß_{0jk}$**:** the intercept for true cancer status **j** and screening modality **k**
$ß_{1jk}$**:** the slope for age for true cancer status **j** and screening modality **k**

The random study effects $((U_{0k}, U_{1k}))$ are assumed to have a bivariate normal distribution with mean zero and covariance matrix Σ_k
given by $\Sigma_k \begin{pmatrix} \sigma^2_{0k} & P_k\sigma_{0k}\sigma_{1k} \\ P_k\sigma_{0k}\sigma_{1k} & \sigma^2_{1k} \end{pmatrix}$.

The model was fitted with the procedure GLIMMIX in SAS software (SAS Institute, Cary, NC), analyzing the data of all modalities simultaneously. The method of estimation was maximum likelihood using the option QUAD with five quadrature points. The differences in sensitivity and specificity between modalities at different levels of age category were estimated using the ESTIMATE statement in the procedure (in logit scale). The inversed logits were used to estimate sensitivity and specificity values from the model based on the LSMEANS statement.

Table A1 Quality assessment of included studies

Study	Representative spectrum?	Threshold specified?	Index tests blinded to one another? (1)	Acceptable reference standard?	Partial verification bias avoided? (2)	Differential verification bias avoided? (3)	Incorporation bias avoided (4)	Reference standard results blinded?	Acceptable delay between index tests?	Acceptable delay between reference and index tests?	Withdrawal explained?	Clinically relevant?
Toronto, Ontario, Canada[9]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Unclear	Yes	Yes
Italy (HIBCRIT I Study) [21]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Unclear	Yes	Yes
United Kingdom (MARIBS) [11]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Unclear	Yes	Yes
Austria [30]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Unclear	Yes	Yes
The Netherlands (MRISC) trial[10]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Unclear	Yes	Yes
Montreal, Quebec, Canada [33]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Unclear	Yes	Yes

Abbreviations: HIBCRIT I, High Breast Cancer Risk Italian 1; MARIBS, Magnetic Resonance Imaging for Breast Screening; MRI, magnetic resonance maging; MRISC, Magnetic Resonance Imaging Screening.

(1) Were MRI and mammography results read independently by different radiologists?
(2) Partial verification bias occurs when not all the study group members receive confirmation by reference standard.
(3) Differential verification bias occurs when study groups receive different reference standard. In this case, in all studies, women with positive imaging test result were referred to biopsy whereas one woman with negative positive imaging test result was confirmed by follow-up.
(4) Incorporation bias occurs when the index test result is used to guide reference standard outcome or a part of the reference standard.

Fig A1 Literature search and study identification

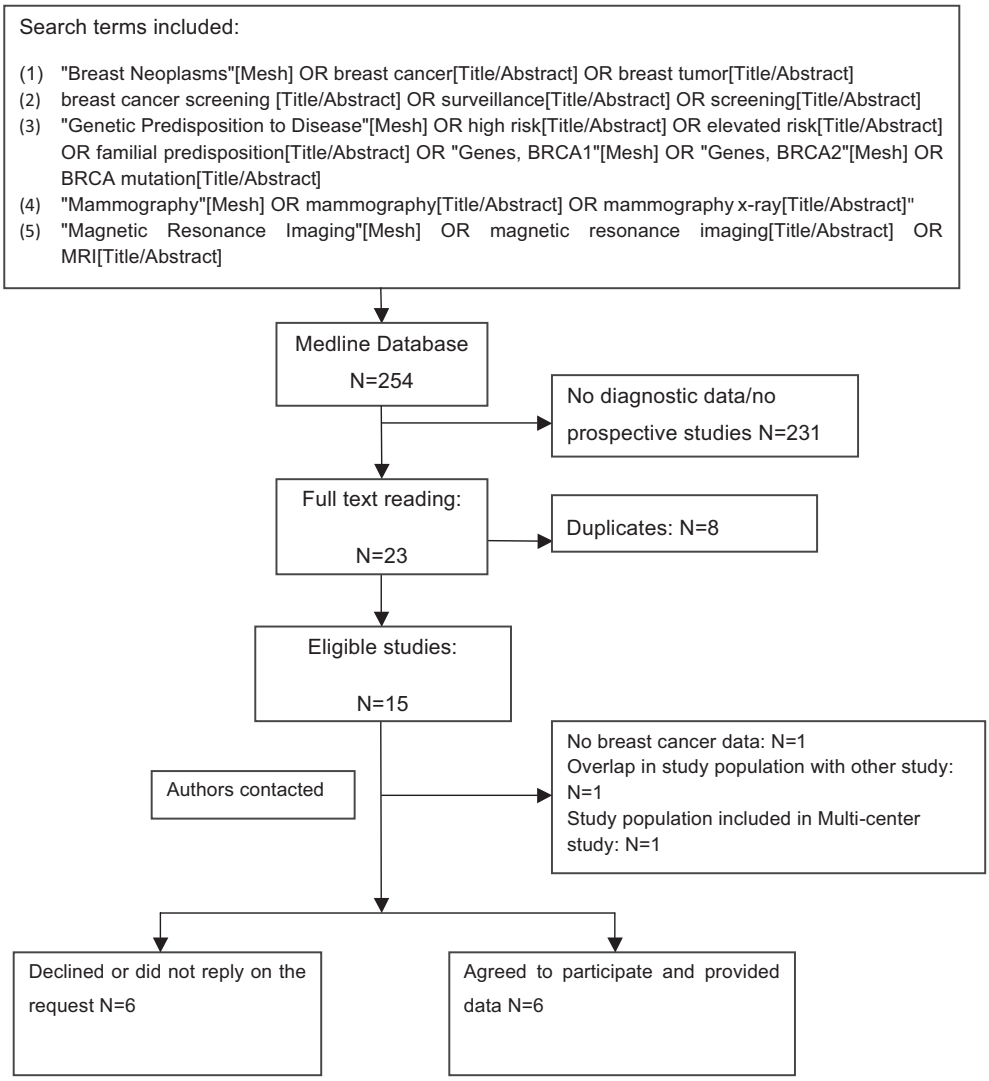
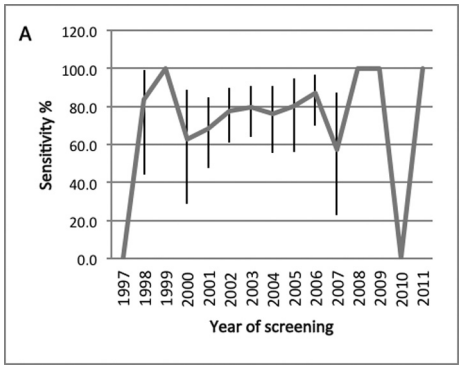
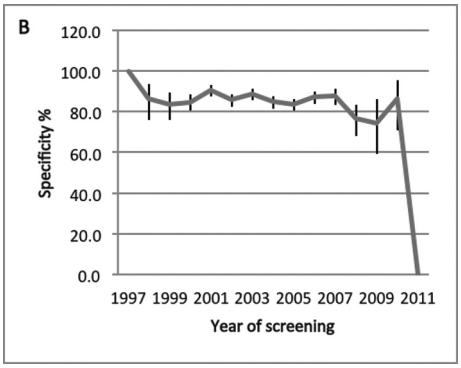
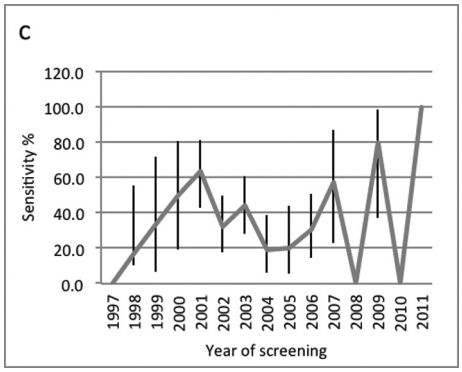
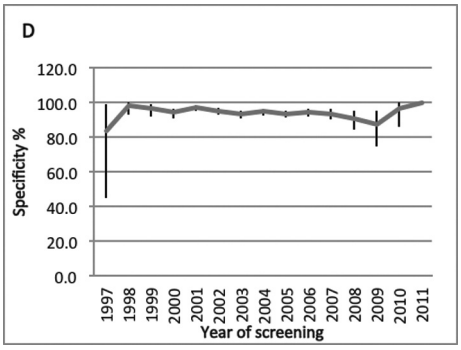


Fig A2. For (A,B) magnetic resonance imaging and (C,D) mammography, (A,C) sensitivity and (B, D) specificity by year of total six studies









8

Preoperative breast MRI can reduce the rate of tumor positive resection margins and reoperations in patients undergoing breast conserving surgery

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American Journal of Röntgenology 2013;200:304-310

ABSTRACT

Objective
In breast cancer patients eligible for breast-conserving surgery, we evaluated whether the information provided by preoperative Magnetic Resonance Imaging (MRI) of the breast would result in fewer tumor-positive resection margins and fewer reoperations.

Subjects and methods
The study group consisted of 123 consecutive patients diagnosed with either breast cancer or ductal carcinoma in situ eligible for breast-conserving surgery, included between April 2007 and July 2010. For these patients a first plan for breast-conserving surgery was made based on clinical examination and conventional imaging. The final surgical plan was made with knowledge of the preoperative breast MRI. The rates of tumor-positive resection margins and reoperations were compared with those of historical control group consisting of 119 patients who underwent 123 breast-conserving procedures between January 2005 and December 2006. The percentage of change in the surgical plan was recorded.

Results
Preoperative breast MRI changed the surgical plan to more extensive surgery in 42 patients (34.1%), mainly to mastectomy (29 patients (23.6%)). Ninety-four patients underwent 95 breast-conserving procedures. Significantly fewer patients had tumor positive resection margins than in the control group (15.8%, 15/95 versus 29.3%, 36/123; $p<0.01$). Patients In the study group underwent significantly fewer reoperations compared with the historical control group (18.9 %, 18/95 versus 37.4%, 46/123; $p<0.01$).

Conclusions
Preoperative breast MRI can substantially decrease the rate of tumor-positive resection margins and reoperations in breast cancer patients eligible for breast-conserving surgery.

INTRODUCTION

Breast-conserving surgery is the standard therapy for early-stage breast cancer. Breast-conserving surgery requires complete removal of the tumor, necessitating histological negative margins to decrease the risk of local recurrence. In case of close or tumor-positive resection margins, a reexcision or mastectomy will be performed to achieve an excision with adequate margins. Consequently, patients eligible for Breast-conserving surgery may require more than one operation. Reoperations are associated with a higher emotional and physical burden for the patient, worse cosmetic outcome and higher costs and have to be reduced to a minimum.

Accurate preoperative assessment of tumor size and disease extent is essential for surgical planning. Clinical examination, mammography and ultrasound are the standard techniques to assess tumor size and location. However, clinical examination correlates poorly with histopathological tumor size (1). Mammography is able to detect clinically occult cancer, including the majority of ductal carcinoma in situ (DCIS), but tends to underestimate the size of invasive breast cancer as well as DCIS, multifocality, and multicentrality, especially in patients with dense fibroglandular tissue (1,2). Ultrasound is limited in the detection of both multifocality and ductal carcinoma in situ (1). MR is the imaging modality with the highest sensitivity and can detect mammographically, sonographically and clinically occult breast cancer (3-7). Breast MRI has a better correlation with histology concerning size than mammography for DCIS as well as invasive breast cancer (8-11). Several studies (6, 10, 12) have shown that when preoperative MRI is added to the work-up of patients with early stage breast cancer the detection of clinical and mammographically unsuspected multifocal, diffuse or bilateral cancer will change treatment from lumpectomy into wider local excision, mastectomy or contralateral surgery in a substantial proportion of patients. However, there is no evidence that preoperative MRI improves a patient's care or prognosis.

The primary objective of this study was to evaluate whether the additional information of preoperative MRI of the breast would result in a reduction of lumpectomies with tumor-positive resection margins and a reduction of reoperations in comparison with a historical control group. Second, we aimed to determine the percentage of change in the surgical plan as a consequence of the additional information from the preoperative MRI and whether this change was justified by the pathology results.

SUBJECTS AND METHODS

In this before and after study we evaluated the rate of tumor-positive resection margins and reoperations in breast cancer patients (including DCIS) who underwent a preoperative MRI of the breast and who were scheduled to undergo breast-conserving surgery. We compared the results of the study group (preoperative MRI group) with that of a historical control group. Second, the percentage of change in the surgical plan as a consequence of the additional information from the preoperative MRI was evaluated. Approval for this study was obtained from the local ethical committee. All patients gave written informed consent.

Patients

From April 2007 till July 2010, 131 consecutive patients with a histopathologically proven breast cancer or DCIS who were eligible breast-conserving surgery were included in this study. All 131 patients underwent a preoperative MRI as extra investigation. Exclusion criteria were contra-indications for MRI. Eight patients were excluded from evaluation because of benignity of the lesion (n=1), metastatic disease (n=1), operation abroad (n=1), rejection of treatment (n=1) and neo-adjuvant chemotherapy (n=4). The remaining 123 patients constitute the preoperative MRI group (Table 1).
The historical control group consisted of all patients who underwent breast-conserving surgery between January 2005 and December 2006. These 119 patients underwent 123 lumpectomies for 132 lesions: 28 DCIS (21.2%) and 104 invasive malignancies (78.8%) (Table 1).

Imaging protocols

Mammography was performed with a digital mammographic unit (Selenia, Hologic). Standard mediolateral oblique and craniocaudal projections were obtained with additional views when necessary. For ultrasound, a Prosound Alpha unit (Aloka) with a linear array 13-MHz transducer was used.
Dynamic contrast-enhanced preoperative MRI performed using a 1.5-T system (Signa Exite HDXT, GE Healthcare) with a dedicated double breast coil. Before scanning venous access was established in an antecubital vein. All patients were investigated in prone position. First we performed a 3D axial vibrant multiphase with the following parameters: TR/TE, 5/2; flip angle, 10°; FOV, 340 mm; acquisition time, 72 s; and slice thickness, 2.2 mm. Then a bolus of contrast material (gadobutrol, Gadovist, Bayer Schering Pharma)

Table 1 Patient and tumor characteristics of the preoperative MRI Group and the historical control group

Parameter	Preoperative MRI group (123 patients with 140 malignant lesions)	Historical control group (119 patients with 132 malignant lesions)	p
Age (y)	Mean, 54.0; range 26-73	Mean, 55.2; range 29-79	0.32
Palpable lesions	73 (52.1)	61 (46.2)	0.23
Visible on mammography	112 (80.0)	110 (83.3)	0.98
DCIS	22 (15.7)	28 (21.2)	0.24
Size (mm)	Mean, 31.5; range 4-90	Mean, 21.4; range 4-50	0.03
Invasive malignancy[a]	118 (84.3)	104 (78.8)	0.24
Size (mm)	Mean, 21.5; range 4-80	Mean,16.2; range 3-55	<0.01
Invasive ductal carcinoma	101 (85.6)	95 (91.4)	0.17
Invasive lobular Carcinoma	12 (10.2)	4 (3.8)	
Other	5 (4.2)	5 (4.8)	

Note: Data in parentheses are percentages. DCIS= ductal carcinoma in situ.
[a]with or without accompanying DCIS.

was administered using an automated injector at 2 ml/sec followed by 20-mL saline flush at the same injection rate. The standard dose was 7.5 mL. In case of very small or very large women the dose was adjusted and 0.1 ml/kg body weight was given. Thereafter, five contrast-enhanced axial vibrant multiphase series were made. Subtraction images were obtained with the use of a software subtraction function. For evaluation, a dedicated breast MRI workstation (CADstream, Confirma) was used. Experienced breast radiologists (3-17 years of experience) evaluated the ultrasound, mammographic and MRI examinations according to the Breast Imaging Data and Reporting System or BI-RADS lexicon (13).

