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CLINICAL TRIAL

High-risk breast cancer surveillance with MRI: 10-year experience from the German consortium for hereditary breast and ovarian cancer

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Abstract

Purpose To report on 10 years of high-risk service screening with annual MRI in the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC).

Methods A cohort of 4,573 high-risk, previously unaffected women (954 BRCA1 carriers, 598 BRCA2 carriers, 3021 BRCA1/2 non-carriers) participating in the GC-HBOC surveillance program was prospectively followed. Screening outcomes for 14,142 screening rounds with MRI between 2006 and 2015 were analyzed and stratified by risk group, type of screening round, and age.

Results A total of 221 primary breast cancers (185 invasive, 36 in situ) were diagnosed within 12 months of an annual screening round with MRI. Of all cancers, 84.5% (174/206, 15 unknown) were stage 0 or I. In BRCA1 carriers, 16.9% (10/59, 5 unknown) of all incident cancers (screen-detected and interval cancers combined) and in BRCA2 carriers 12.5% (3/24, 4 unknown) were stage IIA or higher, compared to only 4.8% (2/42, 2 unknown) in high-risk BRCA1/2 non-carriers. Program sensitivity was 89.6% (95% CI 84.9–93.0) with no significant differences in sensitivity between risk groups or by age. Specificity was significantly lower in the first screening round (84.6%, 95% CI 83.6–85.7) than in subsequent screening rounds (91.1%, 95% CI 90.6–91.7), $p < 0.001$. Cancer detection rates (CDRs) and as a result positive predictive values were strongly dependent on type of screening round, risk group and patient age. CDRs ranged from 43.5‰ (95% CI 29.8–62.9) for the first screening round in BRCA2 carriers to 2.9‰ (95% CI 1.3–6.3) for subsequent screening rounds in high-risk non-carriers in the age group 30 to 39 years.

Conclusions High-risk screening with MRI was successfully implemented in the GC-HBOC with high sensitivity and specificity. Risk prediction and inclusion criteria in high-risk non-carriers need to be adjusted to improve CDRs and thus screening efficacy in these patients.

Keywords Hereditary breast and ovarian cancer syndrome · BRCA1 gene · BRCA2 gene · Breast cancer · Early detection of cancer · Magnetic resonance imaging

Introduction

Women with a genetic predisposition develop breast cancer more frequently and at a younger age than women in the general population, with more than half of the of the breast cancers in *BRCA1/2* carriers occurring before the age of 50 [1]. Several prospective cohort studies have demonstrated that contrast-enhanced MRI of the breast has a significantly higher sensitivity for detecting breast cancer in high-risk

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women than mammography and/or ultrasound [2–5]. Even though conclusive evidence for the effectiveness of high-risk screening with MRI is still missing [6], many countries have implemented MRI-based surveillance programs for high-risk women [7]. While there is broad consensus that *BRCA1* and *BRCA2* carriers should be offered surveillance with annual MRI starting at age 25 to 30 [8–10], recommendations for women with a strong family history of breast cancer but without a pathogenic *BRCA1* or *BRCA2* mutation are much more difficult to establish and vary significantly between countries [11].

The German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) was founded in 1996 with the support of the German Cancer Aid and embeds genetic counseling and testing of high-risk women into an evidence-generating clinical care concept including intensified surveillance measures [12]. In 2005, a multimodal surveillance program including MRI, mammography and ultrasound was implemented through special contracts with health insurers in Germany. It is now one of the largest and longest running structured high-risk surveillance programs in the world. Here we report on the outcome of the program after 10 years of operation. The results from this study will be used to further refine and adjust our surveillance recommendations for high-risk women.

Materials and methods

High-risk surveillance program

During 2005, a multimodal high-risk surveillance program was established by the GC-HBOC at 12 University Centers across Germany based on expert consensus and the results from several studies including a pilot study by the GC-HBOC [13, 14]. The surveillance program was offered to female *BRCA1/2* mutation carriers as well as to women with a remaining breast cancer lifetime risk of at least 30% and/or with a *BRCA1/2* carrier probability of at least 20% predicted by the extended Claus model (as implemented in the commercial pedigree drawing software Cyrillic 2.1.3, Cherwell Scientific, London, UK) [15, 16]. Further prerequisites for participation in the surveillance program were coverage of the program by the patient's insurance carrier and written consent by the patient for participation in the program.

