

The impact of a false-positive MRI on the choice for mastectomy in *BRCA* mutation carriers is limited

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Received 19 October 2007; accepted 22 October 2007

Purpose: To assess the false-positive rate of breast cancer surveillance by magnetic resonance imaging (MRI) in *BRCA* mutation carriers and the impact of an abnormal mammography or breast MRI on the patients' decision for prophylactic mastectomy.

Patients and methods: A total of 196 *BRCA* mutation carriers were included with a median follow-up of 2 years (range 1–9) with annual mammography and MRI. Preference for prophylactic mastectomy was registered at first surveillance after the mutation carriership was revealed.

Results: In all, 41% (81 of 196) of the women had at least one positive MRI or mammography. Malignancy was detected in 17 women: 11 at surveillance, 4 at an intended prophylactic mastectomy and 2 had an interval cancer. Imaging by mammography and MRI had a sensitivity of 71% and a specificity of 90%. The probability that a positive MRI result is false positive was 83%. In the group with a prior preference for mastectomy with and without a false-positive imaging, prophylactic mastectomy was carried out in 89% and 66%, respectively ($P = 0.06$), in the group with prior preference for surveillance these percentages were 15% and 11%, respectively ($P = 0.47$).

Conclusion: Although the rate of false-positive MRI results is high, the impact on the choice for prophylactic mastectomy is limited and is determined by the woman's preference before the establishment of a *BRCA* mutation.

Key words: *BRCA*, breast cancer, mastectomy, MRI, prevention, surveillance

introduction

Women with an inherited *BRCA1* or *BRCA2* mutation have a lifetime risk for breast cancer of up to 85% and for ovarian cancer of up to 60%, often diagnosed at young age [1].

Although it is generally accepted that women with a pathogenic germline mutation in the *BRCA1* or *BRCA2* gene are candidates for prophylactic mastectomy, many decline this possibility and seek effective breast cancer surveillance [2, 3]. For women with a *BRCA* mutation, current surveillance protocols recommend annual mammography and annual contrast-enhanced breast magnetic resonance imaging (MRI) starting at the age of 25 years [4]. Whether either prophylactic mastectomy or surveillance is optimal in terms of benefits and risks is still a subject of debate with major implications for the cancer risk management counseling. Good quantification of the diagnostic accuracy of surveillance in daily practice is needed as preventive surgery is irreversible.

Accurate instruments are required for effective surveillance of *BRCA* mutation carriers. Both ductal carcinoma *in situ*

(DCIS) and invasive cancer need to be detected with high accuracy in *BRCA* mutation carriers, since accelerated progression from DCIS to invasive cancer may occur in these patients and because relatively small-sized invasive cancers can metastasize [5–8]. Due to the addition of MRI to breast cancer surveillance in high-risk women, breast cancer is detected at an earlier stage, but entails an increasing rate of false-positive test results [9].

In this study, we evaluated the false-positive rate of breast cancer surveillance by MRI in *BRCA* mutation carriers in daily practice and investigated the impact of an abnormal mammogram or MRI on a woman's choice for prophylactic mastectomy.

materials and methods

patients and methods

The study population comprised in total 196 women with a pathogenic *BRCA1* or *BRCA2* mutation detected at the Human Genetics Department of the Radboud University Nijmegen Medical Centre from September 1999 to September 2005. Women with a *BRCA*-unclassified variant and women with only one surveillance visit were not included in this study. Patients were recruited a few weeks after the genetic counseling session in which the mutation carriership was disclosed. At first surveillance visit,

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their preference for either mastectomy (within ≥ 1 year) or surveillance was documented. Surveillance encompassed a clinical breast examination by an experienced medical specialist every 6 months and imaging. The imaging included a mammography (oblique and craniocaudal views), and whenever possible, a dynamic breast MRI with a gadolinium containing contrast medium. Exclusion criteria for MRI were claustrophobia and obesity. Mammography and MRI were carried out on the same day, between day 5 and day 12 of the menstrual cycle. The results of mammography and MRI were scored according to the Breast Imaging Reporting and Data System (BIRADS) classification by the same radiologist [10]. The results of MRI and mammography were not blinded for each other. In case the results of clinical breast examination were uncertain or if BIRADS was category 3 or higher, further investigation by ultrasound was carried out whenever possible with a histological evaluation of a core needle biopsy specimen. When the suspected lesion could not be evaluated by ultrasound, a stereotactic or MRI-guided biopsy was carried out. The diagnosis of a malignant tumor was on the basis of the results of histological examination. For women undergoing a prophylactic mastectomy, physical breast examination, mammography and MRI were carried out in the 3-month period leading up to surgery.

