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Efficacy of MRI and Mammography for Breast-Cancer Screening in Women with a Familial or Genetic Predisposition

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ABSTRACT

BACKGROUND

The value of regular surveillance for breast cancer in women with a genetic or familial predisposition to breast cancer is currently unproven. We compared the efficacy of magnetic resonance imaging (MRI) with that of mammography for screening in this group of high-risk women.

METHODS

Women who had a cumulative lifetime risk of breast cancer of 15 percent or more were screened every six months with a clinical breast examination and once a year by mammography and MRI, with independent readings. The characteristics of the cancers that were detected were compared with the characteristics of those in two different age-matched control groups.

RESULTS

We screened 1909 eligible women, including 358 carriers of germ-line mutations. Within a median follow-up period of 2.9 years, 51 tumors (44 invasive cancers, 6 ductal carcinomas in situ, and 1 lymphoma) and 1 lobular carcinoma in situ were detected. The sensitivity of clinical breast examination, mammography, and MRI for detecting invasive breast cancer was 17.9 percent, 33.3 percent, and 79.5 percent, respectively, and the specificity was 98.1 percent, 95.0 percent, and 89.8 percent, respectively. The overall discriminating capacity of MRI was significantly better than that of mammography ($P<0.05$). The proportion of invasive tumors that were 10 mm or less in diameter was significantly greater in our surveillance group (43.2 percent) than in either control group (14.0 percent [$P<0.001$] and 12.5 percent [$P=0.04$], respectively). The combined incidence of positive axillary nodes and micrometastases in invasive cancers in our study was 21.4 percent, as compared with 52.4 percent ($P<0.001$) and 56.4 percent ($P=0.001$) in the two control groups.

CONCLUSIONS

MRI appears to be more sensitive than mammography in detecting tumors in women with an inherited susceptibility to breast cancer.

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*Other investigators in the Magnetic Resonance Imaging Screening (MRISC) study are listed in the Appendix.

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THE CUMULATIVE LIFETIME RISK OF breast cancer among Dutch women is approximately 11 percent.[1] A family history of breast cancer or the presence of a germ-line mutation of the *BRCA1* or *BRCA2* gene increases this risk considerably and is often associated with a diagnosis at a young age.[2,3] Among high-risk women, the risk of breast cancer can be reduced by prophylactic mastectomy,[4,5] prophylactic oophorectomy,[6,7] or chemoprevention.[8] Early diagnosis as a result of intensive surveillance may also decrease the rate of death from breast cancer.

Randomized trials have shown that mammographic screening of all women who are between 50 and 70 years of age can reduce mortality from breast cancer by about 25 percent.[9] Although these findings were recently disputed,[10] there is a consensus among clinicians that breast-cancer screening of women in this age group is effective. Screening is one of the main factors contributing to the decrease in mortality associated with breast cancer in the Netherlands.[11] However, there is no consensus about the value of breast-cancer screening among women who are 40 to 49 years old.[12-14] One of the reasons for the lack of agreement is the difficulty in detecting tumors by mammographic screening in younger women, who have denser breasts than postmenopausal women.[15,16] Although screening is frequently offered to women with a genetic predisposition to breast cancer who are under the age of 50 years, the efficacy of this approach is unproven. Preliminary results of surveillance by mammography and clinical breast examination in such women showed that mammographic screening has a low sensitivity for detecting tumors, especially in carriers of a *BRCA* mutation.[17-21] Possible reasons, apart from the high rate of growth of tumors in women with such mutations, include the atypical changes seen on screening mammograms and specific histopathological characteristics in carriers of *BRCA* mutations, as compared with noncarriers of the same age.[22-24]

In a diagnostic setting, magnetic resonance imaging (MRI) is a sensitive method of breast imaging, and it is virtually uninfluenced by breast density, but the specificity is variable and the costs are high.[25-27] Because MRI may improve the sensitivity of screening in women with a familial or genetic predisposition to breast cancer, we prospectively compared MRI with mammography for screening women with such a predisposition in order to determine whether screening with MRI facilitated the early diagnosis of hereditary breast cancer.

METHODS

STUDY POPULATION

The design of our MRI screening study, in which six subcommittees in different disciplines were involved, has been described previously.[28] Between November 1, 1999, and October 1, 2003, 1952 women with a genetic risk of breast cancer were recruited for the study by six familial-cancer clinics in the Netherlands. The six centers were Erasmus Medical Center–Daniel den Hoed Cancer Center, Rotterdam; the Netherlands Cancer Institute, Amsterdam; University Medical Center Nijmegen, Nijmegen; Leiden University Medical Center, Leiden; University Hospital Groningen, Groningen; and Free University Medical Center, Amsterdam. The study was approved by the ethics committees of all the centers. All the women who participated gave written informed consent.