Initially the same program was offered to all eligible women from age 25 (or 5 years before the earliest breast cancer diagnosis in the family if earlier, but not before age 18) to 55. The program consists of annual MRI supplemented by clinical exam and ultrasound every 6 months. In accordance with the German regulations, an individual decision whether to include mammography at a screening round was made based, e.g., on age, risk profile, and findings on MRI. At the beginning of the program, mammography was in most cases offered annually starting at age 30. With growing evidence of the relative small contribution of mammography to the detection of breast cancer if MRI is available [17, 18], this was gradually changed to offering mammography only every 1 to 2 years starting at age 40. In 2013, the 6-month interval ultrasound was discontinued in *BRCA1/2*-negative women and the starting age of the program was increased to 30 for these women. Surveillance was extended until age 70 for mutation carriers and discontinued after age of 50 in non-carriers.

All imaging studies were performed according to standard operating procedures defined by the GC-HBOC. The use of digital mammography was recommended, but not a requirement for participation in the program. Digital breast tomosynthesis could be used if available in the centers, but not for primary screening as a replacement for 2D mammography. MR-guided biopsy was available in all participating centers. Reading of the imaging studies was performed by the radiologist(s) on site. Breast Imaging Reporting and Data System (BI-RADS®) scores [19] for each modality and each breast separately as well as a final management recommendation based on the joint review of all imaging studies performed during that particular screening round were recorded.

Patient cohort

For this IRB-approved, registry-based, prospective cohort study a total of 4573 women without a personal history of breast cancer and/or another malignancy from three well-defined risk groups were included: (1) 954 (20.9%) women carrying a pathogenic *BRCA1* mutation, (2) 598 (13.1%) women carrying a pathogenic *BRCA2* mutation, and (3) 3021 (66.1%) high-risk women from *BRCA1/2*-negative families. To be eligible for the study, the woman must had given written consent to the pseudonymized central documentation of the surveillance data at the University of Leipzig and must had at least one documented screening round with MRI in one of the 12 participating centers between January 1, 2006, and December 31, 2015. Women with a prior risk reducing mastectomy were excluded. All subsequent screening rounds with MRI up to December 31, 2015, were included, as long as the patient remained without the diagnosis of a breast cancer or other malignancy and no prophylactic mastectomy was performed. Time under active surveillance was considered the time from the first eligible screening round with MRI until 12 months after the last screening round with MRI in the program, censored for patient death. Follow-up data were collected through clinic visits, follow-up phone calls and mailed questionnaires. Patient details including number of cancer events and risk reducing surgeries by risk group are given in Table 1.

Table 1 Patient characteristics by risk group

	BRCA1 carriers	*BRCA2* carriers	*BRCA1/2*non-carriers with high risk	Total
Number of patients (% of total)	954 (20.9)	598 (13.1)	3,021 (66.1)	4,573
Age at first screening round, years				
Mean ± SD	37.4 ± 9.8	39.4 ± 9.8	39.2 ± 8.0	38.8 ± 8.7
Median	35.7	38.3	39.0	38.5
Range	18.8–69.4	21.0–68.8	20.4–68.0	18.8–69.4
Patient years under active surveillance[a] (% of total)	2,986 (19.1)	1,882 (12.0)	10,798 (68.9)	15,666
Continued active surveillance in the consortium at the end of follow-up[b]	557/954 (58.4)	384/598 (64.2)	1,840/3,021 (60.9)	2,781/4,573 (60.8)
Active surveillance within the study terminated due to				
Cancer event or death	96/954 (10.1)	54/598 (9.0)	92/3,021 (3.0)	242/4,573 (5.3)
Bilateral mastectomy	121/954 (12.7)	66/598 (11.0)	17/3,021 (0.6)	204/4,573 (4.5)
Upper age limit reached	1/954 (0.1)	0/598 (0.0)	478/3,021 (15.8)	479/4,573 (10.5)
Other reasons[c]	179/954 (18.8)	94/598 (15.7)	594/3,021 (19.7)	867/4,573 (19.0)

Numbers in parenthesis represent percentages of patients in specified subgroup unless indicated otherwise

[a]Cumulative time in years for all patients under active surveillance from the date of the first surveillance round with MRI in the study until 12 months after the last surveillance round with MRI, censored for patient death

[b]Patient status at the end of the follow-up period (December 31, 2016)

[c]Termination of surveillance for other reasons, e.g., patient preference or lack of coverage for the program by the patient's insurance carrier

Evaluation of the screening performance

Screening accuracy was measured against all primary breast cancers with histological confirmation within 12 months of a regular annual screening round with MRI. For interval cancers diagnosed within 12 months of a negative annual screening round, no distinction was made between cancers found at a scheduled 6-month interval exam, cancers found at prophylactic surgery, and symptomatic interval cancers. In cases, in which a bilateral breast cancer was diagnosed within 12 months of an annual screening round with MRI, the cancer detected earlier was considered the primary cancer. For purposes of evaluating the individual modalities, a cancer was considered detected by a particular screening modality, if the unilateral BI-RADS® score of the particular modality for the affected breast was 0, 3, 4, or 5. The combined evaluation for the entire screening round was done on a per-patient basis, whereby screening rounds with a final management recommendation of biopsy or shorter-term follow-up outside the regular screening schedule were considered as positive.