Additional BI-RADS 3, 4 and 5 lesions found by MRI were investigated by second-look ultrasound and/or reevaluation of the mammographic examination. In case an additional BI-RADS 3 lesion could be identified FNA or biopsy was performed, otherwise follow-up MRI was advised. In case of additional BI-RADS 4 or 5 lesions FNA or biopsy was always performed. This was done under stereotactic, ultrasound or MR guidance.

Surgical plan

For all included patients a first plan for breast-conserving surgery was made based on clinical examination, mammography, ultrasound and fine needle aspiration (FNA) or core or vacuum biopsy. Subsequently, the patients underwent a dynamic contrast enhanced preoperative MRI. The additional information from the preoperative MRI, including the cytology and histology results, was discussed by a multidisciplinary team of surgeons, oncologists, pathologists and radiologists, who were all specialized in breast cancer, to make a final plan of treatment. The MRI examination was discussed in detail with the surgeon who was scheduled to operate the patient.

Histopathological evaluation

Histopathological evaluation of the specimen was performed according to national guidelines, including extensive sampling of the lesion and the resection margins.

An invasive lesion with or without surrounding DCIS was defined as completely excised in case of a margin of tumor free tissue around the tumor and the DCIS. Invasive tumor or surrounding DCIS reaching the edge at a limited extent was called focally positive, which is defined as less than two microscopical low power fields (10x). According to the Dutch guidelines (14, 15) this was in principle, not an indication for reexcision. More extensive tumor tissue in the specimen edge (more than focally positive) was considered as positive and was indication for reoperation. In case of pure DCIS a reoperation was indicated in case the tumor free margin was less than 5 mm.

Data analysis

Continuous data are presented as means and SDs. Discrete data are given as numbers and percentages. To assess the differences in the patients and tumor characteristics between the pre-operative MR group and the historical control group, two-sample Student t tests or the Mann-Whitney U test was used for continuous data if appropriate, whereas the chi-square test was used for dichotomous data. To compare the differences in positive resection margins and rate of reoperations between the two groups, a multivariable logistic regression analysis was performed. The co-variables included were the group and size of the lesions. The differences between the groups were expressed as odds ratios (ORs) and 95% CI. To compare the differences in positive resection margins and rate of reoperations between the two groups for DCIS and invasive malignancy separately, an interaction term (group* DCIS versus

invasive) was added to the model. A significance level of .05 (two-sided) was considered statistically significant. Calculations were performed by using Stata software (version 12, Statacorp).

RESULTS

In four of the 123 patients of the preoperative MRI group, multifocal and contralateral lesions were already found with conventional imaging. MRI detected 13 additional lesions in 12 patients (9.7%): in four patients (3.2%), synchronous contralateral breast cancer, in three patients, multifocal, and in five patients, multicentric malignancy. In total 140 malignant lesions were detected in 123 patients. The size of the DCIS lesions as well as the size of the invasive lesions were significantly larger in the preoperative MRI group compared with the historical control group ($p=0.03$ and $p< 0.01$ respectively). For all other parameters no significant differences were found between the two groups.

Change in surgical management

In 13 patients (10.5%) a more extensive lumpectomy (Fig. 1) or a contralateral lumpectomy was performed as the result of the information obtained from the MRI examination. In two patients (1.6%) MRI overestimated the tumor extent and the wider excision proved to be incorrect. In 29 patients (23.6%) 33 mastectomies were performed. In 10, the larger disease extent seen on MRI was confirmed by histopathological examination (mean size 55.5 mm) and the change from breast-conserving surgery to mastectomy was correct. In seven patients, the surgical plan was correctly changed to mastectomy because of preoperatively proven multifocal (n=1) or multicentric disease (n=4) or because of a central position of a relatively large lesion (n=2). The treatment decision for nine patients was changed during the diagnostic route and the patients choose to undergo mastectomy. In three 3 of those nine patients, the treatment decision was changed because a giant fibroadenoma in the same breast had to be removed also (n=1), fear to undergo radiotherapy (n=1) and a BRCA1 mutation (n=1). In three patients (2.4%) the disease extent on MRI proved to be overestimated and the mastectomy pathologically unnecessary. This finding involved patients in whom the additional lesion was not accessible for MRI- guided biopsy, a patient with an additional biopsy proven malignancy but overestimated lesion size, and a patient in whom MRI-guided biopsy was advised but erroneously not performed. Four

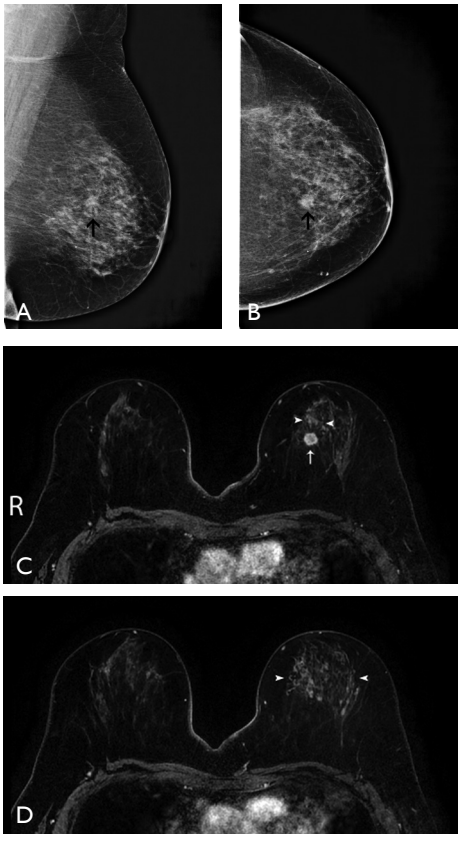

Fig.1 Screening mammography (mediolateral oblique (A) and craniocaudal view (B)) in a 65-year-old woman shows lobulated, ill-defined mass (arrow) classified as BI-RADS IV at a middle depth in the upper-inner quadrant of the left breast. Some unsuspicious round microcalcifications are seen in and around mass. Ultrasound- guided biopsy showed invasive ductal adenocarcinoma. Preoperative gadolinium-enhanced T1-weighted fat-suppressed axial vibrant multiphase breast MRI show proven malignancy as a lobulated mass with rim enhancement (C, arrow) within area of clumped enhancement suspicious for ductal carcinoma in situ (C,D arrowheads). Therefore, the surgical plan was changed from standard lumpectomy to a more extensive lumpectomy. Histopathologic diagnosis was grade 1 invasive ductal adenocarcinoma 0.9 mm diameter, surrounded by 4 cm grade 2 ductal carcinoma in situ.

patients with a synchronous contralateral breast cancer chose to undergo bilateral mastectomy.

Tumor positive resection margins

Ninety-four patients of the preoperative MRI group underwent 95 breast conserving operations. In the preoperative MRI group significantly fewer patients had tumor- positive resection margins than in the historical control group (15.8% versus 29.3%; adjusted OR, 0.33; 95% CI 0.15 to 0.69; p<0.01) (table 2a). In the preoperative MRI group significantly fewer patients had tumor-positive resection margins in case of invasive malignancy (14.3% versus 26.0%; adjusted OR 0.37 (95% CI 0.16 to 0.82; p=0.02), whereas for DCIS there was no statistically significant difference between preoperative MRI group and the historical control group (27.2% versus 40.7%; adjusted OR 0.28 (95% CI 0.05 to 1.55; p=0.14) (table 2).

Rate of reoperations

In the preoperative MRI group, significantly fewer patients underwent a reoperation compared to the historical control group (18.9 % versus 37.4%; adjusted OR 0.29; 95% CI 0.15 to 0.58; p<0.01) (table 2b). In the preoperative MRI group, significantly fewer patients had a reoperation in case of inva-

Table 2. Tumor-positive resection margins in the preoperative MRI group in comparison with the historical control group

	Tumor positive resection margins			
Parameter	Preoperative MRI group	Historical control group	Adjusted Odds Ratio[a] (95% CI)	Adjusted p[a]
All lesions	15/95 (15.8)	36/123 (29.3)	0.33 (0.16 - 0.69)	< 0.01
Invasive malig nancy[b]	12/84 (14.3)	25/96 (26.0)	0.37 (0.16 - 0.82	0.02
DCIS	3/11 (27.2)	11/27 (40.7)	0.28 (0.05 - 1.55)	0.14

Note Except for 95% CI, data in parentheses are percentages. DCIS= ductal carcinoma in situ.
[a]Adjusted for size of lesions.
[b]with or without accompanying DCIS.

Table 3. Rate of reoperations in the preoperative MRI group in comparison with the historical control group

	Rate of reoperations			
Parameter	Preoperative MRI group	Historical control group	Adjusted Odds Ratio[a] OR (95% CI)	Adjusted p[a]
All lesions	18/95 (18.9)	46/123 (37.4)	0.29 (0.15 - 0.58)	< 0.01
Invasive malig nancy[b]	12/84 (14.3)	25/96 (26.0)	0.38 (0.17 - 0.84)	0.02
DCIS	6/11 (54.5)	21/27 (77.7)	0.34 (0.08 - 1.53)	0.16

Note Except for 95% CI, data in parentheses are percentages. DCIS= ductal carcinoma in situ.
[a]Adjusted for size of lesions.
[b]with or without accompanying DCIS.

sive malignancy (14.3% versus 26.%; adjusted OR 0.38; 95% CI 0.17 to 0.84; p=0.02), whereas for DCIS there was no statistically significant difference between Pre-op MR Group and the Historical Control group (54.5% versus 77.7%; adjusted OR 0.34; 95% CI, 0.07 to 1.52; p=0.16) (table 3).
The average specimen weight in de preoperative MRI Group was 64.1 g (range, 6-226 g) versus 57.3 g (range 12-144 g) in the historical control group and was not statistically different (5.6 g; 95% CI -5.6 to 17.0; p=0.32)

DISCUSSION

The main purpose of this study was to investigate whether the additional information of preoperative MRI in the workup of patients eligible for breast-conserving surgery reduces the percentages of tumor positive resection margins and reoperations. We found that the overall percentages of positive resection margins as well as the percentage of reoperations in the preoperative MRI group were significantly lower than those of the historical control group.
One could argue whether this positive outcome is indeed a consequence of the preoperatively added MRI or that it is the result of differences in criteria for reoperation, differences between the two groups or other causes. Comparison of both groups showed that the lesions in the preoperative MRI group were significantly larger, especially the DCIS. In order to take that into account we performed a multivariable logistic analysis with size of lesions as co-variable. For all other parameters no significant differences were found. Also the criteria for reexcision were uniform over the study period and the specimen weights did not differ significantly. Furthermore, the same surgeons operated on the patients in both groups using the same techniques. Only the residents-in-training changed. These conditions should plead for a favourable effect of the preoperatively added MRI.
For invasive breast cancer, the percentages of both tumor-positive resection margins and reoperations decreased significantly after preoperatively added MRI. However, for the DCIS lesions the improvement did not reach significance. Some explanation can be found in the disease extent. In 4 patients the size of DCIS on pathology measured more than 5 cm. This was in all but one patient correctly visible on mammography or MRI. Patients with such an extensive DCIS may need to undergo a mastectomy but these patients had the explicit wish to undergo breast-conserving surgery. In such cases, the risks of margin involvement and a second operation is much higher, which was discussed with the patients.
In multiple studies, the impact of the preoperative MRI on surgical management has been investigated; however, few discuss the influence of preoperative MRI on the rate of positive resection margins and reoperation. In most of these studies little or no (16-18) or even an unfavourable effect (19) is seen. A significant reduction in the rate of incomplete excisions was found in the study by Mann et al. (20) when preoperative MRI was added to conventional work-up. They retrospectively evaluated 267 patients with invasive lobular carcinoma who underwent breast-sparing surgery. In the group without MRI, 27% of excisions had positive margins versus 9% in the MRI group. In 2010 the results of the Comparative Effectiveness of MRI in Breast Cancer (COMICE) trial (21) were published. This English multicenter trial was the first and, until, the largest randomized controlled study on this subject with the per-

centage of reoperations as primary end point. The reoperation rate in two groups of about 800 patients with and without preoperative MRI was compared and proven to be the same: 18.7% and 19.3% respectively. Although a randomized controlled trial provides the best available evidence, these results are surprising and would signify that the information from MRI does not benefit the patient at all. The COMICE trial, however, should be interpreted in the light of a number of important limitations. The study involved 45 centers with different levels of MRI experience and limited availability of MRI-guided biopsy (21,22). In addition, a large number of patients (14%) were recruited by surgeons who recruited only a few patients a year. Although the authors argue that this reflects the real world it will undoubtedly have negatively influenced the MRI evaluation and the study results. An increased level of experience of radiologists is related to improved MRI interpretation (23,24). The fact that MRI is performed in prone position whereas surgery is performed in supine position partly explains why the additional information from the MRI is not automatically translated into better surgical results.

We believe that to improve surgical outcomes, not only the expertise of the radiologist counts (in our clinic there are more than 15 years of experience in breast MRI), but also it is obligatory for the surgeon to be familiar with the MR images. Consequently, in our study, all patients were not only discussed by a multidisciplinary team but their MRI examinations were also thoroughly reviewed with the operating surgeon to better formulate a treatment plan. The MR images were visible in the operating theatre during the procedure.

Our second goal was to investigate the influence of preoperative MRI on the surgical plan. In agreement with other studies (12) we found that preoperative MRI changed the surgical plan to more extensive surgery in a substantial proportion of patients (34%), mainly to mastectomy (26%). This effect of more extensive surgery and, in particularly the higher mastectomy rate, has raised the concern of overtreatment in patients undergoing MRI staging (25-27). The low recurrence rate in patients who underwent breast-sparing surgery without a preoperative MRI could be explained if tumor foci left behind in the breast (28), are successfully eliminated by radiotherapy and hormonal or chemotherapy.

In the current study, MRI identified 17 patients (13.8%) preoperatively for whom conversion to mastectomy was histopathologically justified. We made the assumption that removal of the additional multifocal and multicentric lesions (mean size 13.5 mm, range 5-35 mm) was beneficial for the patient. Or in other words, why should a MRI- detected malignancy be less clinically relevant than a mammographically detected one, as sometimes is suggested? On the other hand, we saw that adding MRI in the preoperative workup influenced the patients' treatment decisions: six patients chose to undergo mastectomy and four of them with synchronous contralateral breast cancer

chose to undergo bilateral mastectomy. Another three patients in whom the presumed larger disease extent was not confirmed underwent mastectomy. These 9 patients (7.3%) underwent a medically unnecessary mastectomy. Histological verification of the presumed more extended malignancy is mandatory before converting from breast conservation to mastectomy. In 3 other patients the change to mastectomy was not MRI related.
In the majority of patients with breast cancer, preoperative breast MRI will offer no additional information (12). Complementary value can be expected in patients with a high mammographic density, in case of discrepancy between imaging and clinical findings and between imaging findings, in patients with invasive lobular carcinoma and with high grade DCIS (6,9,20). Selecting these patients for preoperative MRI would reduce the rate of medically unnecessary mastectomy rate.

