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ORIGINAL REPORT

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.

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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]

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

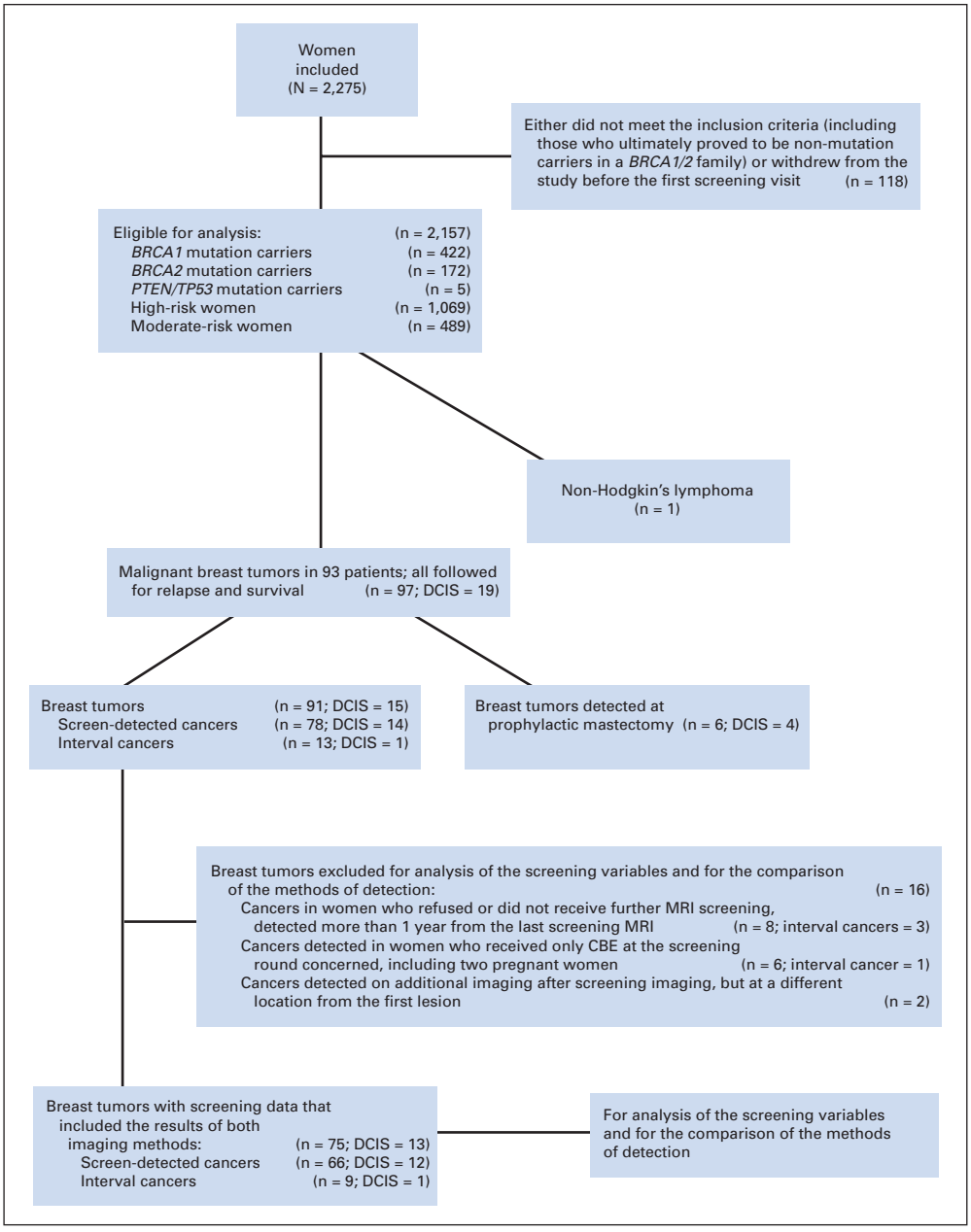

Fig 1. Flow chart describing the number of women and number of breast tumors available for statistical analysis. The numbers of DCIS and interval cancers are included in the total number of breast tumors. DCIS, ductal carcinoma in situ; MRI, magnetic resonance imaging; CBE, clinical breast examination.

BI-RADS score 3, 0, 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). 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

Table 1. Total No. of Breast Cancers Detected, Divided Into Screen-Detected Cancers and Interval Cancers, According to Risk Group

Parameter	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 carrier										
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
Risk group										
High	1,069	27	23	4	26	22	4	1	1	0
Moderate	489	16	11	5	15	11	4	1	0	1
Total	2,157	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*

Parameter	No. of Women	Woman-Years at Risk	No. of Screen-Detected and Interval Cancers		Rate of Detection†			
					All Cancers		Invasive Cancers	
			Total	Invasive	Detection Rate	95% CI	Detection Rate	95% CI
Mutation carrier								
BRCA1	422	1,178	31	29	26.3	17.9 to 37.3	24.6	16.5 to 35.3
BRCA2	172	408	16	13	39.2	22.4 to 63.7	31.9	17.0 to 54.5
PTEN/TP53	5	13	1	0	—	—	—	—
Risk group								
High	1,069	4,838	27	23	5.6‡	3.7 to 8.1	4.8‡	3.0 to 7.1
Moderate	489	2,324	16	11	6.9	3.9 to 11.2	4.7	2.4 to 8.5
Total	2,157	8,760	91	76	10.4	8.4 to 12.8	8.7	6.8 to 10.9

*The number of cancers and rates of detection are excluding the six 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 1,000 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 1,000 woman-years at risk for the total study group and *BRCA1* mutation carriers, respectively.

†Rates shown are per 1,000 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.

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*

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 − CBE Screening + or −	MRI Screening + Mmg Screening + CBE Screening + or −	MRI Screening − Mmg Screening + CBE Screening + or −	MRI Screening − Mmg Screening − CBE Screening +	Interval Cancers	Total No. of Breast Cancers
Mutation carrier						
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)
Risk group						
High	9 (1)	8	2 (1)	2	1	22 (2)
Moderate	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.

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 ($P = .04$).

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.

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

Table 5. Characteristics of Primary Breast Cancers Detected, Including Screen-Detected Cancers (n = 78) and Interval Cancers (n = 13), According to Risk Group*†

Characteristic	*BRCA1*		*BRCA2*		Risk Group: High		Risk Group: Moderate		Total		*P*: Overall Comparison Between Four Subgroups	*P*: Comparison *BRCA1 v BRCA2*
	No.	%	No.	%	No.	%	No.	%	No.	%		
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.

years). 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 present 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 nonenhancing 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 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 nonsignificantly 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 (ie, 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).[44,46,47] 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 (eg, 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.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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