Statistics

Ninety-five percent confidence intervals for proportions were calculated using Wilson's score method [20]. For comparisons of proportions between groups, the Chi-square or Fisher's exact test was used, where appropriate. All reported p values are two-sided. p values < 0.05 were considered significant. Statistical analyses were conducted using IBM SPSS Statistics for Windows version 23.0 (IBM Corp, Armonk, NY, USA).

Results

Screening participation

A total of 14,142 eligible screening rounds with MRI were performed in 4573 study patients, with 9569 (67.7%) being subsequent screening rounds. Annual patient recruitment gradually increased over time from 363 in 2006 to 699 in 2015 and 60.1% (2750/4573) of the patients had their first screening exam in the study after January 1, 2011. Median time between two screening rounds with MRI was 1.05 years (IQR 0.98–1.21 years). In 60.5% (8557/14,142) of the annual screening rounds, a mammography was performed in addition to the MRI and in 95.1% (13,451/14,142) the patient attended the recommended supplementary clinical exam and ultrasound.

Primary breast cancers

A total of 221 primary breast cancers (185 invasive cancers and 36 ductal carcinoma in situ) were diagnosed during the active surveillance period (Table 2). Type and stage of detected cancers by risk group are shown in Tables 2 and 3. The proportion of in situ cancers was lower in *BRCA1*

Table 2 Primary breast cancers diagnosed during active surveillance within the study

	BRCA1 carriers (%)	*BRCA2* carriers (%)	*BRCA1/2* non-carriers with high risk (%)	Total (%)	*P*[a]
Primary breast cancers (all)[b]	83/221 (37.6)	53/221 (24.0)	85/221 (38.5)	221 (100.0)	
Invasive cancers[c]	76/83 (91.6)	44/53 (83.0)	65/85 (76.5)	185/221 (83.7)	
Histology					0.085
Ductal (NST)	68/76 (89.5)	37/44 (84.1)	51/65 (78.5)	156/185 (84.3)	
Lobular	3/76 (3.9)	3/44 (6.8)	8/65 (12.3)	14/185 (7.6)	
Medullary	4/76 (5.3)	0/44 (0.0)	1/65 (1.5)	5/185 (2.7)	
Mucinous	0/76 (0.0)	1/44 (2.3)	0/65 (0.0)	1/185 (0.5)	
Tubular	0/76 (0.0)	0/44 (0.0)	2/65 (3.1)	2/185 (1.1)	
Unknown	1/76 (1.3)	3/44 (6.8)	3/65 (4.6)	7/185 (3.8)	
Invasive cancer grade					< 0.001
Grade 1	1/76 (1.3)	4/44 (9.1)	19/65 (29.2)	24/185 (13.0)	
Grade 2	20/76 (26.3)	32/44 (72.7)	36/65 (55.4)	88/185 (47.6)	
Grade 3	53/76 (69.7)	6/44 (13.6)	10/65 (15.4)	69/185 (37.3)	
Unknown	2/76 (2.6)	2/44 (4.5)	0/65 (0.0)	4/185 (2.2)	
Receptor Status					< 0.001
ER and/or PR positive, Her2 negative	26/76 (34.2)	31/44 (70.5)	49/65 (75.4)	106/185 (57.3)	
Her2 positive	4/76 (5.3)	3/44 (6.8)	11/65 (16.9)	18/185 (9.7)	
Triple-negative	43/76 (56.6)	5/44 (11.4)	3/65 (4.6)	51/185 (27.6)	
Incomplete or unknown	3/76 (3.9)	5/44 (11.4)	2/65 (3.1)	10/185 (5.4)	
In situ cancers[d]	7/83 (8.4)	9/53 (17.0)	20/85 (23.5)	36/221 (16.3)	
In situ cancer grade					0.091
DCIS low-grade	0/7 (0.0)	0/9 (0.0)	7/20 (35.0)	7/36 (19.4)	
DCIS intermediate-grade	4/7 (57.1)	6/9 (66.7)	6/20 (30.0)	16/36 (44.4)	
DCIS high-grade	3/7 (42.9)	2/9 (22.2)	6/20 (30.0)	11/36 (30.6)	
Unknown	0/7 (0.0)	1/9 (11.1)	1/20 (5.0)	2/36 (5.6)	