The major limitation of this study is its non-randomized design. However, apart from lesion size for which analyses were adjusted, there were no significant differences between the two groups and other factors. Despite the modest size of our study, the data show that discussing preoperative MRI results with the operating surgeon and having the MRI examination in the operating theatre have a benefit in empowering breast-conserving surgery. A major limitation of the study was the small sample size and especially the small size of the subgroups. Larger randomized controlled trials are needed to determine the role of MRI in breast cancer staging.

CONCLUSION

We compared the results of our study group with those of a historical control group and found a substantial decrease in the rate of tumor-positive resection margins and reoperations in breast cancer patients eligible for breast-conserving surgery when MRI is added to the work-up. Discussing preoperative MRI results with the operating surgeon and having the MRI examination in the operating theatre can have a beneficial impact on the surgical approach and resection margins. MRI is better than mammography in identifying patients who require a mastectomy but also makes more patients choose for mastectomy.

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9

MR imaging-guided sonography followed by fine-needle aspiration cytology in occult carcinoma of the breast

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American Journal of Roentgenology. 2000;174:1079-1084

ABSTRACT

Objective

In patients with axillary metastases as clinical evidence of possible occult breast cancer, a combined approach of MR imaging, sonography, and aspiration biopsy cytology was evaluated.

Subjects and Methods

Thirty-one women with metastatic adenocarcinoma in their axillary lymph nodes originating from an unknown primary site underwent MR imaging of the breast because physical examination and mammography findings were normal. Twenty of the 31 women had no history of malignancy, 10 had been previously treated for contralateral breast cancer, and one patient had nodal metastases in the contralateral axilla at the time breast cancer was detected. When a contrast-enhancing lesion was revealed on MR imaging of the breast, sonography and fine-needle aspiration cytology were also performed.

Results

MR imaging revealed the primary breast cancer in eight (40%) of the 20 patients without a history of malignancy. MR imaging of the breast revealed a second primary cancer in three (27%) of the 11 patients with previous or simultaneous breast cancer. All lesions were identified with sonography and verified by cytology and histology.

Conclusion

In women with axillary lymph node metastases from adenocarcinoma, MR imaging of the breast should be added to clinical examination and mammography before defining the breast cancer as occult. The combined approach of MR imaging, sonography, and aspiration fine-needle cytology is a good alternative to the MR imaging-guided biopsy.

INTRODUCTION

Breast cancer presenting as isolated axillary nodal metastases without any clinically or radiologically detectable breast tumor is an uncommon presentation of a relatively common disease first described by Halsted (1) in 1907. The overall incidence of breast cancer presenting with axillary metastases is estimated at less than 0.5% of all women with breast cancer (2-4). If after clinical examination and mammography no primary breast cancer is found, the cancer is defined as occult.

A potential source of metastatic adenocarcinoma in axillary lymph nodes is a previously treated carcinoma of the contralateral breast; however, patients with a previous history of breast cancer also have a significantly higher risk (as much as 2-6 times) of developing a second primary cancer in the other breast. In these patients, knowing whether the lymph node cancer metastasis originated from the first malignancy or from a second primary cancer in the other breast is important (5,6).

Several groups of investigators have shown that MR imaging can reveal a mammographically and clinically occult breast cancer (7-13); however, in each study, the number of patients was small. Morris et al. [11] found the occult malignancy with MR imaging in nine of 12 patients presenting with axillary metastases of an unknown primary cancer. Beatty et al.(12) found the occult breast cancer in 15 of 20 patients presenting with axillary nodal metastases. Davis et al. (9) also found occult breast cancer and performed wire localization using MR imaging. Identification of an otherwise occult malignancy with MR imaging leads to optimal therapeutic decisions and dispels the patient's uncertainty.

The aim of our study was to evaluate the combined role of MR imaging, sonography, and cytology in patients with axillary metastases as clinical evidence of a possible occult breast cancer and in patients with previous or simultaneous breast cancer and contralateral axillary nodal metastases. MR imaging combined with sonographically guided biopsy was investigated as an alternative to MR imaging-guided biopsy, which is a more extensive, less cost-effective, and less available method.

SUBJECTS AND METHODS

Between January 1995 and July 1998, 31 consecutive patients with metastatic adenocarcinoma in the axillary lymph nodes originating from an unknown primary site were prospectively examined with MR imaging of the breast. The women were 28-79 years old (mean, 51 years).

In this study, the histopathological findings of all axillary masses were lymph nodes containing metastases from an adenocarcinoma, possibly originating from a primary breast cancer. Pathology of the lymph nodes was evaluated by fine-needle aspiration cytology (three patients) or by histologic examination of the surgically excised lymph node (28 patients). In 25 of these 28 patients, a histologic examination was performed instead of an axillary lymph node dissection.

Twenty patients had no history of malignancy. In the 10 patients with a history of contralateral breast cancer, the metastatic lymph node became evident after a period of 3-17 years. Another patient had lymph node metastasis in the contralateral axilla at the time breast cancer was detected.

MR imaging of the breast was performed in the patients with no history of malignancy because clinical examination and mammographic findings were interpreted as negative. In patients with previous or simultaneous contralateral breast cancer, MR imaging of the breast was performed to exclude or detect a second primary cancer. Sixteen patients were referred to us from other hospitals for MR imaging of the breast. Physical examination and mammography were performed at those hospitals. We reviewed the mammograms at the time of the MR imaging. In our hospital, mammography was performed on a Senographe 600T unit (General Electric Medical Systems, Milwaukee, WI) with a Kodak film-screen combination (Eastman Kodak, Rochester, NY). Standard oblique and craniocaudal projections were obtained with additional magnification views when necessary. The mammography of 15 patients revealed dense mammographic fibroglandular tissue; 16 patients had mild to moderate fibroglandular breasts.

All patients underwent MR imaging of the breast at our institution, performed with a 1.5-T MR imaging system (Vision; Siemens, Erlangen, Germany). Before scanning, venous access was established in a cubital vein through which a bolus of contrast material, consisting of 20 ml of gadopentate dimeglumine (Magnevist; Schering, Berlin, Germany) was administered during the examination. The women lay prone with the breasts suspended in a double breast surface coil.

After an initial localizer, a fat-suppressed short tau inversion recovery (STIR) T2 turbo spin-echo sequence was performed with the following scan parameters: field of view, 350 × 350 mm; contiguous axial slice, 5-mm thickness; matrix size, 256 × 256; TR/TE, 9128/60 msec; scan time, 3 min 11 sec; ac-

quisitions, one; inversion time delay, 150 msec; echo-train length, 11; and flip angle, 180°. Next, gradient-echo T1-weighted imaging was performed, initially with a two-dimensional fast low-angle shot (FLASH) sequence (15 patients). Since January 1997, a three-dimensional FLASH sequence (16 patients) has been performed before and 1, 3, and 5 min after contrast administration. The two-dimensional scan parameters were field of view, 320 × 320 mm; axial slice, 4-mm thickness; matrix size, 256 × 256; TR/TE, 290/5; scan time, 1 min; acquisitions, one; and flip angle, 90°. The three-dimensional scan parameters were field of view, 160 × 320 mm; coronal slice acquisition effective slice, 1.5-mm thickness; and reformatted axial slice, 4-mm thickness; matrix size, 256 × 256; TR/TE, 8.1/4; scan time, 1 min 26 sec; acquisitions, one; and flip angle, 20°. Subtraction images were obtained with the use of a software subtraction function.

The breast MR images were interpreted by consensus of two radiologists who were aware of the clinical history and mammographic information. Any regional or focal contrast enhancement in the breast was considered abnormal and possibly malignant. Regional enhancement was defined as an area of enhancement without discrete borders. The border characteristics of focal enhancing lesions were examined. Ill-defined, irregular, or spiculated borders and peripheral enhancement were considered suggestive of malignancy. MR imaging was followed by sonography when regional or focal enhancement was seen and by fine-needle aspiration cytology when a lesion was identified. The biopsy technique used was similar to that described by Fornage (13). For sonography of the breast, a 128XP/(ART) unit (Acuson, Mountain View, CA) with a 7.5-MHz linear array transducer was used. Three patients underwent sonography before MR imaging. In patients with negative MR imaging findings, the follow-up period was 12-53 months (mean, 25 months).

RESULTS

In the group of patients without known malignancy, MR imaging detected primary breast cancer in eight (40%) of 20 patients. In the group of patients with previous breast cancer, MR imaging revealed a second primary cancer in three (33%) of 10 patients (Fig. 1). In the patient presenting with breast cancer and simultaneously metastatic contralateral lymph nodes, MR imaging showed only the malignancy already detected on mammography and no second primary cancer in the other breast.

In total, MR imaging revealed breast cancer in 11 (36%) of the 31 patients. In these patients, MR imaging showed 11 enhancing lesions in nine patients (two patients each had two lesions) and two enhancing areas in two patients.

These patients underwent subsequent MR imaging—guided sonography. All 13 lesions were identified on sonography so that fine-needle aspiration cytology could be performed. Malignancy was proven in all patients. In three patients, no lesions were found on sonography before MR imaging; however, lesions were seen on subsequent MR imaging-guided sonography. If breast conservation therapy was preferred by the patient, lumpectomy was performed after sonographic localization, depending on the histologic findings.
Infiltrating ductal carcinoma was diagnosed in nine patients; infiltrating lobular carcinoma was found in two patients. In four patients, the malignancy was multifocal or diffusely growing. The range in size of the lesions was 6-50 mm (mean, 16 mm). After initial retrospective mammographic evaluation, malignancy was identifiable as a nonsuspicious density in one patient and as a small cluster of microcalcifications in another. In the two patients with a large infiltrating lobular carcinoma (diameter, 50 mm), the tumor was vaguely palpable after MR imaging identification. Of the 20 patients with negative MR imaging findings, further clinical workup (physical examinations and CT) revealed a bronchogenic adenocarcinoma in three patients and a melanoma in one patient. On follow-up, breast cancer manifested as a palpable lesion (10 mm) in only one patient, 8 months after the MR imaging. In a retrospective analysis, the MR imaging findings of this patient were interpreted as negative.
In the remaining 15 patients with negative MR imaging findings, no malignancy became evident during the follow-up period. Thirteen of these patients were treated with axillary lymph node dissection, 12 of 15 patients received hormonal therapy or chemotherapy, and eight of 15 patients received radiation therapy. A mastectomy was performed in one patient and the mastectomy specimen showed no malignancy.

DISCUSSION

In women, isolated axillary lymph node metastasis without an obvious clinical primary site most often originates from the breast. In addition to breast cancer, many other adenocarcinomas are known to metastasize to axillary lymph nodes. Most commonly, these adenocarcinomas originate from the lung, thyroid, stomach, colorectum, and pancreas (15); however, axillary metastases are rarely the first presentation of the disease in these adenocarcinomas. When neither clinical nor mammographic examination reveals a primary tumor, an occult breast cancer is presumed.
In the past, the standard therapy for these occult primary cancers, staged as TX N1 M0 (stage II), has been mastectomy and axillary lymph node dissection, with or without radiation therapy; however, the patient survival rate is

not improved with mastectomy (16,17) and the prognosis in this stage is determined by the number of nodes involved and the biologic behavior. When the primary tumor in the breast can be detected, it is possible to choose optimal local treatment. The detection of a second primary cancer in patients previously treated for contralateral breast cancer determines the prognosis and offers the opportunity for optimal local treatment in this patient group as well. MR imaging of the breast is the examination with the highest sensitivity for the detection of invasive breast cancer (91-95%) (18-21); therefore, MR imaging of the breast is advocated to identify otherwise occult cancers in patients with or without a history of breast cancer. In the future, when MR imaging can detect occult primary cancers, breast-sparing approaches to treatment will be more often considered for these otherwise occult malignancies. In addition,

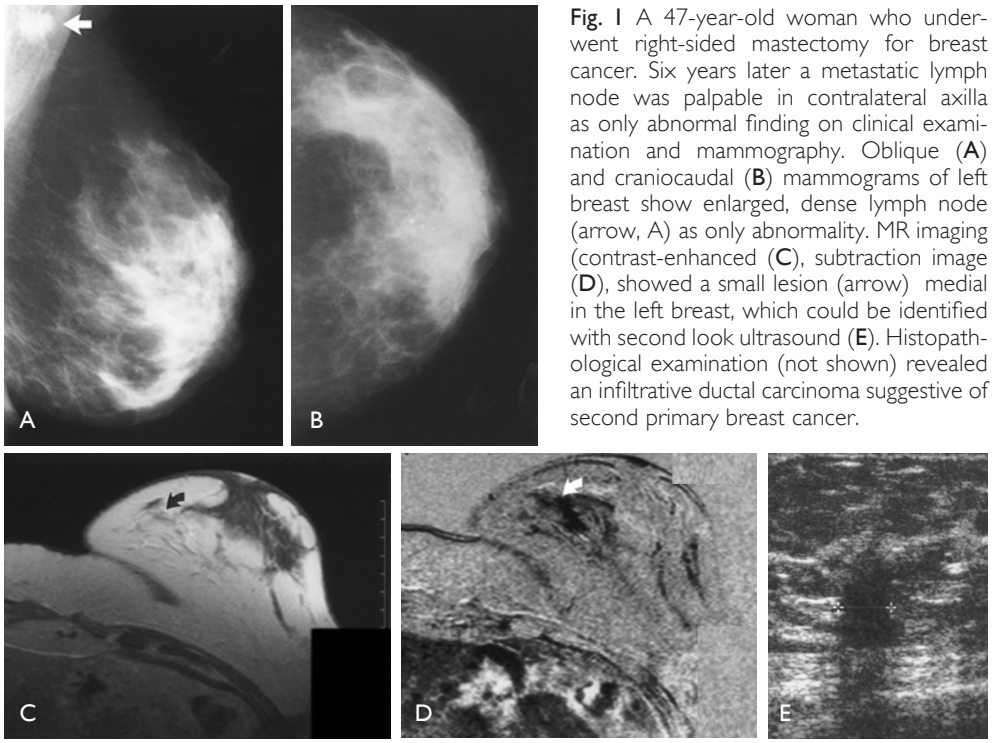

Fig. 1 A 47-year-old woman who underwent right-sided mastectomy for breast cancer. Six years later a metastatic lymph node was palpable in contralateral axilla as only abnormal finding on clinical examination and mammography. Oblique (**A**) and craniocaudal (**B**) mammograms of left breast show enlarged, dense lymph node (arrow, A) as only abnormality. MR imaging (contrast-enhanced (**C**), subtraction image (**D**), showed a small lesion (arrow) medial in the left breast, which could be identified with second look ultrasound (**E**). Histopathological examination (not shown) revealed an infiltrative ductal carcinoma suggestive of second primary breast cancer.

when a tumor is detected on MR imaging in patients undergoing neoadjuvant chemotherapy rather than surgery as first-line treatment, tumor response can be monitored with follow-up MR imaging.