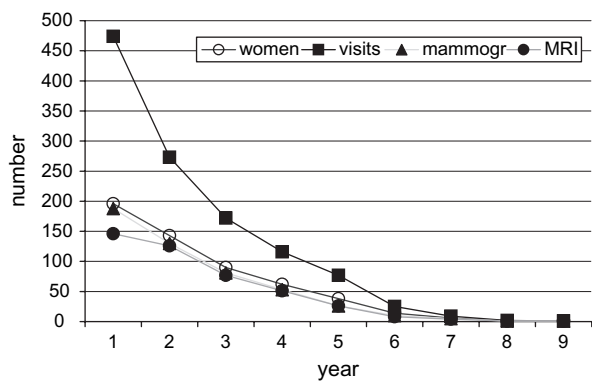
data analysis

Descriptive data are reported as mean \pm standard deviation for continuous variables and as percentages for categorical variables. Group comparisons were tested for statistical significance using *t*-tests for continuous variables and cross tables with Pearson's chi-square tests for categorical variables.

results

study population

In all, 127 women with a *BRCA1* and 69 women with a *BRCA2* mutation participated in the study. The median age at start was 40 years (range 21–68 years). A total of 1149 surveillance visits were carried out. The median follow-up was 2 years (range 1–9 years) for a total follow-up of 544 woman-years. During the observation period, 495 standard and 17 additional mammographies and 439 standard and 64 additional MRI scans were made for surveillance purposes (Figure 1). At the end of the study period, a prophylactic



Number of women	196	143	90	62	38	14	6	1	1
Mammography	188	130	81	54	26	10	5	1	1
MRI	146	126	77	51	25	8	4	1	1
Positive MRI	26	16	3	5	3	-	-	-	-
Positive mammogram	22	11	1	4	2	0	0	0	0

Figure 1. Surveillance activities in 196 women carrying a *BRCA* mutation.

mastectomy and/or a prophylactic salpingo-oophorectomy had been carried out in 36% and 59% of the women, respectively.

performance of the surveillance methods

A positive (abnormal) mammography or MRI (\geq BIRADS 3) was assessed in 41% ($n = 81$) of patients. Seventy-five percent (40 of 53) of the women with a positive MRI had a normal, thus negative mammography at the same time. In only 12 women (6%), mammography and MRI were positive at the same time. A mammography and MRI were found positive in 20% ($n = 40$) and 27% ($n = 53$) of the women, respectively. Of all surveillance MRI scans, 12% (53 of 439) was positive. This percentage was higher in MRIs made at first surveillance (18%) than during follow-up (9%).

Eleven women had a histologically confirmed malignant tumor that was detected at surveillance [nine invasive with a mean diameter of 16 mm (4–21 mm) and two DCIS (33 and 34 mm)] (Table 1). In addition, two women had an interval cancer (12 and 15 mm) that was detected by breast self-examination (Table 1). In 4 of 71 women, an occult cancer was found at what was intended to be a prophylactic mastectomy: one invasive cancer of 4 mm in combination with grade 2 DCIS of 13 mm and three women with grade 2–3 DCIS sized 6, 11 and 15 mm, respectively.

For the detection of invasive cancers and DCIS, mammography, MRI or the combination of the two had a sensitivity of 41%, 60% and 71% and a specificity of 93%, 90% and 90%, respectively. The number of woman-years needed to detect one tumor was 50. In our study, the probability that a positive MRI result could not be confirmed histologically and thus was considered false positive is 83%: five out of every six positive MRI scans.

choice for mastectomy at first surveillance

Table 2 shows a comparison of the group of women with an intention for mastectomy and those who preferred surveillance at first surveillance visit. In the group of patients with an intention for mastectomy at first surveillance visit, more women with a personal history of breast cancer (24% and 12%, $P = 0.03$) or a mother with breast cancer (48% and 33%, $P = 0.05$) that was diagnosed at a younger age (44 ± 10 years and 50 ± 12 years, $P = 0.04$) were present.

the influence of a false positive MRI result on the decision to have a prophylactic mastectomy

At first surveillance visit, 58 of 193 women (30%) gave preference to a prophylactic mastectomy instead of surveillance. Three women did not have a preference for either of the two choices at that time point. The group of women who actually underwent a prophylactic mastectomy and the group that stayed on surveillance was compared, after exclusion of the 13 women with breast cancer detected at surveillance or at interval. Comparison of the characteristics of the group with a prophylactic mastectomy and the group with lasting surveillance showed that the preference for prophylactic mastectomy at the first visit was significantly higher within the group with a mastectomy done (71%) than in

Table 1. Characteristics of invasive breast cancer and DCIS detected during surveillance