DCIS ductal carcinoma in situ, *ER* estrogen receptor, *PR* progesterone receptor

[a]*p* values for the overall comparison between subgroups. Calculation excludes cases with incomplete or missing data

[b]Includes all histologically confirmed primary breast cancers diagnosed within 12 months of a surveillance round with MRI in the study period

[c]In 7 of the 185 invasive cancers the final surgical histology report was unavailable and classification was based on the biopsy results only

[d]In 3 cases the final surgical histology report was unavailable and the in situ status was based on the biopsy results only

carriers (8.4%, 7/83) than in *BRCA2* carriers (17.0%, 9/53, $p = 0.1732$) and other high-risk patients (23.5%, 20/85, $p = 0.0109$). Of all triple-negative breast cancers (TNBC) diagnosed in the study, 84.3% (43/51) occurred in *BRCA1* carriers and 51.8% (43/83) of all cancers (invasive and in situ) diagnosed in *BRCA1* carriers were TNBC. Overall the proportion of low-grade cancers (both invasive and in situ combined) was significantly higher in high-risk patients without a *BRCA1/2* mutation (31.0%, 26/84, 1 unknown) than in *BRCA2* carriers (8.0%, 4/50, 3 unknown, $p = 0.0013$) or *BRCA1* carriers (1.2%, 1/81, 2 unknown, $p = 0.0001$).

Of all cancers with complete stage information in the study, 84.5% (174/206, 15 unknown) and of all incident cancers (excluding cancers detected in the first screening round) 88.0% (110/125, 11 unknown) were stage 0 or I, with the stage distribution being slightly less favorable in *BRCA1/2* carriers. 16.9% (10/59, 5 unknown) of incident cancers in *BRCA1* carriers and 12.5% (3/24, 4 unknown) in *BRCA2* carriers were stage IIA or higher, compared to only 4.8% (2/42, 2 unknown) in the high-risk group (Table 3).

Screening performance

Of the 221 primary breast cancers diagnosed during the study period, 38.5% (85/221) were detected at the first screening round, 51.1% (113/221) at a subsequent screening round, and 10.4% (23/221) during the 12-month interval following a negative annual screening round with MRI (Table 4). Interval cancers were more frequently observed in *BRCA1* carriers (14.5%, 12/83) than in *BRCA2* carriers (11.3%, 6/53) and other high-risk patients (5.9%, 5/85). Type of interval cancers by risk group are shown in Table 4. Of the 23 interval cancers, 65.2% (15/23) were

Table 3 Stage distribution of all primary breast cancers diagnosed in the study[a]

All breast cancers (in situ + invasive)	*BRCA1* carriers		*BRCA2* carriers		*BRCA1/2* non-carrierswith high risk	
	Prevalent[b]	Incident[c]	Prevalent[b]	Incident[c]	Prevalent[b]	Incident[c]
	n = 83		*n* = 53		*n* = 85	
	19/83 (23%)	64/83 (77%)	25/53 (47%)	28/53 (53%)	41/85 (48%)	44/85 (52%)
UICC stage(8th edition)						
Stage 0 (in situ)	4/19 (21%)	2/64 (3%)	5/25 (20%)	4/28 (14%)	8/41 (20%)	10/44 (23%)
Stage IA	11/19 (58%)	47/64 (73%)	11/25 (44%)	17/28 (61%)	25/41 (61%)	30/44 (68%)
Stage IIA	2/19 (11%)	8/64 (13%)	4/25 (16%)	0/28 (0%)	3/41 (7%)	1/44 (2%)
Stage IIB	0/19 (0%)	1/64 (2%)	3/25 (12%)	1/28 (4%)	3/41 (7%)	1/44 (2%)
Stage IIIA	1/19 (5%)	1/64 (2%)	0/25 (0%)	2/28 (7%)	1/41 (2%)	0/44 (0%)
Unknown	1/19 (5%)	5/64 (8%)	2/25 (8%)	4/28 (14%)	1/41 (2%)	2/44 (5%)
Invasive breast cancers only	*BRCA1* carriers		*BRCA2* carriers		*BRCA1/2* non-carrierswith high risk	
	Prevalent[b]	Incident[c]	Prevalent[b]	Incident[c]	Prevalent[b]	Incident[c]
	n = 76		*n* = 44		*n* = 65	
	15/76 (20%)	61/76 (80%)	20/44 (45%)	24/44 (55%)	32/65 (49%)	33/65 (51%)
Tumor size						
T1mi	1/15 (7%)	2/61 (3%)	0/20 (0%)	0/24 (0%)	1/32 (3%)	1/33 (3%)
T1a	1/15 (7%)	7/61 (11%)	3/20 (15%)	1/24 (4%)	3/32 (9%)	8/33 (24%)
T1b	6/15 (40%)	19/61 (31%)	5/20 (25%)	12/24 (50%)	9/32 (28%)	14/33 (42%)
T1c	5/15 (33%)	21/61 (34%)	5/20 (25%)	6/24 (25%)	14/32 (44%)	7/33 (21%)
T2	0/15 (0%)	9/61 (15%)	5/20 (25%)	1/24 (4%)	4/32 (13%)	2/33 (6%)
T3	1/15 (7%)	0/61 (0%)	0/20 (0%)	0/24 (0%)	1/32 (3%)	0/33 (0%)
Unknown	1/15 (7%)	3/61 (5%)	2/20 (10%)	4/24 (17%)	0/32 (0%)	1/33 (3%)
Lymph node status (invasive cancers)						
N0	11/15 (73%)	55/61 (90%)	13/20 (65%)	18/24 (75%)	28/32 (88%)	32/33 (97%)
N1	3/15 (20%)	3/61 (5%)	6/20 (30%)	1/24 (4%)	3/32 (9%)	1/33 (3%)
N2	0/15 (0%)	1/61 (2%)	0/20 (0%)	2/24 (8%)	1/32 (3%)	0/33 (0%)
Unknown	1/15 (7%)	2/61 (3%)	1/20 (5%)	3/24 (13%)	0/32 (0%)	0/33 (0%)