The inclusion criteria for participation were a cumulative lifetime risk of breast cancer of 15 percent or more owing to a familial or genetic predisposition, according to the modified tables of Claus et al.,[29] and an age of 25 to 70 years. Women could be tested at an age younger than 25 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. Women with symptoms that were suggestive of breast cancer or women who had a personal history of breast cancer were excluded.

SURVEILLANCE

Surveillance consisted of a clinical breast examination performed by an experienced physician every six months and imaging studies performed annually by experienced radiologists. The imaging included a mammographic study (oblique and craniocaudal views and, if necessary, compression views or magnifications) and a dynamic breast MRI with gadolinium-containing contrast medium according to a standard protocol.[25] Whenever possible, both imaging investigations were performed on the same day or in the same time period, between day 5 and day 15 of the menstrual cycle. The results of mammography and MRI were scored in a standardized way, according to the Breast Imaging Reporting and Data System (BI-RADS) classification,[30,31] and the results were blinded so that the two examinations were not linked. When one of the examinations was scored as either BI-RADS category 3 ("probably benign [i.e., uncertain] find-

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ing") or category 0 ("need additional imaging evaluation"), further investigation by ultrasonography with or without fine-needle aspiration was advised, or mammography or MRI was repeated. When one of the two examinations was scored as BI-RADS category 4 ("suspicious abnormality") or category 5 ("highly suggestive of malignancy"), a cytologic or histologic evaluation of a biopsy specimen was performed. When the results of mammography and MRI were negative but the findings on clinical breast examination were rated as uncertain or suspicious, additional investigation was also performed. The diagnosis of malignant tumors was based on the results of a histologic examination. One of the investigators, an expert pathologist, reviewed all the biopsy specimens that formed the basis for the diagnosis of breast cancer.

STATISTICAL ANALYSIS

The women were divided into three categories according to the cumulative lifetime risk of breast cancer, as follows: carriers of the *BRCA1* or *BRCA2* or other mutations (cumulative lifetime risk, 50 to 85 percent), a high-risk group (risk, 30 to 49 percent), and a moderate-risk group (risk, 15 to 29 percent).[28,29] The characteristics of the women in each risk group were compared by analysis of variance or Pearson's chi-square test.

The rates of detection of breast cancer for the group as a whole and for each of the three risk groups were calculated, and a Poisson distribution was assumed in order to calculate the 95 percent confidence intervals. Person-years at risk were calculated from the date of the first examination, irrespective of the type of examination, to the date of detection of breast cancer, bilateral prophylactic mastectomy, or death; the date that a patient stopped surveillance; or the cutoff date for this analysis (October 1, 2003). An "interval cancer" was defined as a carcinoma detected between two rounds of screening after initially negative findings on screening. In our analysis, we defined as positive a mammographic or MRI study with a BI-RADS score of 0, 3, 4, or 5 and a clinical breast examination that was classified as "uncertain" or "suspicious," because those were the results that triggered an additional examination.

To compare the three different screening methods, we calculated the sensitivity, specificity, and positive predictive value of each. The sensitivity used is that of one screening method relative to the others, meaning that a test result is a false negative when a proven cancer (diagnosed on the basis of a histologic examination) is detected in the interval or by one of the other methods. Receiver-operating-characteristic (ROC) curves for the two imaging methods were generated. The area under the curve was used as an index in evaluating the inherent capacity of a screening method to discriminate between "positive" and "negative" cases. We used a z-test to compare the area under the curve for the results of mammography and MRI. For the analysis of the screening variables, we used only the screening data that included the results of both mammography and MRI.

To determine whether breast cancer was diagnosed by screening at a stage more favorable to treatment, the characteristics of breast tumors detected in the study group were compared with those in two control groups. The first control group was derived from all women who had breast cancers diagnosed in 1998 in the Netherlands. These data were obtained from the National Cancer Registry. The second control group consisted of unselected patients who had received a diagnosis of primary breast cancer in Leiden or Rotterdam between 1996 and 2002 and who were participating in a prospective study of the prevalence of gene mutations.[32] Subjects in both control groups were matched for age with the patients in the study group (in five-year categories). From this series of consecutive patients in the second control group, we chose all the unscreened patients who were between 25 and 60 years old and whose cumulative lifetime risk of breast cancer was more than 15 percent because of a family history of the disease — information that was routinely recorded in this database. The differences in tumor characteristics between the study group and the control groups were tested with the use of Pearson's chi-square test or the chi-square test for trend. A two-sided P value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed with the use of SPSS software (version 9.0).