Although MR imaging of the breast has a high sensitivity, specificity is low and variable (37-86%) (18-21). Signal-intensity curves of benign and malignant lesions often show a considerable overlap because strong contrast enhance-

ment is seen not only in carcinomas but also in nonmalignant lesions and even in normal breast parenchyma (22-24). In our institution, every enhancing lesion or region on MR imaging is considered possibly malignant and followed up with sonography to perform fine-needle aspiration cytology. The combination of MR imaging and cytology (25) provides a high sensitivity as well as a high specificity. In 11 (36%) of 31 patients, the occult carcinoma could be seen with MR imaging. All these lesions were identified with MR imaging—guided sonography, and malignancy was confirmed with subsequent fine-needle aspiration cytology. Some patients had already undergone sonography of the breast with negative findings before the MR imaging examination. With previous MR images for reference, the sonographer knows where to look for the lesions and consequently will find small carcinomas and carcinomas with less typical malignant features, confirming that sonography is most useful when performed on targeted areas (26,27) (Fig. 2). One can start the search for an occult breast carcinoma with a less expensive sonographic screening, especially when MR imaging is not available; however, we agree with Jackson et al. (26) that sonography alone should not be used to examine breasts because, as a screening technique, sonography has unacceptably high false-positive and false-negative rates.

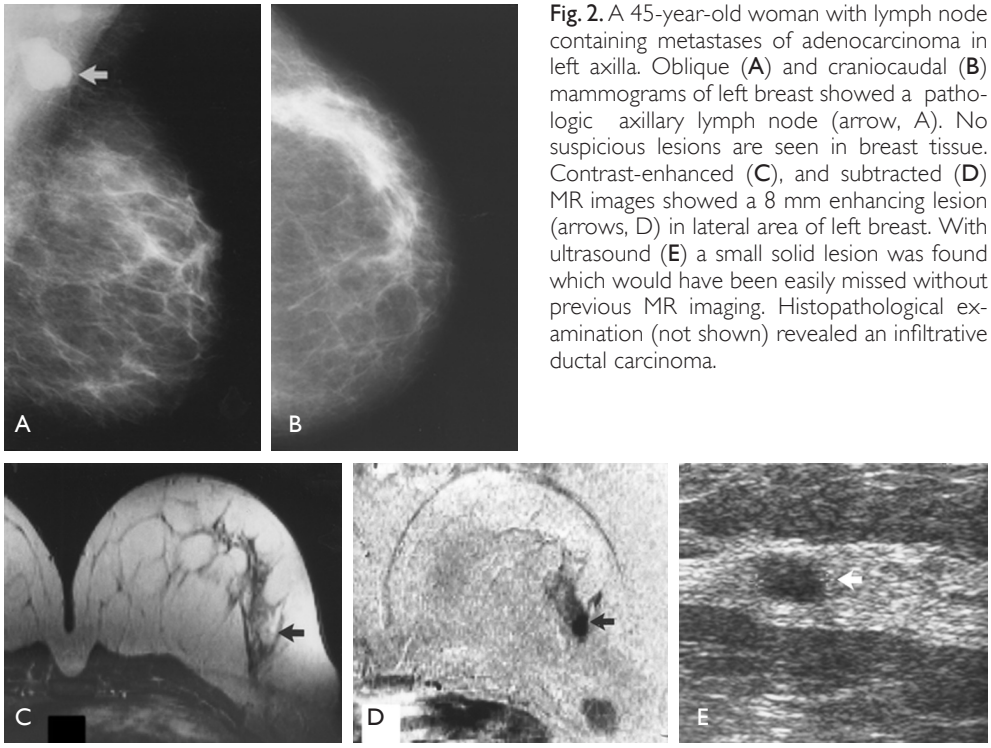

Fig. 2. A 45-year-old woman with lymph node containing metastases of adenocarcinoma in left axilla. Oblique (**A**) and craniocaudal (**B**) mammograms of left breast showed a pathologic axillary lymph node (arrow, A). No suspicious lesions are seen in breast tissue. Contrast-enhanced (**C**), and subtracted (**D**) MR images showed a 8 mm enhancing lesion (arrows, D) in lateral area of left breast. With ultrasound (**E**) a small solid lesion was found which would have been easily missed without previous MR imaging. Histopathological examination (not shown) revealed an infiltrative ductal carcinoma.

Regional or focal contrast enhancement on MR imaging often represents benign breast tissue 924), but sonography would not reveal a lesion when screening this benign tissue. In our selected patient population, every lesion apparent on MR imaging could be identified and characterized with the combination of sonography and fine-needle aspiration cytology (e.g., no false-positive MR imaging findings). This substantially reduces the need for time- and cost-consuming MR imaging-guided biopsies in this particular patient category; however, not every enhancing lesion on MR imaging will be detected with sonography, partly because enhancing lesions do not represent pathology and partly because not all solid lesions are shown with sonography. Therefore, we advise referring the few patients with an unknown primary tumor and a suspicious lesion on MR imaging that cannot be identified on sonography to a center with MR imaging-guided sonography.

Detection of the malignancy determines the treatment policy. A lumpectomy, followed by irradiation, was performed (after sonographically guided localization) in five patients. Mastectomy was performed on three patients with multifocal malignancy. Three other patients underwent induction chemotherapy. The MR imaging findings proved to be false-negative in one patient; a primary cancer with an origin other than the breast was found in four patients. In the remaining 15 patients, MR imaging of the breast did not depict a malignant lesion and no breast cancer or other primary cancer was found during follow-up. The occult primary breast carcinoma in patients presenting with axillary metastases is often very small (4,28,29) or not found; careful histologic examination of mastectomy specimens fails to show the carcinoma in 30-40% (30-32).

Compared with previously published studies, the MR imaging detection rate (67-86%) (8, 11-13) of mammographically and clinically occult tumors is low in this study; however, this study has a different patient population. First, in a cancer center, a higher percentage of patients present with metastatic tumor in the axillary lymph nodes as a symptom of an unknown primary cancer (of another origin). Secondly, a significant part of the studied patient group was known to have contralateral breast cancer. If no second primary breast cancer is found in the other breast on MR imaging, it is plausible that the metastatic tumor in the axillary lymph node is a metastasis of the previously discovered tumor; therefore, MR imaging detects fewer primary breast cancers in this patient population with previously detected cancer.

In our study, the T1-weighted sequences were performed with 4-mm-thick slices. This theoretically implies that very small lesions of 1- to 2-mm diameters can be missed; thus, the current MR imaging techniques have a limited detection capacity. In this study, follow-up showed one patient in whom such a small lesion was missed; however, the lesion size at the time of MR imaging remains unknown.

In four of 20 patients not known to have malignancy, an adenocarcinoma with an origin other than the breast was the cause of the axillary metastases. In three patients, a bronchogenic carcinoma was found, which indicates that workup should include a CT examination of the thorax.

In conclusion, in women with axillary lymph node metastases consistent with breast cancer, MR imaging of the breast should be added to clinical examination and mammography before defining the malignancy as an occult primary cancer. In this study, MR imaging detected an occult breast carcinoma in 40% of the patients without a history of breast cancer. MR imaging of the breast is also advocated in women with a previous or simultaneous breast cancer presenting with contralateral lymph node metastases to more reliably detect or exclude a second primary cancer. A second primary cancer was found in 27% of these patients. Only one of 20 patients with negative MR imaging findings showed breast cancer on clinical follow-up after 8 months.
In this study, all MR imaging lesions could be identified on sonography and therefore MR imaging—guided sonography followed by fine-needle aspiration cytology offered an excellent alternative to MR imaging-guided biopsy.
Identification of an otherwise occult breast cancer with MR imaging eliminates uncertainty about the primary site of the cancer and offers the opportunity for optimal treatment.

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10

Summary and general discussion

In this thesis we address various indications of breast MRI, with the emphasis on the value of MRI in screening of women with high genetic risk for breast cancer, and especially in BRCA1 mutation carriers. Furthermore, we discuss the role of breast MRI in patients with early stage breast cancer who wish to undergo breast conserving surgery. Finally we describe how breast MRI can be of use in patients who present with axillary metastasis of an adenocarcinoma without a clinically or mammographically detectable breast cancer.

MRI SCREENING IN WOMEN WITH HIGH FAMILIAL RISK FOR BREAST CANCER

In **chapter 2** we analyzed the screening results of the Dutch MRI Screening Study (MRISC). Women with a higher than 15% cumulative lifetime risk of breast cancer were included and screened with biannual clinical breast examination (CBE) and annual mammography and MRI.
Between 1999 and 2007, 12,157 eligible women were included, 599 of them were mutation carriers. Ninety-seven breast cancers were found in 93 women, of which 78 were screen-detected, 13 were interval cancers and six were found by chance at prophylactic mastectomy.
Considering only the 75 breast cancers detected during a complete screening round, i.e. with MRI as well as mammography, 66 were screen-detected (sensitivity 88%) and nine interval cancers occurred of which 6 in BRCA1 mutation carriers. The sensitivity was 21% for CBE, 41% for mammography, and 71% for MRI, respectively. Looking specifically at BRCA1 and BRCA2 mutation carriers we found that mammographic sensitivity was significantly lower in BRCA1 than in BRCA2 mutation carriers (25% v 62%), while MRI sensitivity was more or less equal in the two groups (63% v 69%). Only 7% of BRCA1-assocoiated tumors were DCIS; in contrast to 19% of BRCA2-associated tumors. Other observed differences between mutation carriers were that BRCA1 mutation carriers were younger at diagnosis, and that BRCA1-associated tumors were larger, in a higher proportion grade 3 and hormone receptor negative, and more often interval carcinomas.
After a median follow-up of 5 years 11 of the 93 patients with breast cancer developed a recurrence (distant metastasis (n=5), local recurrence (n=5), or contralateral breast cancer (n=3)). One patient developed a contralateral breast cancer as well as a local recurrence and distant metastasis. Four patients died (3 BRCA1 and 1 BRCA2 mutation carriers). Cumulative survival without distant metastases and overall survival at 6 years in all BRCA1 and BRCA2 mutation carriers with invasive breast cancer were 84% and 93%, respectively, and 100% in women with elevated familial risk without a detectable mutation.

The false-negative MRI cases of the MRISC study were subject of the study in **chapter 3**. A false-negative MRI case was defined as a biopsy proven malignancy while the MRI examination, performed within 1 year prior to detection, was evaluated as negative (BI-RADS 1 or 2(1)). Review of the false-negative MRI examinations was done by two experienced radiologists reaching consensus with all available clinical and diagnostic information about location, size, and histology of the malignancy. In case malignancy could be identified in retrospect, it was scored as missed or misinterpreted. In case no lesion could be identified in retrospect, the diagnostic quality of the MR examination was assessed as possible cause of a false-negative diagnosis.
In 21 of 76 patients, with breast cancer detected during a complete screening round, MRI was false-negative. Forty-three percent (9/21) of the false-negative MR cases concerned pure ductal carcinoma in situ (DCIS) or DCIS with invasive foci; in eight of them no enhancement was seen at the review; in the ninth patient DCIS was misinterpreted as benign enhancement. In five patients the features of invasive malignancy were missed or misinterpreted. Small lesion size (n = 3), extensive diffuse contrast enhancement of the breast parenchyma (n = 2), and a technically inadequate examination (n = 1) were other causes of a missed diagnosis. In one patient with invasive breast cancer no explanation could be found for the false-negative diagnosis. The missed and misinterpreted cases reflect the learning curve of a new technique in a multicenter study.

Cancers missed by screening and presented as interval cancers may be larger compared to screen-detected cancers, possibly due to faster tumor growth rates. Knowledge about tumor volume doubling time and tumor growth rate may influence screening frequency in subgroups of patients. In **chapter 4** we assessed the tumor volume doubling time of invasive cancers from the United Kingdom, the Canadian, and the Dutch MRI screening trials (2-4) for women at hereditary risk, by measuring tumor size at diagnosis and on preceding imaging.
We could assess tumor volume doubling time in 100 patients with invasive cancers: concerning 43 BRCA1 mutation carriers, 16 BRCA2 mutation carriers and 41 high risk women without detectable mutation. Tumor volume doubling time correlated significantly with age, both in BRCA1/2 mutations carriers and in high-risk patients. With each 10-year increase in age, the mean tumor volume doubling time increased by a factor of 1.6. Growth was twice as fast in BRCA1 or BRCA2 patients as in high-risk patients of the same age. The mean tumor volume doubling times for women with BRCA1/2 mutations diagnosed below the age of 40 years, between the age of 41 and 50 years, and over 50 were 28, 68, and 81 days, respectively. The mean volume doubling times for women in the high risk group without mutation were 83,

121, and 173 days, respectively. The faster growth in women with BRCA1 mutations below the age of 40 was reflected by their larger tumor size at detection and the occurrence of interval cancers, while BRCA2-related tumors were small and no interval cancers occurred. Nevertheless, we could not show a difference between BRCA1 and BRCA2 mutations in effect on tumor growth rate. To confirm tumor volume doubling times in tumors with BRCA2 mutations, a larger study would therefore be desirable. Neither menopause nor breast density at mammography correlated significantly with tumor volume doubling time.

According to the Dutch guidelines (5), women with a proven BRCA1 mutation are offered annual clinical breast examination, screening with MRI from age 25 and mammography from age 30 onwards. However, especially in BRCA1 mutation carriers, screening studies (2-4) showed a very low sensitivity of mammography while at the same time mammography may potentially be harmful due to the DNA damaging effect of ionizing radiation (6-8). In **chapter 5** we assessed whether mammography contributes sufficiently to early breast cancer detection, taking into account the advancements in breast cancer screening modalities: digital mammography has replaced film-screen mammography and both increased MRI expertise and technology have improved MRI screening performance.
We compared the current efficacy of screening in women with a BRCA1 mutation to previously published results, and investigated the additional value of digital mammography when MRI screening is already performed. In this retrospective multicenter study, we reviewed imaging and pathology reports in order to assess whether the breast cancers were screen-detected or interval cancers and whether they were visible on mammography and MRI, using the BI-RADS classification (1) allocated at the time of diagnosis.
In a cohort of 93 BRCA1 mutation carriers with breast cancer who underwent screening with MRI and digital mammography, 82 invasive breast cancers (mean size 12.2 mm) and 12 DCIS (mean size 17.5 mm) were found. Screening sensitivity was 95.7% (90/94). Four interval cancers occurred (4/94=4.3%), all grade 3 triple negative invasive ductal carcinomas. The sensitivity of MRI was 93.6% (88/94), which is higher than the pooled sensitivity from previous studies (77.6 % (52/67)) (2-4,9). We found a relatively high sensitivity for mammography (51.1% (48/94)) in comparison with previous results (29.2% (14/48) (2-4) indicating a better performance of digital mammography than conventional film-screen mammography. Nevertheless, only two DCIS were detected with mammography alone (2/94=2.1%): these were a grade 3 in a 50-year-old patient and a grade 2 in a 67-year-old.
We concluded that digital mammography added only 2% to the breast cancer detection in BRCA1 patients. There was no benefit of additional mammog-

raphy in women below age 40. Given the potential risk of radiation induced breast cancer in young mutation carriers, we proposed to screen BRCA1 mutation carriers yearly with MRI from age 25 onwards and to start with mammographic screening not earlier than age 40.