UICC Union for International Cancer Control

[a]Primary clinical stage was used in patients treated with neoadjuvant chemotherapy if more advanced than the pathologic stage from final surgery

[b]All primary breast cancers detected at the first screening round with MRI in the program

[c]Includes both screen-detected cancers from subsequent screening rounds and all interval cancers

diagnosed at a scheduled six-month interval exam, 17.4% (4/23) at prophylactic mastectomy, and 13.0% (3/23) were symptomatic interval cancers, all of which occurred in *BRCA1* carriers. The 4 cancers found during prophylactic mastectomy correspond to an occult cancer rate of 1.9% (4 cancers found in 208 patients undergoing prophylactic mastectomy within 12 months of a negative annual screening round with MRI).

Overall program sensitivity for all 14,142 regular screening rounds with MRI in the study was 89.6% (95% CI 84.9–93.0). No significant differences in sensitivity were found between the three risk groups or by age (Tables 5, 6).

Detection performance of the individual imaging modalities by risk group is shown in Table 4. Overall 82.8% (183/221) of all cancers were positive on the screening MRI, compared to 53.3% (98/184) for mammography if performed in addition to MRI and 50.9% (111/218) for ultrasound.

Specificity for the annual screening rounds with MRI, based on the joint reading of all screening modalities combined, was significantly lower in the first screening round (84.6%, 95% CI 83.6–85.7) than in subsequent screening rounds (91.1%, 95% CI 90.6–91.7), $p < 0.001$. For subsequent screening rounds, specificity was slightly higher in women below the age of 30 (93.1%, 95% CI