RESULTS

STUDY POPULATION

Of the women who were invited to participate in the study, 90 percent agreed. Initially, 1952 women were included; 8 withdrew from the study before their first screening visit and another 35 were excluded because they ultimately proved not to be carriers in a family with a proven mutation and there-

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fore had less than a 15 percent cumulative lifetime risk of breast cancer. Of the 1909 remaining women, 88 (4.6 percent) left the study or were lost to surveillance before October 1, 2003; 65 of these 88 women underwent prophylactic mastectomy. Another 89 women (4.7 percent) remained under surveillance but later refused screening by MRI, because of claustrophobia or for other reasons.

Table 1 lists the characteristics of the 1909 women according to risk category. The mean age at en-

Table 1. Characteristics of Participating Women at Study Entry, According to Risk Group.*

Characteristic	Mutation Carriers (N=358)	High-Risk Group (N=1052)	Moderate-Risk Group (N=499)	Total (N=1909)
Mean age — yr†	38	41	40	40
Previous screening — no. (%)				
No screening	56 (16)	161 (16)	72 (15)	289 (15)
Only CBE	10 (3)	17 (2)	13 (3)	40 (2)
Imaging (with or without CBE)				
≤1 yr before entry	189 (53)	543 (52)	268 (54)	1000 (53)
>1–2 yr before entry	79 (22)	259 (25)	111 (22)	449 (24)
>2 yr before entry	17 (5)	46 (4)	23 (5)	86 (5)
Time unknown	2 (1)	8 (1)	4 (1)	14 (1)
Unknown	5	18	8	31
Menopausal status — no. (%)†				
Premenopausal	244 (72)	754 (76)	376 (78)	1365 (75)
Perimenopausal‡	5 (2)	34 (3)	15 (3)	54 (3)
Postmenopausal	20 (6)	121 (12)	52 (11)	193 (11)
Postmenopausal after oophorectomy	66 (19)	42 (4)	12 (3)	120 (7)
Posthysterectomy	3 (1)	48 (5)	24 (5)	75 (4)
Unknown	20	53	29	102
Hormonal contraceptive use — no. (%)				
Never	40 (12)	108 (11)	45 (10)	193 (10)
Past	167 (50)	567 (56)	276 (58)	1010 (56)
Present	128 (38)	329 (33)	154 (32)	611 (34)
Unknown	23	48	24	95
HRT use — no. (%)§				
Never	291 (87)	932 (92)	436 (92)	1659 (90)
Past	19 (6)	44 (4)	19 (4)	82 (5)
Present	25 (7)	38 (4)	19 (4)	82 (5)
Unknown	23	38	25	86
Oophorectomy — no. (%)†				
No	276 (78)	1000 (96)	477 (97)	1753 (93)
Yes	77 (22)	41 (4)	13 (3)	131 (7)
Unknown	5	11	9	25

* Women in the group with mutations were those with *BRCA1, BRCA2, PTEN,* or *TP53* genetic mutations. Women in the high-risk group were those with a cumulative lifetime risk of 30 to 49 percent. Women in the moderate-risk group were those with a cumulative lifetime risk of 15 to 29 percent. CBE denotes clinical breast examination, and HRT hormone-replacement therapy. Percentages are based on the numbers of women with known data; numbers with missing data are also shown.
† P<0.001 for the difference among the three groups.
‡ Perimenopausal status was defined by the occurrence of the last menstruation between 2 and 12 months before entry into the study.
§ P=0.04 for the difference among the three groups.

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try was 40 years (range, 19 to 72). Within the group of 358 carriers of pathogenic mutations, 276 had a *BRCA1* mutation, 77 had a *BRCA2* mutation, 1 had both a *BRCA1* and a *BRCA2* mutation, 2 had a *PTEN* mutation, and 2 had a *TP53* mutation.

BREAST CANCERS

From November 1, 1999, to October 1, 2003, 51 malignant tumors (44 invasive breast cancers, 6 ductal carcinomas in situ, and 1 non-Hodgkin's lymphoma) were detected (Fig. 1), during a median follow-up period of 2.9 years (mean 2.7, range, 0.1 to 3.9 years); 1 lobular carcinoma in situ was also found. Table 2 shows the detection rate for the whole group and separately for the different risk groups. The overall rate of detection for all breast cancers (invasive plus in situ) was 9.5 per 1000 woman-years at risk (95 percent confidence interval, 7.1 to 12.3), with the highest rate (26.5 per 1000) in the group of women who were carriers of the *BRCA1*, *BRCA2*, *PTEN*, and *TP53* mutations.