The main limitation of the above mentioned study (chapter 5) is its retrospective design. Ideally, the next step investigating the efficacy of the proposed modified protocol for BRCA1 mutation carriers, would be a prospective randomized study. However, even with an international multicenter study it would still be very difficult to guarantee sufficient numbers within a reasonable time period. As an alternative method we used in **chapter 6** a validated computer simulation model (MISCAN (10-13)) to evaluate two screening protocols for BRCA1 mutation carriers and to perform a cost-effectiveness analysis comparing both protocols. We compared the current Dutch screening guidelines for BRCA1 mutation carriers: annual MRI from age 25-30, annual MRI and mammography from age 30-60, and biennial mammography in the nationwide program from age 60-74, with the modified protocol: postponing annual mammography until age 40.
Furthermore, we used the radiation risk models of the 7th Biological Effects of Ionizing Radiation Committee (BEIR-VII) (14) to estimate the additional breast cancers and breast cancer deaths due to screening exposure. Historically, epidemiological data concerning health risks from exposure to low levels of ionizing radiation have been analysed with 2 dose response models: Excess Absolute Risk (EAR) and Excess Relative Risk (ERR) (15).
We estimated that current screening guidelines would prevent 13,139 breast cancer deaths per 100,000 BRCA1 mutation carriers using a life-time follow-up. Postponing mammography until age 40 would increase breast cancer deaths by 23 (0.17%), but would also reduce radiation-induced breast cancer deaths by 15 or 105, using the absolute and relative risk model respectively per 100,000 women screened. The estimated net effect is an increase of 8 or a reduction of 82 breast cancer deaths per 100,000 women screened (depending on the risk model used).
The incremental cost-effectiveness ratio comparing the current versus the modified protocol is €272,900 per life year gained. A limitation of our study is that we used two separate models to calculate the effects of screening and the effects of radiation. We estimated the net effects by combining the undiscounted effectiveness result. Our model structure did not allow for combining the effects with discounting.
We concluded that screening according to the modified protocol is only slightly less effective or may even be better than the current guidelines and that it is cost-effective.

There is no consensus on whether breast MRI should be included in breast screening protocols for BRCA1/2 mutation carriers of 50 years and older. The advantages of MRI over mammography might be expected to decline with age because of a progressive reduction in breast density and decreased tumor growth rate. The use of MRI greatly increases cost and clear data demonstrating the effectiveness of screening high-risk women of 50 years and older with MRI are lacking. Therefore we investigated in **chapter 7** the evidence on age-related screening accuracy in BRCA1/2 mutation carriers using individual patient data (IPD) meta-analysis. IPD were pooled from six high-risk prospective screening trials (2, 4, 16-19).
A total of 1,951 of 2,033 BRCA1/2 mutation carriers had both MRI and mammography results in the same screening round and were included. There were 184 breast cancers in 183 women including 23 interval cancers.
Pooled analysis showed that in women aged 50 years and older, the sensitivity of mammography was relatively low (38%) and not higher than the sensitivity in women younger than 50 years (40%). In women aged 50 years and older, combining MRI and mammography significantly increased screening sensitivity compared with mammography alone (94% versus 38%).The combination of MRI and mammography was not significantly more sensitive than MRI alone (94% versus 84%). Combining MRI and mammography in women of 50 years and older resulted in sensitivity similar to that in women younger than 50 years (94% versus 93%).

PREOPERATIVE BREAST MRI

In a before-after study in **chapter 8** we evaluated in 123 breast cancer patients eligible for breast-conserving surgery, whether the information provided by preoperative MRI would result in fewer tumor-positive resection margins and fewer reoperations. For these patients a first plan for breast-conserving surgery was made based on clinical examination and conventional imaging. The final surgical plan was made with the knowledge from the additional preoperative MRI. The rates of tumor-positive resection margins and reoperations were compared with those of a historical control group consisting of 119 patients who underwent 123 breast-conserving procedures without preceding preoperative MRI.
We found that preoperative MRI changed the surgical plan to more extensive surgery in 42 patients (34%), mainly to mastectomy (29 patients (24%)). The remaining 94 patients underwent 95 breast-conserving procedures. Significantly fewer patients had tumor positive resection margins than in the control group (16%, 15/95 versus 29%, 36/123). Patients with preoperative MRI un-

derwent significantly fewer reoperations compared with the historical control group (19%, 18/95 versus 37%, 46/123). By contrast, the COMICE trial (20), the only large randomized controlled trial on this subject, concluded that preoperative breast MRI did not reduce the rate of re-excisions in women who underwent breast conserving surgery. However, in the 45 centers involved in this study, there were different levels of MRI experience and limited availability of MRI-guided biopsy (21). In addition, a large number of patients were included by surgeons who recruited only a few patients per year. In our opinion, it is important that not only the radiologist is experienced in breast MRI but also that the surgeon becomes familiar with the MR images by reviewing the MRI examinations together with the radiologist, especially in more complex cases with larger tumors or extensive DCIS.
We found that MRI was better than mammography in identifying patients who required a mastectomy but also that adding MRI to the work-up made more patients choose for mastectomy.
The higher mastectomy rate in patients undergoing MRI staging has raised concern of overtreatment (22,23). Holland et al. showed that in case of breast-conserving surgery tumor will often be left behind in the breast (24). Nevertheless, the recurrence rate after breast conserving surgery is low. A plausible explanation is that (small) tumor loads, left behind in the breast, are successfully eliminated by radiotherapy and systemic therapy. This would mean that, to prevent overtreatment, conversion from lumpectomy to mastectomy based on preoperative MRI is only indicated in cases in which considerable extra tumor load is detected on MRI, and proven. However, a clear cut-off value will be hard to define.

BREAST MRI IN CLINICALLY AND MAMMOGRAPHICALLY OCCULT BREAST CANCER

Metastases in axillary lymph nodes in women most likely arise from the ipsilateral breast. When the primary tumor cannot be identified with physical examination, mammography or ultrasound, the cancer is defined as occult. In less than 0.5% of all women with breast cancer metastatic lymphadenopathy is the first presenting symptom. In **chapter 9** we assessed whether breast MRI followed by ultrasound and cytology could identify breast cancer in women presenting with metastatic adenocarcinoma in axillary lymph nodes originating from an unknown primary site. Thirty-one women with metastatic axillary lymph nodes underwent breast MRI because physical examination and mammography findings were normal. Twenty of the 31 women had no history of malignancy, 10 had been previously treated for contralateral breast cancer,

and one patient had nodal metastases in the contralateral axilla at the time breast cancer was detected. MR imaging detected the primary breast cancer in eight (40%) of the 20 patients without a history of malignancy. Breast MR demonstrated a second primary cancer in three (27%) of the 11 patients with previous or simultaneous breast cancer. Subsequently all lesions could be identified with ultrasound and confirmed with cytology and histology. In women with axillary lymph node metastases from adenocarcinoma, breast MR should be added to clinical examination and mammography before defining the breast cancer as occult. For suspicious lesions not visible with ultrasound, MR- guided biopsy is indicated. When breast MRI identifies breast cancer, optimal local treatment can be offered, including breast conserving therapy.

IMPACT OF MODERN BREAST MRI

After we had shown that MRI was capable of detecting occult breast cancer (chapter 9), we have investigated the optimal applications of this finding for screening (chapter 2-7) and preoperative staging (chapter 8).

Our study (chapter 9) contributed to recognize occult primary breast cancer presenting as axillary metastases as an indication for breast MRI by the Dutch guidelines (5) as well as by the EUSOMA working group (25).

Breast MRI for staging in patients eligible for breast conserving surgery is an indication still under debate. In the near future the first results of a multicentre international study, the MIPA study (Multicentre International Prospective meta-Analysis of individual patient data) will be published. In this observational study, 35 centers are planned to include 7000 patients undergoing breast conserving surgery. The reoperation rates and the mastectomy rates in the MR group will be compared with the non-MR group. During 5 year of follow-up the rate of ipsilateral recurrence, distant metastases and contralateral breast cancer will be evaluated.

For BRCA1 mutation carriers screened with MRI and mammography we calculated the prevented mortality and the radiation-induced mortality of a decade of mammographic screening, using simulation models (chapter 6). We found that screening with MRI and postponed mammographic screening, from age 30 till age 40, is only slightly less effective or may even be better than screening according to the current guidelines.
BRCA2 mutation carriers are likewise more sensitive to the DNA damaging effect of ionizing radiation. In the MARIBS (2) and the MRISC study (4) a

substantial proportion of the BRCA2-associated breast cancer was detected by mammography only. These were mainly DCIS. However, with increased experience and improved MRI technique, the detection of DCIS by MRI is improved and even better than by mammography (16, 26). We expect that a screening protocol with postponed mammography would also be a better scenario for BRCA2 mutation carriers below age 40.

The little additional value of mammographic screening in BRCA1/2 mutation carriers brings up the issue of screening with MRI alone. In the Canadian study (16) two of the 57 cancers diagnosed in BRCA1/2 mutation carriers were detected with mammography alone. As in our study (two of 94 cancers in BRCA1 mutation carriers (chapter 5)) the breast cancers detected with mammography alone were DCIS. In the initial screening round from the Ontario High Risk Breast Screening Program (27) none of the 25 breast cancers in BRCA1/2 mutation carriers were detected by mammography alone. Recent results from a single-center study (28) investigating screening in high risk women showed that none of the 16 breast cancers diagnosed in BRCA1/2 mutation carriers were found with mammography alone. Although there seams increasing evidence in favor of a screening scenario with MRI alone, numbers are still too small to decide that mammographic screening can be omitted completely.

Our pooled analysis using individual patient data meta-analysis from six high-risk prospective screening trials (chapter 7) demonstrated that the sensitivity of mammography in women aged 50 years and older was relatively low and not higher than the sensitivity in women younger than 50 years. Furthermore, addition of MRI to mammography for screening BRCA1/2 mutation carriers of 50 years and older improved screening sensitivity by a magnitude similar to that observed in younger women. Screening MRI in BRCA1/2 carriers of 50 years and older must be reconsidered but until what age? Our study (chapter 7) included 108 women aged 60 years and older, in whom 10 breast cancers were diagnosed. MRI detected all but one interval cancer; mammography detected only three of 10 cancers.

For BRCA1/2 mutation carriers above age 60 the Dutch guidelines advise screening with only biennial mammography. Saadatmand et al. (29) investigated breast cancer screening in BRCA1/2 mutation carriers above 60 years, comparing tumor stage in patients screened with biennial and annual mammographic screening, respectively. Tumor stage of 148 breast cancers in BRCA1/2 mutation carriers without a history of breast or ovarian cancer, could be compared. Tumors larger than 20 mm, positive lymph nodes, or distant metastases at detection were defined as unfavorable stage. An unacceptable high percentage of breast cancers were detected in unfavorable stage (53%) with biennial versus 21% with annual mammography. Furthermore, biennial screening compared to annual screening resulted in twice as many in-

terval cancers (40% v 20%). These results suggest that annual mammographic screening is advisable in BRCA1/2 carriers of 60 years and older. Since in this age group only few women were screened with MRI, no comparative analysis could be performed.
The best screening policy for BRCA1/2 mutation carriers above 60 years, mammography, MRI, or a combination, has to be assessed in further studies.

Although MR screening is associated with a down-staging of breast cancer, there is little information about the impact of MRI screening on survival in BRCA1/2 mutation carriers. The MRISC study published a first evaluation of survival in high risk women screened with MRI and mammography in 2010 (chapter 2). In a median follow-up time of 5 years 3 of 31 (9.7%) BRCA1 mutation carriers and 1 of 16 (6.3%) BRCA2 mutation carriers with invasive breast cancer developed metastases and died. Only one of these women was lymph node positive at diagnosis. Survival data of BRCA1/2 mutation carriers in the Canadian study (16) showed a 4% breast cancer related mortality rate (one BRCA1 mutation carrier of 28 women with invasive breast cancer), in a median follow-up time of 8 years. Sixty-three percent of the cancers in this study were 10 mm or smaller. Disappointing results were obtained in the Norwegian study (30). Ten of 68 (14.7%) BRCA1 mutation carriers with breast cancer died in a mean follow-up period of 4 years. Tumor size was strongly related with survival: the ten-year survival was 93% for women diagnosed with invasive cancer at or below 10 mm, 58% for women with cancers between 11 and 20 mm and 23% for women diagnosed with cancers larger than 20 mm. Only 40% of the cancers detected in this study were 10 mm or smaller. In 9 of the 10 patients who died tumor size was larger than 10 mm; 8 were lymph node negative.
Would it be possible to increase the proportion of cancers detected at small size and thereby improve survival? We think it is indeed realistic to achieve improved screening results in comparison with previous studies. In our analysis of cases with a false negative MRI diagnosis (chapter 3) we concluded that a substantial part of these tumors were missed or misinterpreted, partly due to a learning curve of a new technique in a multicenter study. Yet, in a more recent evaluation of screening results in BRCA1 breast cancer cases (chapter 5) we showed that improved screening results can be achieved when MRI expertise and technology improves. More than 60% of breast cancers was detected as DCIS or invasive lesions of 10 mm or less and a low interval rate. This was significantly better than the 17% in the unscreened symptomatic group, stressing the necessity of screening. It also meant an improvement in comparison with the screening results in BRCA1 mutation carriers from a meta-analysis of previous studies as presented by Heijnsdijk et al. (31). In that study nearly 50 % of breast cancers in BRCA1 was detected as DCIS or

invasive breast cancer of 10 mm or less. Our recent results are in line with long-term MR screening results of the Canadian study in which women with a BRCA1/2 mutation were included (16). By dividing the inclusion period into two time-periods it was nicely demonstrated that the MRI sensitivity improved over time. The overall interval cancer rate was 2% and 3% for the BRCA1 cohort. These results suggest that also for BRCA1 mutation carriers annual screening is adequate.
However, the mortality rate in BRCA1 mutation carriers from lymph node negative breast cancers is higher than expected, possibly reflecting the natural history of these cancers.

CONCLUSIONS AND FUTURE RESEARCH

We have solid arguments to screen BRCA1 mutation carriers annually with MRI from age 25 onwards and to postpone mammographic screening until age 40. It has to be investigated whether this modified protocol is also beneficial for BRCA2 mutation carriers. We advise to continue MRI screening in BRCA1/2 mutation carriers of 50 years and older. The best screening policy for BRCA1/2 mutation carriers above 60 years, mammography with or without MRI, has to be assessed in further studies.
Although there is increasing evidence in favor of screening BRCA1/2 mutation carriers with MRI alone, the numbers are still too small to decide that mammographic screening can be omitted completely.
Results from screening cohorts with longer follow-up are required to assess long-term survival in BRCA1 and BRCA2 mutation carriers separately, and to judge whether screening is a suitable alternative to preventive mastectomy.
Although breast MRI is a robust technique in experienced centers, it has to be investigated whether new imaging modalities, such as contrast-enhanced dual-energy mammography, may perform better than MRI and at lower cost. Furthermore, two groups are investigating whether it is possible to achieve equivalent diagnostic accuracy with an abbreviated breast MRI screening protocol (32,33). The costs of screening will be reduced when image acquisition time (i.e. MRI system time) and thereby radiologists reading time are shortened.