Table 4 Mode of cancer detection stratified by risk group

	BRCA1 carriers (%)	*BRCA2* carriers (%)	*BRCA1/2* non-carriers with high risk (%)	Total (%)
Number of breast cancers	83/221 (37.6)	53/221 (24.0)	85/221 (38.5)	221 (100.0)
Detected at the first screening round	19/83 (22.9)	25/53 (47.2)	41/85 (48.2)	85/221 (38.5)
Positive on MRI	16/19 (84.2)	24/25 (96.0)	39/41 (95.1)	79/85 (92.9)
Positive on MG[a]	8/14 (57.1)	12/22 (54.5)	19/36 (52.8)	39/72 (54.2)
Positive on US[a]	13/19 (68.4)	12/25 (48.0)	24/40 (60.0)	49/84 (58.3)
MRI only	4/19 (21.1)	9/25 (36.0)	14/41 (34.1)	27/85 (31.8)
MG only	0/19 (0.0)	1/25 (4.0)	1/41 (2.4)	2/85 (2.4)
US only[b]	2/19 (10.5)	0/25 (0.0)	0/41 (0.0)	2/85 (2.4)
Detected at a subsequent screening round	52/83 (62.7)	22/53 (41.5)	39/85 (45.9)	113/221 (51.1)
Positive on MRI	47/52 (90.4)	21/22 (95.5)	36/39 (92.3)	104/113 (92.0)
Positive on MG[a]	29/47 (61.7)	10/19 (52.6)	20/32 (62.5)	59/98 (60.2)
Positive on US[a]	35/52 (67.3)	10/22 (45.5)	17/39 (43.6)	62/113 (54.9)
MRI only	11/52 (21.2)	8/22 (36.4)	15/39 (38.5)	34/113 (30.1)
MG only	3/52 (5.8)	1/22 (4.5)	1/39 (2.6)	5/113 (4.4)
US only	0/52 (0.0)	0/22 (0.0)	0/39 (0.0)	0/113 (0.0)
Detected during the 12-months interval after a normal annual screening round	12/83 (14.5)	6/53 (11.3)	5/85 (5.9)	23/221 (10.4)
At scheduled 6-months interval exam	7/83 (8.4)	4/53 (7.5)	4/85 (4.7)	15/221 (6.8)
Prophylactic mastectomy	2/83 (2.4)	1/53 (1.9)	1/85 (1.2)	4/221 (1.8)
Symptomatic	3/83 (3.6)	0/53 (0.0)	0/85 (0.0)	3/221 (1.4)
Other[c]	0/83 (0.0)	1/53 (1.9)	0/85 (0.0)	1/221 (0.5)

MRI magnetic resonance imaging, *MG* mammography, *US* ultrasound

[a]Percentages relative to the number of first or subsequent screening rounds with MG or US, respectively

[b]In one of the two cancers found only by ultrasound, no mammography was performed during the regular screening exam

[c]One cancer was found on short-term follow-up for a contralateral abnormality, which subsequently was shown to be benign

91.2–94.6) and in women 50 years or older (93.5%, 95% CI 92.1–94.7) compared to the age groups 30–39 (90.2%, 95% CI 89.1–91.2) and 40–49 (90.7%, 95% CI 89.7–91.5) (Table 6), $p_{global}<0.001$.

Cancer detection rates (CDRs) per 1,000 screening rounds varied strongly with type of screening round, risk group and patient age (Table 5). CDRs in BRCA2 carriers and non-carriers were significantly higher in the first screening round compared to subsequent screening rounds (43.5‰, 95% CI 29.8–62.9 versus 19.5‰, 95% CI 12.9–29.4, $p=0.005$ for *BRCA2* carriers and 13.6‰, 95% CI 10.0–18.4 versus 5.7‰, 95% CI 4.3–8.0, $p<0.001$ for non-carriers), which was not the case for *BRCA1* carriers, $p=0.204$. In contrast, CDR's in *BRCA1* carriers were actually lower in the first screening round compared to the subsequent screening rounds (Table 5). When considering subsequent screening rounds only, CDRs in non-carriers dropped rapidly with decreasing age from 10.9‰ (95% CI 5.8–20.7) in women above the age of 50 to 2.9‰ (95% CI 1.3–6.3) in the age group 30–39, whereas CDRs in *BRCA1/2* carriers stayed relatively stable above 20‰ from age 30 to 49.

The positive predictive value (PPV) of an abnormal subsequent screening exam in non-carriers was overall significantly lower (5.7%, 95% CI 4.2–7.8) than in *BRCA1* carriers (27.4%, 95% CI 21.5–34.2) and *BRCA2* carriers (22.0%, 95% CI 15.9–31.1) and decreased with age to 2.8% (95% CI 1.3–6.1) for non-carriers in the age group 30 to 39 years.

Patient follow-up

In the 4,573 study patients, all without a cancer diagnosis at the time of entry in the study, a total of 5 deaths were recorded up to December 31, 2016, only one related to breast cancer. A 36-year-old *BRCA2*-positive patient died of breast cancer 5.6 years after diagnosis of an advanced stage prevalent breast cancer (cT2 ypT1a ypN1) detected in the first round of screening in the study. Two *BRCA1*-positive patients died of ovarian cancer, one *BRCA2*-positive patient died of pancreatic cancer, and one *BRCA1/2*-negative patient died unrelated to an oncologic diagnosis.