PERFORMANCE OF THE SCREENING METHODS

Table 3 shows the results with the three screening methods. Of the 50 breast cancers that were detected, 5 were excluded from the analysis (Table 3). The 45 cancers that were evaluated in the comparison of the methods included 4 interval cancers (i.e., cancers detected between two episodes of screening). The first was symptomatic (30 mm in diameter, node-negative), detected seven months after screening by imaging and clinical breast examination and one month after screening by clinical breast examination only. The second (4 mm, node-negative) was detected in a specimen from a prophylactic mastectomy. The third was symptomatic (45 mm, node-negative) and was detected seven months after screening by imaging; the fourth, also symptomatic

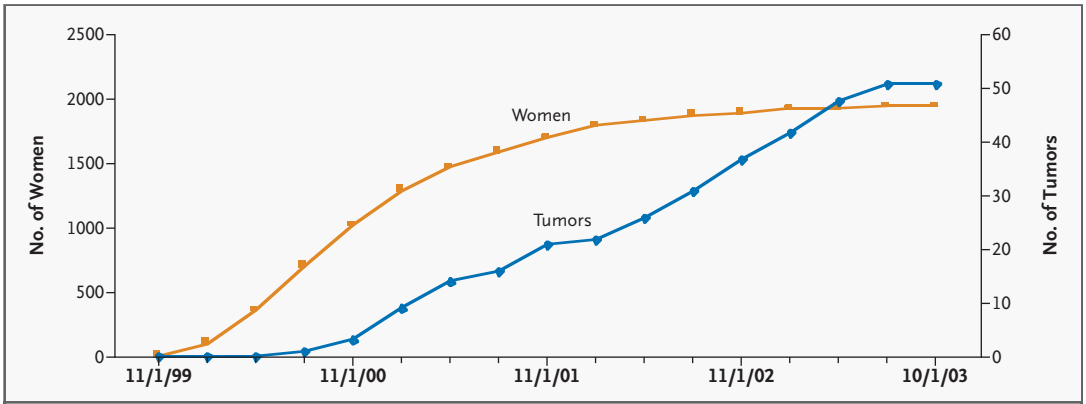

Figure 1. Women at Increased Risk for Breast Cancer Enrolled and Tumors Detected.
A total of 1952 women were enrolled, of whom 1909 were eligible for this analysis.

Table 2. Detection of Cases of Breast Cancer (Including Ductal Carcinoma in Situ) According to Risk Group.

Risk Group	No. of Women	Woman-Years at Risk	No. of Cases Detected by Screening		No. of Cases Detected between Screenings		Rate of Detection (95% CI)*	
			Total	Invasive	Total	Invasive	All Cancers	Invasive Cancers
							no./1000	
Mutation carriers	358	867	19	16	4	4	26.5 (15.3–39.4)	23.1 (14.1–35.6)
High-risk group	1052	2968	15	15	1	1	5.4 (3.1–8.8)	5.4 (3.1–8.8)
Moderate-risk group	499	1414	11	8			7.8 (3.9–13.9)	5.7 (2.4–11.1)
Total	1909	5249	45	39	5	5	9.5 (7.1–12.3)	8.4 (6.1–11.3)

* CI denotes confidence interval. Rates shown are per 1000 woman-years at risk.

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Table 3. Sensitivity, Specificity, and Positive Predictive Value (PPV) of the Three Screening Methods.*