Patient number	Findings at surveillance				Tumor characteristics				Pathology report	
	Detection at MRI	Detection by mammography	Detection by clinical examination	Detection by ultrasound	Year of surveillance	Age at diagnosis	Invasive cancer size (mm)	Cancer differential grade		DCIS size (mm)
1	Interval	Yes	No	Yes	3	44	12	3	—	pT1N2—
2	Interval	Yes	No	Yes	2	57	15	3	—	pT1N0—
3	Surveillance	Yes	No	No	1	36	12	3	n.d.	pT1cN0(i+)
4	Surveillance	Yes	No	Yes	1	40	13	1	15	pT1cN0(i—) (SN)
5	Surveillance	Yes	No	No	4	50	—	—	33	pT1s (DCIS)
6	Surveillance	Yes	Yes	No	2	27	18	3	—	pT1cN(i—) (SN)
7	Surveillance	Yes	Yes	Yes	2	58	18	3	20	pT1(m—)N1a (SN)—
8	Surveillance	Yes	Yes	Yes	1	36	21	3	—	pT2N1—
9	Surveillance	Yes	Yes	Yes	2	48	27	3	—	pT1N1mi (SN)
10	Surveillance	Not done	Yes	Yes	1	33	23	3	—	pT2N0—
11	Surveillance	Not done	Yes	Yes	1	55	—	—	34	pT1s (DCIS)
12	Surveillance	No	No	Yes	1	39	12	3	—	pT1cN0(i+) (SN)
13	Surveillance	No	Yes	No	5	35	4	3	28	pT1a(m)N0(i—) (SN)

DCIS, ductal carcinoma *in situ*; MRI, magnetic resonance imaging; n.d., not determined; SN, sentinel node.**Table 2.** Characteristics of women with either a preference for prophylactic mastectomy ($n = 58$) or intensive surveillance ($n = 135$) at the first surveillance visit after the *BRCA* mutation was established

	Preference mastectomy	Preference surveillance	<i>P</i>
<i>n</i>	58	135	
Patient characteristics			
Age (years)	39 ± 10	41 ± 11	0.45
Previous BC	14 (24%)	16 (12%)	0.03
Age at previous BC diagnosis (years)	38 ± 8	43 ± 8	0.14
Postmenopausal	15 (26%)	32 (24%)	0.70
Preventive surgery at follow-up			
Prophylactic mastectomy	43 (75%)	26 (19%)	0.001
Prophylactic salpingo-oophorectomy	39 (67%)	74 (55%)	0.10
Family history			
Maternal inheritance	40 (69%)	92 (68%)	0.59
Mother with BC	28 (48%)	45 (33%)	0.05
Mother's age at BC diagnosis (years)	44 ± 10	50 ± 12	0.04
Mother with Ovc	12 (21%)	35 (26%)	0.38
Mother's age at Ovc (years)	65 ± 7	59 ± 10	0.12
Sister with BC	13 (22%)	34 (25%)	0.64
Age of youngest sister with BC (years)	41 ± 10	30 ± 7	0.51
Age of youngest relative with BC (years)	39 ± 8	39 ± 11	0.63
Age of youngest relative with Ovc (years)	53 ± 10	53 ± 12	0.81
Daughters	31 (53%)	71 (53%)	0.99
Age of youngest child (years)	12 ± 11	12 ± 11	0.94

BC, breast cancer; Ovc, ovarian cancer.

the group that stayed on breast cancer surveillance (12%) ($P < 0.001$). Other parameters such as having a mother or a sister with breast cancer, their age of cancer diagnosis or outcome of diagnostic surveillance did not show any difference (data not shown). Among the women with an intention for prophylactic mastectomy at the first surveillance visit, 89% (17/19) finally underwent a unilateral or bilateral prophylactic mastectomy after a positive MRI and/or mammography. The percentage of individuals with aberrant imaging that ultimately choose for surgery was significantly lower, 15% (7/47), in the group that initially preferred surveillance ($P < 0.01$). Table 3 shows the limited impact of a false-positive imaging on the actual outcome of mastectomy related to intention for prophylactic mastectomy at first surveillance visit. In the group with a prior preference for mastectomy with and without a false-positive imaging, prophylactic mastectomy was carried out in 89% and 66%, respectively ($P = 0.06$), in the group with prior preference for surveillance these percentages were 15% and 11%, respectively ($P = 0.47$). Thus a woman's choice for preventive mastectomy mainly depends on her intention for prophylactic mastectomy before their first surveillance after mutation carriership was revealed.

Table 3. Impact of a false-positive mammography and/or MRI result on actual prophylactic mastectomy status related to preference at first surveillance visit

Surveillance result	Actual status	
	Surveillance	Prophylactic mastectomy
Intention at first visit: mastectomy $n = 57$, $P = 0.06$		
Mammography and MRI negative	13 (34%)	25 (66%)
Mammography and/or MRI false positive	2 (10%)	17 (89%)
Intention at first visit: surveillance $n = 123$, $P = 0.47$		
Mammography and MRI negative	68 (89%)	8 (11%)
Mammography and/or MRI false positive	40 (85%)	7 (15%)

For this analysis, all 13 patients with breast cancer detected during surveillance or at interval were excluded.