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Samenvatting en algemene discussie

In dit proefschrift belichten we verschillende indicaties voor MRI onderzoek van de borst. De waarde van MRI als screenings onderzoek bij vrouwen met een erfelijke belasting voor borstkanker, en speciaal bij BRCA1 genmutatiedraagsters, komt uitgebreid aan de orde. Vervolgens bespreken we de rol van het MRI onderzoek van de borst als stageringsonderzoek bij vrouwen bij wie borstkanker in een vroeg stadium is ontdekt en die borstsparend behandeld willen worden. Tenslotte beschrijven we hoe MRI van de borst van nut kan zijn bij vrouwen die zich presenteren met metastasen van een adenocarcinoom in de oksel terwijl de tumor noch klinisch noch mammografisch of echografisch gevonden kan worden.

SCREENING MET MRI BIJ VROUWEN MET EEN FAMILIAIR VERHOOGD RISICO OP BORSTKANKER

In **hoofdstuk 2** analyseerden we de resultaten van screening met MRI van de Nederlandse MRI Screening Studie (MRISC). Vrouwen met verhoogd risico op borstkanker van 15% of meer werden geïncludeerd en gescreend met halfjaarlijks klinisch borstonderzoek en jaarlijks mammografie en MRI.
Tussen 1999 en 2007 konden 12.157 vrouwen worden geïncludeerd, waarvan 599 genmutatiedraagsters. Bij 93 vrouwen werden 97 carcinomen gevonden, waarvan 78 ontdekt door screening, 13 intervalcarcinomen en bij 6 tumoren betrof het een toevalsbevinding bij profylactische mastectomie.
Als we ons beperken tot de 75 carcinomen die ontdekt werden tijdens een complete screeningronde (met zowel mammografie als MRI), dan werden er 66 door screening ontdekt (sensitiviteit 88%) en waren er 9 interval carcinomen waarvan 6 bij BRCA1 genmutatiedraagsters. De sensitiviteit van klinisch borstonderzoek was 21%, van mammografie 41% en van MRI 71%. We vergeleken de screenings uitkomsten bij BRCA1 en BRCA2 genmutatiedraagsters en zagen dat de sensitiviteit van mammografie bij BRCA1 duidelijk lager was dan bij BRCA2 genmutatiedraagsters (25% versus 62%) terwijl dit niet gold voor de sensitiviteit van MRI (67% versus 69%). Slechts 7% van de BRCA1 geassocieerde tumoren betrof ductaal carcinoom in situ (DCIS), in vergelijking met 19% van de bij BRCA2 geassocieerde tumoren. Verder waren de BRCA1 genmutatiedraagsters jonger op moment van diagnose en waren de tumoren groter en in een hoger percentage graad 3 en hormoon receptor negatief, en betrof het vaker een intervalcarcinoom.
Na een mediane follow-up periode van 5 jaar kwam bij 11 van 93 patiëntes met borstkanker de ziekte terug als lokaal recidief (n=5), contralateraal mammacarcinoom (n=3) of als afstandsmetastasering (n=5). Bij één patiënte trad zowel een contralateraal mammacarcinoom op als een lokaal recidief

en afstandsmetastasen. Vier patiëntes overleden aan borstkanker (3 BRCA1 en 1 BRCA2 genmutatiedraagsters). De 6 jaar cumulatieve metastase vrije overleving en totale overleving van alle BRCA1/2 genmutatiedraagsters met invasief borstkanker was respectievelijk 84% en 93%. De overleving van de vrouwen met familiaire belasting zonder aangetoonde genmutatie was 100%.

De MRI onderzoeken met een fout negatieve diagnose in de MRISC studie waren onderwerp van het onderzoek in **hoofdstuk 3**. Een MRI diagnose werd gedefinieerd als fout negatief indien in geval van een histologisch bewezen maligniteit het MRI onderzoek, verricht binnen één jaar voorafgaand aan detectie, als negatief (BI-RADS 1 of 2 (1)) was beoordeeld. Twee ervaren radiologen verrichtten een herbeoordeling van deze MRI onderzoeken terwijl zij konden beschikken over alle klinische en diagnostische informatie betreffende de lokalisatie, de afmeting, en de histologie van de tumor. Indien retrospectief de maligniteit kon worden geïdentificeerd werd gescoord of er sprake was van een gemiste laesie of een verkeerde interpretatie. Indien retrospectief geen laesie kon worden gevonden werd bekeken of de kwaliteit van het onderzoek de oorzaak kon zijn van de gemiste diagnose.
Bij 21 van de 76 patiënten, bij wie borstkanker werd vastgesteld tijdens een complete screeningsronde, was het MRI onderzoek fout negatief. In 43% (9/21) van de fout negatieve MRI diagnoses betrof het zuiver ductaal carcinoom in situ (DCIS) of DCIS met invasieve foci; in 8 van de 9 was ook bij de herbeoordeling geen contrastopname zichtbaar terwijl bij de negende patiënte het beeld van DCIS verkeerd geïnterpreteerd was als benigne contrastopname. Bij 5 patiëntes werden de kenmerken van invasieve maligniteit gemist of verkeerd geïnterpreteerd. Geringe omvang (n=3), uitgebreide diffuse contrastopname door het borstklierweefsel (n=2), en een technisch inadequaat onderzoek (n=1) waren andere oorzaken van een gemiste diagnose. Bij één patiënte met een invasief carcinoom kon geen verklaring worden gevonden voor de fout negatieve diagnose.
De gemiste tumoren en de verkeerd geïnterpreteerde MRI onderzoeken weerspiegelen de leercurve van een nieuwe techniek in een multicenter studie.

Tumoren die gemist zijn door screening en als interval carcinoom aan het licht komen, zijn vaak groter dan tumoren ontdekt door screening, mogelijk als gevolg van een grotere groeisnelheid. Kennis over de verdubbelingstijd van het tumor volume en de groeisnelheid zou de screeningsfrequentie in subgroepen van patiënten kunnen beïnvloeden. In **hoofdstuk 4** berekenden we de tijd die nodig is om het volume van invasieve tumoren te verdubbelen door de tumor diameter te meten op het moment van diagnose en op voorafgaande beeldvorming. We gebruikten hiervoor de invasieve tumoren

gevonden in de Engelse, de Canadese en de Nederlandse MRI screening studies (2-4) uitgevoerd bij vrouwen met een erfelijk risico.
De verdubbelingstijd van het tumor volume kon worden berekend bij 100 patiënten met invasief borstkanker. Het betroffen 43 BRCA1 genmutatiedraagsters, 16 BRCA2 genmutatiedraagsters en 41 patiënten met een verhoogd risico zonder een aantoonbare genmutatie. De verdubbelingstijd van het tumor volume correleerde significant met leeftijd, zowel bij BRCA1/2 genmutatiedraagsters als bij patiënten met een verhoogd risico. We stelden vast dat per 10 jaar leeftijdstoename de gemiddelde verdubbelingstijd van het tumor volume toenam met een factor 1.6. De groeisnelheid was twee keer zo hoog in BRCA1/2 genmutatiedraagsters als bij vrouwen met een verhoogd risico zonder aangetoonde genmutatie. De gemiddelde verdubbelingstijd van het tumor volume bij genmutatiedraagsters gediagnosticeerd met borstkanker voor het 40^{e} jaar, tussen het 41^{e} en het 50^{e} jaar en na het 50^{e} jaar was respectievelijk 28, 68 en 81 dagen. Voor vrouwen zonder aangetoonde mutatie was dit respectievelijk 83, 121 en 173 dagen. De snellere groei bij BRCA1 genmutatiedraagsters jonger dan 40 jaar werd weerspiegeld door de grotere tumor diameter op moment van detectie en door het optreden van interval carcinomen terwijl de BRCA2 gerelateerde tumoren klein waren en zich niet als interval carcinoom presenteerden. Desalniettemin konden we geen verschil in groeisnelheid aantonen tussen BRCA1 en BRCA2 geassocieerde tumoren. Een grotere studie zal nodig zijn om de verdubbelingstijden van volume bij BRCA2 geassocieerde tumoren te bevestigen. Noch menopauze noch de borstdichtheid zoals zichtbaar op het mammogram correleerde significant met de verdubbelingstijd van het tumor volume.

Volgens de Nederlandse richtlijn (5) wordt vrouwen met een bewezen BRCA1 genmutatie jaarlijkse screening aangeboden bestaande uit klinisch borstonderzoek, MRI onderzoek vanaf het 25^{e} jaar en mammografie vanaf het 30^{e} jaar. Echter, screening studies (2-4) toonden aan dat met name bij BRCA1 genmutatiedraagsters de sensitiviteit van mammografie erg laag was terwijl mammografie tegelijkertijd mogelijk schadelijk is omdat deze vrouwen gevoeliger zijn voor schade aan het DNA veroorzaakt door ioniserende straling (6-8). In **hoofdstuk 5** onderzochten we of mammografie voldoende bijdraagt aan de vroege detectie van borstkanker, rekening houdend met de voortschrijdende ontwikkelingen: digitale mammografie heeft inmiddels de conventionele film scherm mammografie vervangen en zowel MRI expertise als techniek zijn verbeterd.
We vergeleken de effectiviteit van de huidige screening bij vrouwen met een BRCA1 genmutatie met eerder gepubliceerde resultaten en onderzochten de toegevoegde waarde van digitale mammografie indien al met MRI wordt gescreend. In deze retrospectieve multicenter studie herbeoordeelden we de

beeldvorming en de pathologie uitslagen om vast te stellen of de maligniteiten met screening waren ontdekt, of het interval carcinomen betrof en of ze zichtbaar waren op mammografie en MRI, waarbij de BI-RADS classificatie (1) werd gebruikt zoals toegekend op het moment van diagnose.
In een cohort van 93 BRCA1 genmutatiedraagsters met borstkanker gescreend met MRI en digitale mammografie, werden 82 invasieve maligniteiten (gemiddelde diameter 12,2 mm) en 12 DCIS (gemiddelde diameter 17,5 mm) gevonden. De sensitiviteit van de screening was 95,7% (90/94). Er waren 4 intervalcarcinomen (4/94= 4,3%), in alle vier de gevallen betrof het een graad 3 triple negatief invasief ductaal carcinoom. De sensitiviteit van MRI was 93,6% (88/94), hetgeen hoger is dan de gepoolde sensitiviteit van eerdere studies (77,6% (52/67)) (2-4,9). We vonden een relatief hoge sensitiviteit voor mammografie (51,1% (48/94)) in vergelijking met eerdere studies (29,2% (14/48)) wijzend op een beter resultaat van digitale mammografie in vergelijking met conventionele mammografie. Desalniettemin werden slechts 2 gevallen van DCIS gedetecteerd door mammografie alleen (92/94=2,1%): respectievelijk een graad 3 DCIS bij een patiënte van 50 jaar en een graad 2 DCIS bij een patiënte van 67 jaar.
We concludeerden dat digitale mammografie slechts 2% toevoegde aan de detectie van borstkanker bij BRCA1 genmutatiedraagsters. Er was geen toegevoegde waarde van mammografie bij vrouwen jonger dan 40 jaar. Gezien het potentiele risico op stralingsgeïnduceerde borstkanker bij jonge genmutatiedraagsters stelden wij voor om BRCA1 genmutatiedraagsters vanaf 25 jaar jaarlijks te screenen met MRI en om de screening met mammografie niet eerder te starten dan op het 40e jaar.

De belangrijkste beperking van bovengenoemde studie (hoofdstuk 5) is dat het een retrospectieve studie betreft. Idealiter zou een prospectieve gerandomiseerde studie de volgende stap zijn om het voorgestelde gemodificeerde protocol te testen. Echter, zelfs met een internationale multicenter studie zal het erg moeilijk zijn om binnen een redelijke periode voldoende aantallen te halen. Als alternatief hebben we in **hoofdstuk 6** gebruik gemaakt van een gevalideerd simulatiemodel (MISCAN (10-13)) om twee screeningsprotocollen te evalueren en om de kosteneffectiviteit van beide protocollen te vergelijken. We vergeleken de huidige Nederlandse richtlijn voor screening van BRCA1 genmutatiedraagsters: jaarlijks MRI vanaf 25 tot 30 jaar, jaarlijks MRI en mammografie vanaf 30 tot 60 en iedere twee jaar mammografie in het nationale bevolkingsonderzoek van af 60 tot 74 jaar, met het gemodificeerde protocol waarbij jaarlijkse screening met mammografie wordt uitgesteld tot het 40e jaar.
Bovendien hebben we stralingsrisico modellen (7e Biological Effects of Ionizing Radiation Committee (BEIR VII)) (14) gebruikt om het aantal gevallen

van stralingsgeïnduceerde borstkanker en stralingsgeïnduceerde borstkanker doden in te schatten. Epidemiologische data betreffende gezondheidsrisico's door blootstelling aan lage dosis ioniserende straling worden geanalyseerd door middel van twee dosis-respons modellen: Excess Absolute Risk (EAR) en Excess Relative Risk (ERR) (15).
We berekenden dat met screening volgens de huidige richtlijnen 13.139 borstkanker doden voorkomen zouden worden per 100.000 BRCA1 genmutatiedraagsters, die gescreend worden gedurende hun leven. Uitstellen van screening met mammografie tot het 40e jaar zou het aantal borstkanker doden met 23 (0,17%) doen toenemen, maar zou tegelijkertijd het aantal stralingsgeïnduceerde borstkanker doden doen afnemen met 15 of 105 (respectievelijk voor het absolute en relatieve risico model) per 100.000 gescreende vrouwen. Het geschatte netto effect is een toename van 8 of een afname van 82 borstkanker doden per 100.000 gescreende vrouwen. Nogmaals, de uitkomst is afhankelijk van het gebruikte risico model.
De incrementele kosteneffectiviteitsratio waarbij het huidige protocol met het gemodificeerde protocol wordt vergeleken is €272.900 per gewonnen levensjaar.
Een beperking van dit onderzoek is dat we twee verschillende modellen hebben gebruikt om het effect van screening en het effect van radiatieschade te berekenen. Het netto effecten hebben we geschat door zonder indexatie te combineren. De structuur van het model liet combinatie van de effecten met indexatie niet toe. We concludeerden dat screening volgens het gemodificeerde protocol slechts gering minder effectief of zelfs beter is dan het huidige protocol en dat het kosteneffectief is.