Screening Method and BI-RADS Cutoff	No. of Tests	No. of Breast Cancers	Cumulative No. of Tests	Cumulative No. of True Positive Results	Sensitivity (%)		Specificity (%)	PPV (%)	No. of Biopsies Performed
					Any Breast Cancer	Invasive Breast Cancer			
Clinical breast examination									
Suspicious	6	3	6	3	6.7	7.7	99.9	50.0	4
Probably benign	77	5	83	8	17.8	17.9	98.1	9.6	8
Negative	3862	37	3945	45	100	100	0	1.1	55
Mammography									
5 (highly suggestive)	3	3	3	3	6.7	7.7	100	100	3
4 (suspicious)	20	8	23	11	24.4	20.5	99.7	47.8	8
0 (need additional imaging)	32	4	55	15	33.3	28.2	99.0	27.3	9
3 (probably benign)	170	3	225	18	40.0	33.3	95.0	8.0	5
2 (benign)	240	2	465	20	44.4	38.5	89.2	4.3	4
1 (negative)	3704	25	4169	45	100	100	0	1.1	38
MRI									
5 (highly suggestive)	10	6	10	6	13.3	15.4	99.9	60.0	7
4 (suspicious)	55	15	65	21	46.6	51.3	98.9	32.3	22
0 (need additional imaging)	112	8	177	29	64.4	71.8	96.4	16.4	15
3 (probably benign)	275	3	452	32	71.1	79.5	89.8	7.1	12
2 (benign)	383	1	835	33	73.3	82.1	80.6	4.0	0
1 (negative)	3334	12	4169	45	100	100	0	1.1	11

* The results have been calculated on the basis of data on 45 of the 50 cancers. The reasons that five cases were omitted are as follows. In three cases, neither MRI nor mammography was performed (in two of these cases the women became pregnant, and in one case the woman refused MRI). In the fourth case, a tumor was detected on an additional mammogram, after a screening mammogram had been classified as Breast Imaging Reporting and Data System (BI-RADS) 0, but at a different location from the first lesion. The fifth cancer was detected at a screening visit that consisted of only a clinical breast examination. The cumulative number of true positive results is the number of cancers found at a specific BI-RADS level or higher; sensitivity is the percentage of cancers with a positive test result at a specific BI-RADS level or higher (the cumulative number of true positive results divided by the total number of cancers); specificity is the percentage of negative test results in women without a cancer; PPV is the percentage of true positive test results in women who ultimately appeared to have cancer, at a specific BI-RADS level or higher (the cumulative number of true positive test results divided by the cumulative number of tests).

(13 mm, with isolated tumor cells in a lymph node), was detected three months after screening by imaging.

Overall, 32 breast cancers were found by MRI (22 of these were not visible on mammography), whereas 13 were missed by MRI (8 of the 13 were visible on mammography, including 5 ductal carcinomas in situ; 4 were interval cancers; and 1 tumor was detected only by clinical breast examination). In this group of 45 breast cancers, mammographic screening detected 18 tumors (10 of these were visible by MRI) and missed 27 tumors (including the 22 that were visible on MRI, the 4 interval cancers, and the 1 that was detected only by clinical breast examination).

With respect to all breast cancers (invasive and ductal carcinoma in situ), the sensitivity of clinical breast examination, mammography, and MRI was 17.8 percent, 40.0 percent, and 71.1 percent, respectively, when the BI-RADS score was 3 or higher (Table 3). For invasive cancers only, the respective percentages were 17.9 percent, 33.3 percent, and 79.5 percent. The specificity was 98.1 percent for clinical breast examination, 95.0 percent for mammography, and 89.8 percent for MRI.

Of the 41 cancers found by screening, 22 were detected at the first imaging screening in the study; of the women in whom cancer was detected, 16 had undergone mammographic screening before the start of the study. Two of the interval cancers were

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detected after the first imaging screening, and two others after a subsequent imaging screening. The sensitivity of mammography was 37.5 percent for the first screening and 42.9 percent for subsequent screening (P=0.71). The sensitivity of MRI was 79.2 percent for the first screening and 61.9 percent for subsequent screening (P=0.20).

Among the 83 clinical breast examinations with findings that were judged as probably benign or suspicious, or highly suggestive of cancer, 8 cases of malignant disease were confirmed, for a positive predictive value of 9.6 percent (Table 3). Among the 225 mammograms with findings categorized as BI-RADS 3 or higher, 18 cases of malignant disease were confirmed, for a positive predictive value of 8.0 percent. A total of 32 cancers were confirmed among 452 MRI screenings with such findings, for a positive predictive value of 7.1 percent (Table 3). With a cutoff level of BI-RADS 4, the sensitivity for both imaging methods decreased, whereas the specificity increased.

To evaluate the discriminating capacity of the imaging methods, we generated ROC curves (Fig. 2). The area under the curve was 0.686 for mammography and 0.827 for MRI; the difference between the areas was 0.141 (95 percent confidence interval, 0.020 to 0.262; P<0.05).