MRI, magnetic resonance imaging.

discussion

This study shows that the probability that a positive MRI made for breast cancer surveillance in *BRCA* mutation carriers is false positive is 83%. During the first 2 years after the establishment of a *BRCA* mutation, four out of every 10 female carriers were confronted with an abnormal MRI or mammography result. Aberrant findings on imaging were found to have limited impact on the choice for prophylactic mastectomy of women carrying a *BRCA* mutation. The final decision to actually undergo prophylactic mastectomy appeared to be determined more frequently by a woman's prior preference to mastectomy than abbreviate findings on MRI of mammography. Significantly more women with a prior preference to prophylactic mastectomy opted for a prophylactic mastectomy after a positive MRI or mammography than did women without such prior intention. Both in our study and in previous studies, it was found that especially women with a mother with breast cancer have a first preference for prophylactic mastectomy [11]. Previous studies reported that a woman's preference for prophylactic mastectomy is emphasized by breast cancer anxiety and overestimating one's lifetime risk for breast cancer [12, 13]. Although very high levels of anxiety may interfere with a decision-making process, it is understandable that women at very high risk for breast cancer consider mastectomy in an attempt to reduce their breast cancer risk as well as their level of anxiety. It is likely that this may occur especially in a period of roused anxiety because of an abnormal MRI or mammography result. The clinical indication for prophylactic mastectomy in *BRCA* mutation carriers remains controversial: the effects of prophylactic mastectomy on quality of life are not precisely known [14] and the gain in life expectancy may not be large [15]. Breast conserving treatment remains a reasonable option in the treatment for *BRCA* mutation carriers [7, 16–18]. Therefore, we conclude

that as long as the medical arguments concerning prophylactic mastectomy are controversial, physicians should counsel nondirective by giving detailed information including breast cancer risk and the number of malignancies that are not identified at breast cancer surveillance, recall on risk perception and eventually support the patients' decision.

In our study, sensitivity to detect malignancy of the breast by MRI was higher than by mammography, being 60% and 41%, respectively. Sensitivity and specificity of MRI for the detection or exclusion of both invasive breast cancer and DCIS in our group with a *BRCA* mutation are comparable to that reported by others for invasive cancer: sensitivity of mammography and MRI varying between 33%–40% and 77%–80%, respectively, and specificity between 81%–100% and 90%–95%, respectively, in slightly different populations of high-risk women with and without a *BRCA* mutation [9, 19, 20]. A limitation of our study is that for practical reasons, a small number of women did not have an MRI in addition to surveillance with mammography. This may have had an effect on the choices women eventually made.

Although MRI is known to be more sensitive in detecting invasive malignancies compared with mammography, it has been assumed that mammography was better in detecting DCIS than MRI [8]. Kuhl et al. [21], however, recently described that mammography depicts DCIS in only 56% of the cases, which is in contrast to MRI demonstrating 92% of all cases of DCIS. Mammography usually detects DCIS because of its microcalcifications, but if microcalcifications are absent, DCIS is missed by mammography. Pisano et al. [22] showed that only 60% of the DCIS could be detected by mammography and Lehman et al. [23] and Pediconi et al. [24] described that ~50% of the lesions detected by MRI only were DCIS. One should, however, keep in mind that DCIS on MRI does not always show the characteristic washout curve. Moreover, by MRI the morphology of DCIS may be more difficult to detect than an invasive malignancy. In our present study, two women appeared to have an interval breast cancer. Also in retrospect, there were no abnormalities seen on the last carried out MRI. Next to interval cancers, four malignant lesions were detected at an intended prophylactic mastectomy. One lesion had a size of 4 mm. Lesions of this relatively small size can be easily missed on MRI. The likelihood that a malignancy of size <5 mm is detected by MRI is only 3% [25]. Additionally in our study cases, three cases of DCIS of 6, 11 and 15 mm were missed by both mammography and MRI. In retrospect, the two lesions of 11 and 15 mm were visible on MRI, but these lesions did not show a washout curve and showed only a small linear branching enhancement that was misinterpreted as enhancing glandular tissue.

In our study, ~6% of the *BRCA* mutation carriers with normal findings at surveillance mammography and MRI, that underwent an intended prophylactic mastectomy, had an unsuspected malignancy. This indicates that further improvement of early breast cancer detection is still necessary.

We conclude that although the rate of false-positive MRI results is high, the impact of a positive MRI or mammography on the choice for prophylactic mastectomy is

limited. The choice for prophylactic mastectomy is largely determined before the first breast cancer surveillance after the establishment of a *BRCA* mutation.

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