Er is geen overeenstemming over het nut van screening met MRI bij BRCA1/2 genmutatiedraagsters van 50 jaar en ouder. Men zou verwachten dat de voordelen van screening met MRI boven mammografie zouden afnemen met toenemende leeftijd vanwege een afname van de dichtheid van het borstklierweefsel en een minder snelle groei van de tumoren. Het gebruik van MRI verhoogt de kosten aanzienlijk terwijl data, die het effect aantonen van screening met MRI bij vrouwen met een verhoogd risico van 50 jaar en ouder, ontbreken. Daarom onderzochten we in **hoofdstuk 7** de leeftijd gerelateerde effectiviteit van screening bij BRCA1/2 genmutatiedraagsters waarbij gebruik werd gemaakt van individuele patiëntengegevens in een meta-analyse. De individuele patiëntengegevens van zes prospectieve screening trials bij vrouwen met een verhoogd risico werden gecombineerd(2, 4, 16-19).
In totaal werden 1951 van de 2033 BRCA1/2 genmutatiedraagsters met zowel MRI als mammografie in dezelfde screeningsronde geïncludeerd. Bij 183 vrouwen werden 184 mammacarcinomen gevonden, inclusief 23 interval carcinomen.

De gecombineerde analyse toonde dat bij vrouwen van 50 jaar en ouder, de sensitiviteit van mammografie relatief laag was (38%) en niet hoger dan de sensitiviteit bij vrouwen jonger dan 50 jaar (40%). Bij vrouwen van 50 jaar en ouder vergrootte de combinatie van MRI en mammografie de sensitiviteit van de screening significant in vergelijking met screening met mammografie alleen (94% versus 38%). De combinatie van MRI en mammografie was niet significant sensitiever sensitief dan MRI alleen (95% versus 84%). Combinatie van MRI en mammografie bij vrouwen van 50 jaar en ouder resulteerde een eenzelfde sensitiviteit als bij vrouwen jonger dan 50 jaar (94% versus 93%).

PREOPERATIEF MRI ONDERZOEK VAN DE BORST BIJ VROUWEN DIE IN AANMERKING KOMEN VOOR EEN BORSTSPARENDE BEHANDELING

In **hoofdstuk 8** onderzochten we bij 123 borstkanker patiënten die in aanmerking kwamen voor borstsparende chirurgie, of de informatie afkomstig van het preoperatieve MRI onderzoek resulteerde in minder tumor positieve snijranden en minder re-operaties. Voor deze patiënten werd een eerste plan voor borstsparende chirurgie gemaakt op basis van klinisch onderzoek en conventionele beeldvorming. De bevindingen van de preoperatieve MRI bepaalden het definitieve chirurgische plan.
De percentages tumor positieve snijranden en re-operaties werden vergeleken met die van een historische controle groep bestaande uit 119 patiënten die 123 borstsparende operaties ondergingen zonder voorafgaande preoperatief MRI onderzoek. We zagen dat preoperatieve MRI het chirurgisch plan bij 42 patiënten (34%) veranderde in uitgebreidere chirurgie, meestal mastectomie (29 patiënten (24%)). De overige 94 patiënten ondergingen 95 borstsparende operaties. Significant minder patiënten hadden tumor positieve snijranden in vergelijking met de controle groep (19% (18/95) versus 37% (46/123)). De COMICE studie (20), de enige grote gerandomiseerde studie op dit gebied, concludeerde daarentegen dat preoperatieve MRI bij vrouwen die een borstsparende operatie ondergaan het percentage re-operaties niet vermindert. Echter, in de 45 centra betrokken in dit onderzoek was het niveau van MRI expertise wisselend en was MR geleid biopteren beperkt beschikbaar (21). Bovendien bleek dat een groot aantal patiënten geïncludeerd was door chirurgen die slecht een paar patiënten per jaar includeerden. Volgens ons is het belangrijk dat niet alleen de radioloog ervaren is op het gebied van MRI van de borst maar dat ook de chirurg vertrouwd raakt met de MRI beelden door de MRI onderzoeken samen te bekijken met de radioloog, speciaal in meer complexere gevallen met grotere tumoren of uitgebreide DCIS.

We stelden vast dat MRI beter dan mammografie in staat was om patiënten te identificeren voor wie een mastectomie geïndiceerd was maar ook dat de toevoeging van MRI meer patiënten voor mastectomie deed kiezen.
Het hogere mastectomie percentage bij vrouwen die een preoperatieve MRI ondergaan heeft geleid tot bezorgdheid ten aanzien van overbehandeling (22, 23). Holland et al. toonde aan dat in geval van een borstsparende behandeling er vaak tumor in de borst zal achterblijven (24). Desondanks is het recidiefpercentage na borstsparende behandeling laag. Een logische verklaring is dat indien (geringe) tumormassa achter blijft dit met succes onschadelijk gemaakt wordt door radiotherapie en chemotherapie. Dit zou betekenen dat, om overbehandeling te voorkomen, de conversie van lumpectomie naar mastectomie op basis van preoperatieve MRI alleen geïndiceerd is als evidente extra tumormassa door het MRI onderzoek wordt aangetoond, en wordt bewezen. Echter, het zal moeilijk zijn hiervoor een exacte maat te geven.

MRI VAN DE BORST BIJ KLINISCH EN MAMMOGRAFISCH OCCULT BORSTKANKER

Metastasen in axillaire lymfklieren bij vrouwen zijn het meest waarschijnlijk afkomstig van de ipsilaterale borst. Indien de primaire tumor niet kan worden geïdentificeerd met klinisch onderzoek, mammografie of echografie, wordt de tumor als occult gedefinieerd. In minder dan 0,5% van alle vrouwen met borstkanker is metastatische lymfadenopathie het eerste symptoom. In **hoofdstuk 9** onderzoeken we of met MRI van de borst gevolgd door echografie en cytologie het mammacarcinoom geïdentificeerd kan worden bij vrouwen die zich presenteren met metastatisch adenocarcinoom in axillaire lymfklieren zonder dat een primaire tumor bekend is.
Eenendertig vrouwen met metastasen in axillaire lymfklieren ondergingen een MRI onderzoek omdat bij lichamelijk onderzoek en mammografie geen tumor kon worden vastgesteld. Twintig van de 31 vrouwen hadden een blanco voorgeschiedenis, 10 vrouwen waren eerder behandeld voor contralateraal borstkanker en bij één patiënte was er sprake van borstkanker terwijl gelijktijdig in de contralaterale axillaire lymfadenopathie werd vastgesteld.
Met behulp van MRI werd bij 8 (40%) van de 20 patiënten zonder borstkanker in de voorgeschiedenis het primair mammacarcinoom gevonden. MRI toonde een tweede primair mammacarcinoom aan bij 3 (27%) van de 11 patiënten bekend met eerder of gelijktijdig borstkanker. Alle laesies konden met echografie worden gevonden en bewezen worden via cytologie en histologie. Bij vrouwen met metastasen van een adenocarcinoom in axillaire lymfklieren moet MRI worden toegevoegd aan klinisch onderzoek en mammografie

voordat de borstkanker als occult wordt beschouwd. In geval van verdachte laesies op het MRI onderzoek die niet met gerichte echografie kunnen worden gevonden, is MR geleide biopsie geïndiceerd. Indien het MRI onderzoek de primaire borsttumor aantoont kan optimale lokale behandeling worden geboden, inclusief borst sparende behandeling.

DE IMPACT VAN HET HUIDIGE MRI ONDERZOEK VAN DE BORST

Nadat we aantoonden dat MRI in staat is occult borstkanker te detecteren (hoofdstuk 9) hebben we onderzocht hoe we van deze bevinding optimaal gebruik konden maken in screening (hoofdstuk 2-7) en bij preoperatieve stagering (hoofdstuk 8).

Ons onderzoek (hoofdstuk 9) droeg bij aan het erkennen van primair occult borstkanker zich presenterend als axillaire metastasen als indicatie voor MRI onderzoek van de borst, zowel door de Nederlandse Richtlijn Mammacarcinoom (5) als door de EUSOMA working group (25).

MRI onderzoek van de borst als stageringsonderzoek voor vrouwen die in aanmerking komen voor borstsparende behandeling is een indicatie die nog steeds ter discussie staat. In de nabije toekomst zullen de eerste resultaten van een internationale multicenter studie, de MIPA studie (Multicenter International Prospective meta-Analysis of individual patient data) gepresenteerd worden. In deze observationele studie zullen door 35 centra 7000 patiënten die in aanmerking komen voor borstsparende behandeling, geïncludeerd worden. Het percentage re-operaties en het percentage ablatio's in de MR groep zullen worden vergeleken met die van de groep zonder MRI. Na een follow-up van 5 jaar zullen de percentages ipsilateraal recidief, afstandsmetastasen en contralateraal borstkanker worden geëvalueerd en vergeleken.

Voor BRCA1 genmutatiedraagsters gescreend met MRI en mammografie berekenden we de mortaliteit die met 10 jaar mammografie screening wordt voorkomen en de mortaliteit die door de ioniserende straling van 10 jaar mammografie wordt veroorzaakt. We gebruikten hiervoor simulatiemodellen (hoofdstuk 6). We concludeerden dat screening met MRI en met mammografie uitgesteld van het 30^{e} tot het 40^{e} jaar slechts gering minder effectief was of zelfs beter dan screening volgens de huidige richtlijn.
BRCA2 genmutatiedraagsters zijn eveneens gevoeliger voor het DNA beschadigende effect van ioniserende straling. In de MARIBS (2) en in de MRISC

studie (4) een substantieel deel van de BRCA2- geassocieerde tumoren werd alleen met mammografie gedetecteerd. Het ging hier hoofdzakelijk om DCIS. Echter, met toegenomen expertise en verbeterde MRI techniek is de detectie van DCIS met MRI verbeterd en zelfs beter dan met mammografie (16, 26). We verwachten dat een screeningsprotocol uitgestelde mammografie ook een beter scenario zal zijn voor BRCA2 genmutatiedraagsters jonger dan 40 jaar.

Door de geringe toegevoegde waarde van screening met mammografie bij BRCA1/2 genmutatiedraagsters dringt de vraag zich op of er niet alleen met MRI gescreend zou kunnen worden. In de Canadese studie (16) werden twee van de 57 maligniteiten bij BRCA1/2 genmutatiedraagsters alleen met mammografie gediagnosticeerd. Net als in onze studie (2 van de 94 maligniteiten in BRCA1 genmutatiedraagsters (hoofdstuk 5)) betrof dit in beide gevallen DCIS. In de eerste screeningsronde van de Ontario High Risk Breast Screening Program (27) werden geen van de 25 maligniteiten bij BRCA1/2 genmutatiedraagsters gevonden door mammografie alleen. Recente resultaten van een single-center studie (28) toonden dat geen van de 16 tumoren bij BRCA1/2 genmutatiedraagsters gedetecteerd waren met mammografie alleen.

Alhoewel steeds meer resultaten pleiten voor een screening met MRI alleen, zijn de aantallen nu toch nog te klein om screening met mammografie helemaal weg te laten.

Onze meta-analyse van de individuele patiënten gegevens afkomstig van zes prospectieve screenings trials (hoofdstuk 7) toonde aan dat de sensitiviteit van mammografie bij vrouwen met een BRCA1/2 genmutatie van 50 jaar en ouder tamelijk laag was en niet hoger dan bij genmutatiedraagsters jonger dan 50 jaar. Bovendien bleek dat toevoeging van MRI aan mammografie voor screening van BRCA1/2 genmutatiedraagsters van 50 jaar en ouder, de sensitiviteit van de screening in dezelfde mate verbeterde als bij vrouwen jonger dan 50 jaar. Continuering van screening met MRI bij genmutatiedraagsters na het 50^{e} jaar moet overwogen worden, maar tot welke leeftijd? Onze studie (hoofdstuk 7) includeerde 108 vrouwen van 60 jaar en ouder. Bij 10 van hen werd borstkanker gediagnosticeerd. Met MRI werden alle carcinomen behalve één interval carcinoom gevonden; mammografie detecteerde slechts 3 van de 10.

Voor BRCA1/2 genmutatiedraagsters boven de 60 jaar adviseert de Nederlandse Richtlijn Mammacarcinoom screening eens in de twee jaar met mammografie in het bevolkingsonderzoek. Saadatmand (29) onderzocht de resultaten van borstkanker screening bij BRCA1/2 genmutatiedraagsters ouder dan 60 jaar waarbij het tumorstadium werd vergeleken tussen vrouwen die jaarlijks en die iedere twee jaar mammografie ondergingen. De tumor stadia van 148 carcinomen gevonden bij BRCA1/2 genmutatiedraagsters

zonder een voorgeschiedenis van ovarium of borstkanker, konden worden vergeleken. Tumoren groter dan 20 mm, positieve lymfklieren of afstandsmetastasen op het moment van detectie werd gedefinieerd als ongunstig stadium. Een onacceptabel hoog percentage carcinomen werd gedetecteerd in een ongunstig stadium (53%) bij vrouwen eens per twee jaar gescreend met mammografie versus 21% bij vrouwen die jaarlijks met mammografie werden gescreend. Bovendien was het aantal intervalcarcinomen twee keer zo hoog (40 versus 20%) in de groep die twee jaarlijks werd gescreend. Deze resultaten suggereren dat BRCA1/2 genmutatiedraagsters ouder dan 60 jaar jaarlijks gescreend moeten worden met mammografie. Er kon geen vergelijkende analyse worden gemaakt voor screening met of zonder MRI omdat in deze leeftijdsgroep slechts weinig vrouwen met MRI werden gescreend. Wat het beste screeningsregime is voor BRCA1/2 genmutatiedraagsters ouder dan 60 jaar, mammografie, MRI of een combinatie, zal met verdere studies moeten worden vastgesteld.