ADDITIONAL INVESTIGATIONS

Ultrasonography was performed 889 times in 627 different women according to the protocol. Fine-needle aspiration was carried out 312 times: 267 times in combination with ultrasonography and 45 times with palpation. Biopsy was performed 85 times in 82 women and showed malignant disease in 50 cases and 1 lobular carcinoma in situ, making the rate of positive histologic findings 60.0 percent. Sixty-seven of these 85 biopsies were performed after a screening visit at which both MRI and mammography were performed. Of the 25 biopsies in women who had mammographic findings with a score of 3 or higher, 7 (28.0 percent) showed no cancer. Of the 56 biopsies in women who had MRI findings with a score of 3 or higher, 24 (42.9 percent) showed no cancer (Table 3). One of the 51 tumors was found in a specimen from a prophylactic mastectomy.

TUMOR CHARACTERISTICS

Table 4 compares the characteristics of tumors found in the study group with those of tumors in the two age-matched control groups. In the study group, 19 of the 44 women with an invasive breast cancer (43.2 percent) had a small tumor (≤10 mm in diameter) — a proportion that was significantly higher than that in the first control group (14.0 percent, P<0.001) or the second control group (12.5 percent, P=0.04). Six of 42 invasive tumors (14.3 percent) with known axillary status in the study group were node-positive and 3 (7.1 percent) had micrometastases (combined total, 21.4 percent). This rate was significantly lower than those in both control groups, in which the rates of node-positive cancer were 52.4 percent (P<0.001) and 56.4 percent (P=0.001), respectively. There were no major differences between the study and control groups with respect to histologic features, with the exception of a relatively high incidence of the medullary type in the study group (11.3 percent, vs. 1.8 percent in the first control group). In the study group, a high proportion of grade 1 tumors were in women at high risk (68.8 percent) or moderate risk (75.0 percent); however, the group of women with *BRCA1*, *BRCA2*, or other mutations had a high percentage of grade 3 tumors (63.2 percent), in addition to a high percentage of tumors that were negative for steroid receptors (Table 4).

DISEASE-FREE AND OVERALL SURVIVAL

In the study group, none of the 50 patients with breast cancer (44 with invasive cancer and 6 with ductal carcinoma in situ) died before the end of the study period; the total follow-up after diagnosis was 87.6 woman-years for these 50 patients (median, 1.5 years). Contralateral breast cancer occurred in one patient. The patient with non-Hodgkin's lymphoma died.

DISCUSSION

In this prospective study, we compared the efficacy of mammographic and MRI screening for breast cancer in women with a family history of the disease or a genetic predisposition to breast cancer. Among the women examined by both methods at the same screening visit, we detected 45 breast cancers (including 6 ductal carcinomas in situ): 32 by MRI (sensitivity, 71.1 percent) and 18 by mammography (40.0 percent); five other patients were excluded from this comparison for various reasons (Table 3). Thus, the sensitivity of MRI was higher than that of mammography, but both the specificity and positive predictive value of MRI were lower.

In our sensitivity and specificity calculations, we

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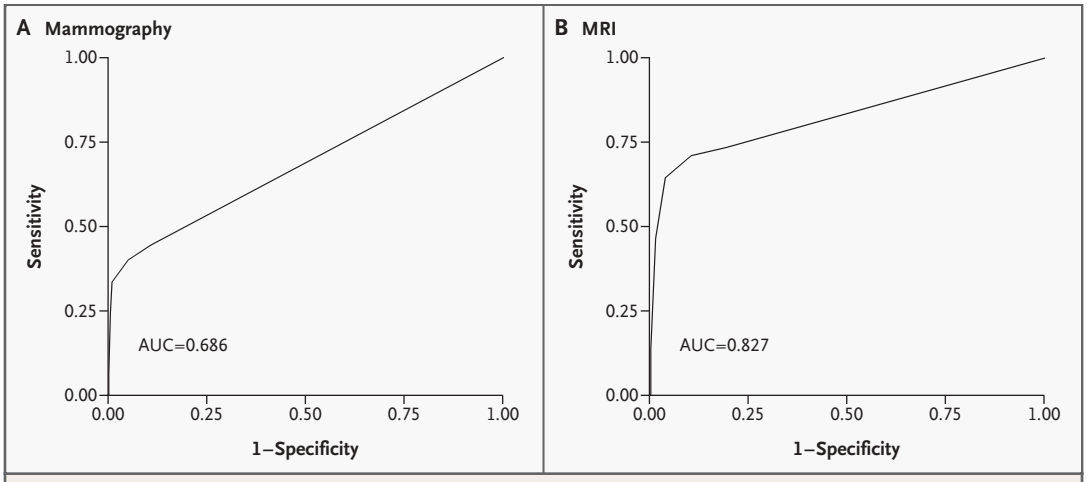