Table 5 Detection performance of annual multimodality screening rounds with MRI by risk group, type of screening round and age

	No. of rounds	No. of cancers	Detection rate		Sensitivity		Specificity		PPV	
			‰	95% CI	%	95% CI	%	95% CI	%	95% CI
BRCA1 carriers	2,750	83	25.5	20.2 to 32.0	84.3	75.0 to 90.6	90.1	88.9 to 91.2	21.0	17.0 to 25.7
First rounds	954	24	19.9	12.8 to 30.9	79.2	59.5 to 90.8	86.2	83.9 to 88.3	12.9	8.4 to 19.3
Subsequent rounds	1,796	59	28.4	21.7 to 37.1	86.4	75.5 to 93.0	92.2	90.9 to 93.4	27.4	21.5 to 34.2
< 30 years	247	3	8.1	2.2 to 29.0	66.7	20.8 to 93.9	94.3	90.6 to 96.6	12.5	3.5 to 36.0
30–39 years	579	28	43.2	29.4 to 63.0	89.3	72.8 to 96.3	89.1	86.2 to 91.4	29.4	20.8 to 39.8
40–49 years	642	17	21.8	13.0 to 36.3	82.4	59.0 to 93.8	93.4	91.2 to 95.1	25.5	15.8 to 38.3
≥ 50 years	328	11	30.5	16.6 to 55.2	90.9	62.3 to 98.4	93.7	90.5 to 95.9	33.3	19.2 to 51.2
BRCA2 carriers	1,724	53	27.8	21.1 to 36.7	90.6	79.7 to 95.9	90.2	88.7 to 91.6	22.7	17.6 to 28.9
First rounds	598	27	43.5	29.8 to 62.9	96.3	81.7 to 99.3	85.1	82.0 to 87.8	23.4	16.5 to 32.1
Subsequent rounds	1,126	26	19.5	12.9 to 29.4	84.6	66.5 to 93.8	92.9	91.2 to 94.3	22.0	15.0 to 31.1
< 30 years	119	0	0.0	0.0 to 31.3			89.1	82.2 to 93.5	0	0.0 to 22.8
30–39 years	309	9	22.7	11.0 to 46.0	77.8	45.3 to 93.7	92.3	88.8 to 94.8	23.3	11.8 to 40.9
40–49 years	452	12	24.3	13.6 to 43.0	91.7	64.6 to 98.5	93.4	90.7 to 95.4	27.5	16.1 to 42.8
≥ 50 years	246	5	16.3	6.3 to 41.1	80.0	37.6 to 96.4	94.6	91.0 to 96.8	23.5	9.6 to 47.3
BRCA1/2 non-carriers with high risk	9,668	85	8.3	6.7 to 10.3	94.1	87.0 to 97.5	88.5	87.9 to 89.2	6.8	5.5 to 8.4
First rounds	3,021	41	13.6	10.0 to 18.4	100	91.4 to 100	84.1	82.7 to 85.3	7.9	5.9 to 10.6
Subsequent rounds	6,647	44	5.9	4.3 to 8.0	88.6	76.0 to 95.0	90.6	89.8 to 91.2	5.9	4.3 to 8.0
< 30 years	481	0	0.0	0.0 to 7.9			93.6	91.0 to 95.4	0	0.0 to 11.0
30–39 years	2,089	6	2.9	1.3 to 6.3	100	61.0 to 100	90.2	88.8 to 91.4	2.8	1.3 to 6.1
40–49 years	3,254	28	7.4	5.0 to 11.0	85.7	68.5 to 94.3	89.7	88.6 to 90.7	6.8	4.6 to 9.9
≥ 50 years	823	10	10.9	5.8 to 20.7	90.0	59.6 to 98.2	93.1	91.2 to 94.7	13.8	7.5 to 24.3
Total	14,142	221	14.0	12.2 to 16.1	89.6	84.9 to 93.0	89.1	88.5 to 89.6	11.5	10.1 to 13.1

CI confidence interval, *PPV* positive predictive value

Table 6 Sensitivity and specificity of annual multimodality screening rounds with MRI by type of screening round and age

	No. of rounds	No. of cancers	Sensitivity		Specificity	
			%	95% CI	%	95% CI
First screening rounds (all)	4573	92	93.5	86.5 to 97.0	84.6	83.6 to 85.7
< 30 years	826	7	100	64.6 to 100	86.8	84.3 to 89.0
30–39 years	1747	29	86.2	69.4 to 94.5	84.0	82.2 to 85.7
40–49 years	1562	38	97.4	86.5 to 99.5	83.9	81.9 to 85.6
≥ 50 years	438	18	94.4	74.2 to 99.0	86.0	82.3 to 89.0
Subsequent screening rounds (all)	9569	129	86.8	79.9 to 91.6	91.1	90.6 to 91.7
< 30 years	847	3	66.7	20.8 to 93.9	93.1	91.2 to 94.6
30–39 years	2977	43	88.4	75.5 to 94.9	90.2	89.1 to 91.2
40–49 years	4348	57	86.0	74.7 to 92.7	90.7	89.7 to 91.5
≥ 50 years	1397	26	88.5	71.0 to 96.0	93.5	92.1 to 94.7
Total	14,142	221	89.6	84.9 to 93.0	89.1	88.5 to 89.6