Alhoewel door screening met MRI borstkanker in een vroeger stadium wordt ontdekt, is er weinig informatie over de impact van MRI screening bij BRCA1/2 genmutatiedraagsters op de overleving. De MRISC studie publiceerde in 2010 een eerste evaluatie van de overleving van vrouwen met een verhoogd risico gescreend met MRI en mammografie (hoofdstuk 2). In een mediane follow-up tijd van 5 jaar ontwikkelden 3 van de 31 (9.7%) BRCA1 genmutatiedraagsters en 1 van de 16 (6.3%) BRCA2 genmutatiedraagsters met invasief borstkanker, metastasen en overleden. Slechts één van deze vrouwen had positieve lymfklieren ten tijde van diagnose. Gegevens over overleving van de van BRCA1/2 genmutatiedraagsters in de Canadese studie (16) toonden een 4% borstkanker gerelateerde sterfte (één van de 28 BRCA1 genmutatiedraagsters met invasief borstkanker) in een mediane follow-up tijd van 8 jaar. In deze studie waren 63% van de carcinomen 10 mm of kleiner. Teleurstellende resultaten werden gezien in de Noorse studie (30). Tien van de 68 (14.7%) BRCA1 genmutatiedraagsters met borstkanker overleed na een mediane follow-up van 4 jaar. Er bleek een sterke relatie tussen de tumor diameter en overleving: de 10-jaars overleving was 93% voor vrouwen gediagnosticeerd met een invasieve maligniteit kleiner of gelijk aan 10 mm, de 10-jaars overleving was 58% voor vrouwen met een invasieve maligniteit tussen de 11 en 20 mm en 23% voor vrouwen bij wie de tumor groter was dan 20 mm. Slechts 40% van de tumoren gedetecteerd in deze studie waren kleiner of gelijk aan 10 mm. Bij 9 van 10 vrouwen die overleden aan borstkanker was de tumor groter dan 10 mm; bij 8 vrouwen waren er geen lymfkliermetastasen.
Kunnen we het percentage kleine tumoren verhogen om zo de overleving te verbeteren? Naar ons idee is het inderdaad haalbaar om, in vergelijking met eerdere studies, betere screenings resultaten te behalen. In onze analyse van

gevallen met een fout negatieve MRI diagnose (hoofdstuk 3) concludeerden we dat een substantieel deel van deze tumoren gemist of verkeerd geïnterpreteerd was hetgeen gedeeltelijk te verklaren was door de leercurve van een nieuwe techniek in een multicenter studie. Daarentegen, in een recentere evaluatie van screeningsresultaten bij BRCA1 genmutatiedraagsters met borstkanker (hoofdstuk 5) lieten we zien dat inderdaad betere resultaten bereikt worden als de MRI expertise en technologie verbetert. In deze studie werd meer dan 60% van de borstkanker gedetecteerd als DCIS of invasieve maligniteit met een diameter van 10 mm of kleiner. Dit was significant beter dan de 17% in de niet gescreende, symptomatische groep hetgeen de noodzaak van screening onderstreept. Het betekende ook een verbetering in vergelijking met de screeningsresultaten bij BRCA1 genmutatiedraagsters in een meta-analyse van eerdere studies zoals gepubliceerd door Heijnsdijk et al. (31). In deze meta-analyse werd 50% gedetecteerd als DCIS of invasieve maligniteit van 10 mm of kleiner. Onze recente resultaten zijn in overeenstemming met de lange termijn MR screenings resultaten van de Canadese studie waarin vrouwen met een BRCA1/2 mutatie werden geïncludeerd (16). Door de inclusie periode in twee periodes op te delen werd mooi zichtbaar gemaakt dat de sensitiviteit van MRI verbeterde in de loop van de tijd. Het overall interval percentage was 2% en 3% voor het BRCA1 cohort. Deze resultaten geven aan dat ook voor BRCA1 genmutatiedraagsters jaarlijkse screening adequaat is.
Echter, de mortaliteit bij BRCA1 genmutatiedraagsters met invasieve maligniteit en negatieve lymfklieren is hoger dan verwacht en weerspiegelt mogelijk het natuurlijk beloop bij deze tumoren.

CONCLUSIES EN TOEKOMSTIG ONDERZOEK

We hebben solide argumenten om BRCA1 genmutatiedraagsters jaarlijks te screenen met MRI vanaf het 25e jaar en om screening met mammografie uit te stellen tot het 40e jaar. Het zal onderzocht moeten worden of dit gemodificeerde protocol ook gunstiger is voor BRCA2 genmutatiedraagsters. We adviseren om screening met MRI bij BRCA1/2 genmutatiedraagsters na het 50e jaar te continueren. Het optimale screeningsprotocol voor BRCA1/2 genmutatiedraagster ouder dan 60 jaar, jaarlijks mammografie met of zonder MRI, zal met verdere studies moeten worden vastgesteld.
Alhoewel steeds meer resultaten pleiten voor screening van BRCA1/2 genmutatiedraagsters alleen met MRI zijn de aantallen toch te klein om nu al te besluiten dat mammografie helemaal weggelaten kan worden.
Om de lange termijn overleving vast te stellen, apart voor BRCA1 en BRCA2 genmutatiedraagsters, en om vast te stellen of screening een volwaardig alter-

natief is voor preventieve mastectomie, zijn resultaten van screeningscohorten met langere follow-up nodig.
Alhoewel MRI van de borst in ervaren handen een solide techniek is, moet onderzocht worden of nieuwe beeldvorming zoals mammografie na intraveneuze contrasttoediening (Contrast-Enhanced Spectral Mammography (CESM)), beter presteert dan MRI en tegen lagere kosten. Verder onderzoeken op dit moment twee groepen of het mogelijk is om gelijkwaardige resultaten te verkrijgen als het MRI protocol voor screening verkort wordt (32, 33). De kosten van screening zullen lager zijn als de acquisitietijd (de MRI tijd) en daardoor de tijd die de radioloog nodig heeft om het onderzoek te beoordelen, verkort worden.

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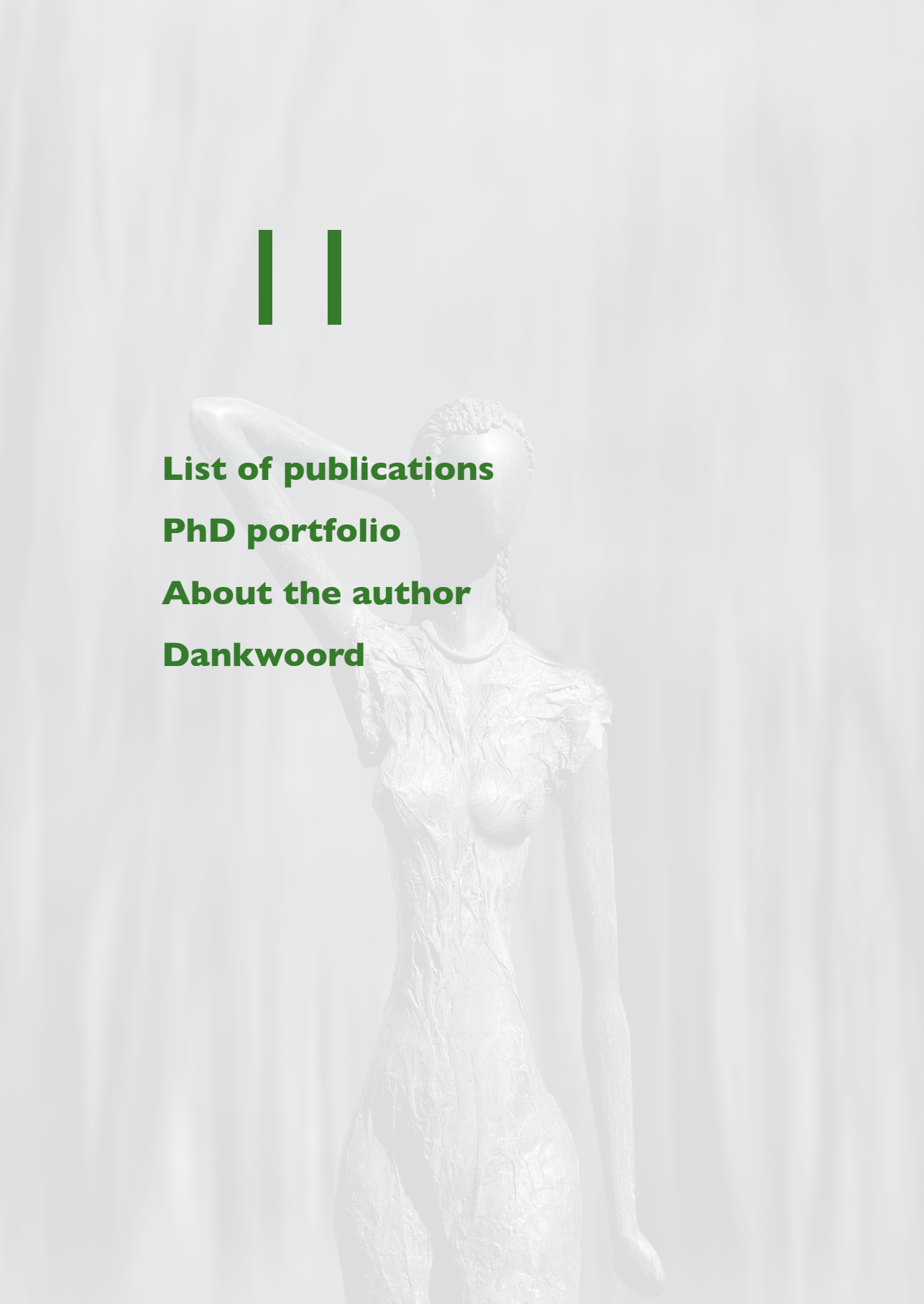

List of publications

PhD portfolio

About the author

Dankwoord

LIST OF PUBLICATIONS

1. **Inge-Marie Obdeijn***, Eveline A.M. Heijnsdijk*, M.G. Myriam Hunink, Madeleine M.A. Tilanus-Linthorst, Harry J. de Koning. Mammographic screening in BRCA1 mutation carriers postponed until age 40: benefits, costs and radiation risks
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Training Implementatie Portfolio Radiologie, EMC, Rotterdam	2010	1
Teach-the-Teacher module III EMC, Rotterdam		1
NIHES EWP05 Diagnostic Research, EMC Rotterdam	2012	1
BROK ´Basis Cursus Regelgeving Klinisch Onderzoek EMC Rotterdam	2013	1
Cursus Stralingsbescherming 5A, EMC Rotterdam	2013	1
Intermediate level "Decision Making in Medicine" EMC Rotterdam	2014	1
NIHES ESPO3 Introduction to data-analysis, EMC Rotterdam	2015	1
National and international conferences		
European Conference of Radiology (ECR) Vienna, Austria	2007	1
	2009	1
	2010	1
	2011	1
	2013	1
	2014	1
	2015	1

European Society of Breast Imaging(Eusobi) Vienna, Austria	2009	1
Barcelona, Spain	2012	1
Rome, Italy	2013	1
Amsterdam	2014	1
NKI-AVL Breast Cancer Symposium Amsterdam	2009	0.2
	2010	0.2
	2011	0.2
	2012	0.2
	2014	0.2
European Breast Cancer Conference (EBCC) Nice, France	2006	1
Vienna, Austria	2008	1
LRCB Symposium Nijmegen	2006	0.5
The Breast Course Quebec City, Canada	2008	1
Breast MRI Interpretation for Radiologists London, England	2008	1
International Congress on MR Mammography Jena, Germany	2009	1
	2012	1
MR mammography Special Gottingen	2009	1
Sandwichcursus Mammaradiologie Ede	2011	1
1st International Breast Biopsy Class Paris, France	2011	0.5
Workshop "Challenging techniques in vacuum assisted biopsy and marking" Brasschaat, Belgium	2011	1
Annual HEBON congress Utrecht	2012	1
	2013	

Cambridge Conference on Breast Cancer imaging Cambridge, England	2013	1
Update in Breast Imaging Ostend, Belgium	2013	1
Participation in projects		
EU FP7 project "Dedicated CT of the female breast" Erlangen, Germany	2009	2
National guidelines Breast Cancer	2012	3
Oral presentations		
Workshop "Challenging techniques in vacuum assisted biopsy and marking" Brasschaat, Belgium	2011	
Sandwichcursus Mammaradiologie Ede	2011	
Annual HEBON Congress	2013	
Cambridge Conference on Breast Cancer imaging Cambridge, England	2013	
Update in Breast Imaging Ostend, Belgium	2013	
Teaching activities		
Course Onco-plastic Breast Surgery Skillslab, EMC, Rotterdam	2008	1
	2009	1
	2010	1
	2011	1
	2012	1
	2013	1
	2014	1
	2015	1
		45.0

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ABOUT THE AUTHOR

Inge-Marie Obdeijn was born in Eindhoven. She obtained her Gymnasium β degree at the Mill Hill College Tilburg and her medical degree at the Radboud University of Nijmegen. After two years working at the Departments of Gynaecology and Obstetrics (St Elisabeth Ziekenhuis in Venray and Groot Ziekengasthuis in 's-Hertogenbosch) she performed her residency in Radiology at the Radboud University Medical Center in Nijmegen.
Since 1992 she is working as a radiologist with special interest in breast imaging at the Erasmus MC-Daniel den Hoed Clinic in Rotterdam. Her research is mainly on breast MRI, the results of which are described in this thesis.

Member of the steering committee of the Dutch Society of Breast Radiology.
Member of the steering committee of HEBON (Hereditary Breast and Ovarian cancer investigation in the Netherlands).

DANKWOORD

De twaalfde stelling zou kunnen zijn: promoveren doe je niet alleen. Deze stelling is trouwens makkelijk te verdedigen. Tijdens het hele traject hebben velen mij geholpen. Soms door het stellen van een vraag of door een stimulerende opmerking. Maar ook vaak door indringende gesprekken over het onderwerp van dit proefschrift. Aan allen, onafhankelijk van de impact van de bijdrage, ben ik dank verschuldigd. Een aantal mensen wil ik in het bijzonder noemen.

Allereerst mijn twee promotoren, prof. dr. M.G.M. Hunink en prof. dr. G.P. Krestin, hoofd afdeling Radiologie Erasmus MC.
Beste Myriam, uiteindelijk heb jij mij gestimuleerd om toch te gaan promoveren en heb je mij in dit hele proces fantastisch begeleid! Ondanks je volle agenda vond je telkens tijd om mijn teksten snel een zeer accuraat te reviseren en mijn vragen te beantwoorden. Ik wil je hiervoor hartelijk bedanken.
Beste Gabriel, heel hartelijk dank voor het vertrouwen in mij. Vanaf het moment dat jij hoofd van de afdeling werd was zeer duidelijk dat wetenschappelijk onderzoek voor onze afdeling jouw prioriteit had. Het onderzoek en het schrijven van de artikelen in dit proefschrift is door jou dan ook daadwerkelijk gestimuleerd en mogelijk gemaakt.

De leden van de kleine promotiecommissie, prof. dr. H.J. de Koning, prof. dr. C.C.D. van der Rijt en prof. dr. R.M. Pijnappel. Ik wil u allen hartelijk bedanken voor de tijd en de aandacht die u heeft besteed aan het beoordelen van mijn proefschrift. Ook de overige leden van de promotiecommissie wil ik hartelijk danken voor de bereidheid om met mij hierover van gedachten te wisselen.

Dr. M.M.A. Tilanus-Linthorst, lieve Madeleine, wij hebben vanaf mijn eerste dag in de Daniel intensief samengewerkt zowel in de dagelijkse praktijk als op het gebied van onderzoek. De onderwerpen van dit proefschrift hebben we uitgebreid besproken en bijna bij alle artikelen staat ook jouw naam. Ik waardeer je zeer om je gedegen kennis, je enorme doorzettingsvermogen, je passie voor het vak en je niet aflatende zorg voor je patiënten.
Eind van dit jaar zal jij je carrière beëindigen. Ik zal je missen!

Ook mijn overige co-auteurs bedank ik voor het meedenken, de kritische opmerkingen en de waardevolle suggesties. Alle collega's van het Academisch Borst Centrum bedank ik graag voor de goede dagelijkse samenwerking en de inspirerende discussies. Ik heb er vertrouwen in dat verder gezamenlijk onderzoek tot nog betere patiëntenzorg zal leiden.

Gerard en Ellen Obdeijn, ik wil jullie bedanken voor alle kansen die jullie me geboden hebben, voor jullie belangstelling en jullie vertrouwen!

Loek Wijchers, de belangrijkste en liefste man in mijn leven, was al bezig met de organisatie van een feest terwijl het manuscript nog goedgekeurd moest worden. De cover (bedankt voor de prachtige foto!) was toen overigens al klaar. Wat heerlijk dat je zo trots op mij bent!

Inge-Marie

Breast MRI in high risk patients

Inge-Marie Obdeijn