Figure 2. Receiver-Operating-Characteristic Curves for Mammography and MRI.
The difference between the area under the curve (AUC) for mammography and the AUC for MRI was 0.141 (95 percent confidence interval, 0.020 to 0.262; P<0.05).

defined lesions that were in BI-RADS category 3 and higher as positive, but most other authors have included in their calculations only lesions in BI-RADS categories 4 and 5 as positive.[21,33,34] If we had followed that policy, the sensitivity would have been 24.4 percent for mammography and 46.6 percent for MRI, in accord with the higher sensitivity previously reported for MRI.[21,33,35,36] However, the previous studies enrolled small groups of women, included some retrospective data,[35] evaluated heterogeneous groups that included women with previous breast cancers,[21,33,36] or had a plan for follow-up after a suspicious finding on MRI that differed from the follow-up plan for a suspicious mammographic finding.[33] All these factors might have artificially increased the sensitivity of MRI. We also investigated sensitivity in relation to specificity as determined by ROC curves, showing that the area under the curve was significantly higher for MRI than for mammography; this means that MRI screening could better discriminate between malignant and benign cases.

When we included only invasive breast cancers, the difference between the sensitivity of the MRI and mammography (79.5 percent vs. 33.3 percent) was even greater than the difference overall (71.1 percent vs. 40.0 percent). MRI detected 20 cancers (including 1 ductal carcinoma in situ) that were not found by mammography or clinical breast examination. The stage of these 20 cancers was favorable; 11 of the 19 invasive tumors were smaller than 10 mm, and only 1 was associated with a positive node.

Another important matter that we addressed was the best method for detecting carcinoma in situ. Our study showed that mammography had a higher sensitivity than MRI for detecting ductal carcinoma in situ: 83 percent (five out of six cancers detected), as compared with 17 percent (one out of six) for MRI (P=0.22).

To investigate whether screening improves the chance of diagnosing breast cancer at an early stage, we compared the distribution of tumor stages in our study with the distribution in two external control groups. The first group consisted of age-matched women in a database of all breast cancers diagnosed in 1998 in the Netherlands. A drawback of this group is that we had no information about whether or not they had been screened or the family history. Therefore, we added a second control group from a prospective population-based study of the prevalence of mutations in patients with breast cancer. From this group, we selected all patients with an age and a family history of breast cancer that were similar to the women in our surveillance study. The tumors in our study group were significantly smaller and were less likely to be node-positive than those in the two control groups. Most screening studies (without MRI) in high-risk women have shown a higher incidence of positive nodes (30 to 45 percent) than we found (21 percent).[17,18,37] Moreover, Kollias et al.[38] found no

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Table 4. Characteristics of Women with Breast Cancer and Breast Cancers Detected in the Three Risk Groups and in the Two Control Groups.*

Characteristic	Mutation Carriers†	High-Risk Group	Moderate-Risk Group	Total Screened	Control Group 1 (National Cancer Registry)	Control Group 2 (Prospective Study)
No. of women	23	16	11	50	1500	45
			number of cancers (percent)			
Age at diagnosis						
20–29 yr	2 (8.7)	0	0	2 (4.0)	60 (4.0)	3 (6.7)
30–39 yr	13 (56.5)	5 (31.3)	1 (9.1)	19 (38.0)	570 (38.0)	13 (28.9)
40–49 yr	6 (26.1)	7 (43.7)	7 (63.6)	20 (40.0)	600 (40.0)	21 (46.6)
50–69 yr	2 (8.7)	4 (25.0)	3 (27.3)	9 (18.0)	270 (18.0)	8 (17.8)
Tumor size						
Ductal carcinoma in situ	3 (13.0)	0	3 (27.3)	6 (12.0)	120 (8.0)	—
Invasive tumors						
≤1 cm	7 (35.0)	8 (50.0)	4 (50.0)	19 (43.2)‡§	193 (14.0)	5 (12.5)
1–2 cm	6 (30.0)	5 (31.2)	3 (37.5)	14 (31.8)	508 (36.8)	15 (40.0)
>2 cm	7 (35.0)	3 (18.8)	1 (12.5)	11 (25.0)	679 (49.2)	19 (47.5)
Nodal status¶						
Negative	12 (63.2)	9 (60.0)	7 (87.5)	28 (66.7)‡‖	657 (47.6)	17 (43.6)
Isolated cells	3 (15.8)	2 (13.3)	0	5 (11.9)	—	—
Positive	2 (10.5)	3 (20.0)	1 (12.5)	6 (14.3)	723 (52.4)	22 (56.4)
Micrometastasis (0.2–2.0 mm)	2 (10.5)	1 (6.7)	0	3 (7.1)	—	—
Histologic type						
Ductal	14 (70.0)	11 (68.7)	5 (62.5)	30 (68.2)	1146 (83.0)	—
Lobular	1 (5.0)	1 (6.3)	2 (25.0)	4 (9.1)	128 (9.3)	—
Tubular	1 (5.0)	2 (12.4)	1 (12.5)	4 (9.1)	34 (2.6)	—
Medullary	4 (20.0)	1 (6.3)	0	5 (11.3)	25 (1.8)	—
Adenoid cystic	0	1 (6.3)	0	1 (2.3)	1 (0.7)	—
Other	0	0	0	0	46 (3.3)	—
Histologic grade**						
Grade 1	2 (10.5)	11 (68.8)	6 (75.0)	19 (44.2)‡††	99 (11.0)	4 (10.8)
Grade 2	5 (26.3)	1 (6.2)	2 (25.0)	8 (18.6)	339 (37.7)	14 (37.8)
Grade 3	12 (63.2)	4 (25.0)	0	16 (37.2)	462 (51.3)	19 (51.4)
Estrogen-receptor status**						
Positive	6 (33.3)	11 (73.3)	7 (87.5)	24 (58.5)	—	20 (60.6)
Negative	12 (66.7)	4 (26.7)	1 (12.5)	17 (41.5)	—	13 (39.4)
Progesterone-receptor status**						
Positive	7 (36.8)	11 (73.3)	7 (87.5)	25 (59.5)	—	14 (46.7)
Negative	12 (63.2)	4 (26.7)	1 (12.5)	17 (40.5)	—	16 (53.3)

* Percentages are based on the numbers of women with known data; numbers with missing data are not shown. In the control groups, zero denotes none, and the dash denotes not analyzed.
† There were 16 *BRCA-1*–related tumors (including 1 ductal carcinoma in situ), 6 *BRCA-2*–related tumors (including 1 ductal carcinoma in situ), and 1 *PTEN*-related tumor (ductal carcinoma in situ).
‡ P<0.001 for the comparison with the National Cancer Registry control group.
§ P=0.04 for the comparison with control group 2.
¶ Nodal biopsy was not performed in two cases in the study group.
‖ P=0.001 for the comparison with control group 2.
** Histologic status was unknown in some cases in the study group.
†† P=0.01 for the comparison with control group 2.

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significant differences in the size or grade of invasive tumors or in lymph-node status between women who had symptoms of cancer and women whose cancers had been found on screening by mammography. So we may conclude that MRI screening did indeed contribute to the early detection of hereditary breast cancer.

However, larger tumors (>2 cm in diameter) were found more often in the women with *BRCA1*, *BRCA2*, *PTEN*, and *TP53* mutations than in the other two risk groups in our study, suggesting that more frequent screening is needed for women with these mutations. A drawback of MRI screening is that it has a lower specificity than mammography, and as a result, MRI will generate more findings judged as uncertain, which require short-term follow-up or additional investigations.[39] In our study, screening by MRI led to twice as many unneeded additional examinations as did mammography (420 vs. 207) and three times as many unneeded biopsies (24 vs. 7).

In conclusion, our study shows that the screening program we used, especially MRI screening, can detect breast cancer at an early stage in women at risk for breast cancer.

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APPENDIX

In addition to the authors, the following investigators participated in the MRISC Study: Erasmus Medical Center, Rotterdam — C.C.M. Bartels, A. Ciurea, A.N. van Geel, E.J. Meijers-Heijboer, M. Menke, A.J. Rijnsburger, C. Seynaeve, D. Urich; Leiden University Medical Center, Leiden — C. van Asperen, M.N.J.M. Wasser; Netherlands Cancer Institute, Amsterdam — R. Kaas, W. Koops, M. Piek-den Hartog, M. van de Vijver; University Hospital Groningen, Groningen — C. Dorbritz, S. van Hoof, A.M. van der Vliet, J. de Vries; University Medical Center Nijmegen, Nijmegen — J.O. Barentsz, H. Brunner, J.H.C.L. Hendriks, R. Holland, N. Hoogerbrugge, M. Stoutjesdijk, A.L.M. Verbeek, T. Wobbes; Free University Medical Center, Amsterdam — F. Menko, A. Taets van Amerongen.

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