CI confidence interval

Discussion

The main goal of a breast cancer screening program is to prevent advanced stage breast cancer as much as possible. The stage distribution in our cohort with 84.5% (174/206, 15 unknown) of all observed primary breast cancers in the study being stage 0 or I is similar to previous high-risk surveillance studies [3, 5] and compares favorably to the stage distribution in premenopausal women with a family history of breast cancer undergoing no screening or annual mammography alone [21]. In the UK FH01 cohort, which

consisted of women younger than 50 with an intermediate familial risk undergoing annual mammography, 30% of the observed invasive cancers (screen-detected and interval combined) were larger than 2 cm and 32% were lymph node positive [21]. In comparison in our cohort, overall only 13.2% (23/174, 11 unknown) of invasive cancers were larger than 2 cm and only 11.8% (21/178, 7 unknown) were lymph node positive.

The slightly higher frequency of advanced stage breast cancers in *BRCA1* carriers undergoing surveillance with MRI was also observed in other studies [17, 22–25] and can be explained by the higher proportion of aggressive, fast-growing cancers in these patients (Table 2) [26].

This study demonstrates that it is possible to implement multimodal screening with MRI on a large scale in clinical routine with high accuracy. Overall program sensitivity and specificity were 89.6% and 89.1%, respectively, which is comparable to data from the literature [3, 5, 27]. In our cohort, no significant differences in sensitivity between risk groups or by age were found, which was also reported by others [18, 28]. Sensitivity was slightly, but not significantly higher for the first screening round (93.5%) compared to subsequent rounds (86.8%), but this can easily be explained by the higher proportion of larger prevalent cancers at the onset of intensified surveillance.

Our data clearly confirm the importance of MRI in high-risk screening, as 30.8% (61/198) of all screen-detected cancers were detected by MRI alone. Overall, 82.8% (183/221) of all cancers (both screen-detected and interval) which occurred in the patient cohort during the period of active surveillance and 92.4% (183/198) of all screen-detected cancers were positive on the screening MRI. These results are similar to data reported in the literature [2–5, 27, 29–31].

The added contribution of mammography to the detection of breast cancer in the presence of a MRI screening exam is generally low [3, 27]. In a recent meta-analysis by Phi et al. [32], the overall contribution to breast cancer detection was higher in *BRCA2* carriers (12.6%) compared to *BRCA1* carriers (3.9%). This difference between *BRCA1* and *BRCA2* carriers was not observed in our cohort, where overall only 3.6% (3/83) of cancers in *BRCA1* carriers were found by mammography alone and 3.8% (2/53) in *BRCA2* carriers (Table 4). As in the study by Phi et al. [32], more than half of the cancers detected by mammography alone (4 of 7 in our study) were in situ cancers. The smaller number of cancers detected by mammography alone in *BRCA2* carriers in our cohort may be related to an improved DCIS detection with MRI in recent years [33].

As reported by others [34], the added contribution of ultrasound to breast cancer detection in the presence of MRI and mammography is low. Only two cancers in our cohort were found by ultrasound alone, both were DCIS cases in *BRCA1* carriers detected at the first screening round.

Specificity in the first round is typically lower due to preexisting benign abnormalities, which need to be evaluated further [3, 5]. This was also observed in our study. The slightly lower specificity in subsequent rounds in women age 30–50 compared to women below age 30 and 50 years and older (Table 6) may be related to a higher degree of background activity and non-specific findings in older premenopausal women, which then diminishes after menopause.

Pathogenic mutations in the *BRCA1/2* genes predispose for earlier onset breast cancer reaching an incidence plateau in *BRCA1* carriers between 30 and 40 years and in *BRCA2* carriers between 40 and 50 years [1]. This explains the consistently high CDRs of more than 20‰ observed in young *BRCA1/2* carriers between the age of 30 and 50. In contrast to this, non-carriers showed a sharp drop in CDRs in subsequent screening rounds with decreasing age. As sensitivity and specificity of screening changes little with age, these deceasing CDR's translate into a drop in PPVs from 13.8% for high-risk non-carriers over the age of 50 to 2.8% under the age of 40.

These low PPVs in young premenopausal high-risk patients without a *BRCA1/2* mutation have to be weighed against the almost complete prevention of advanced-stage breast cancer in this risk group through annual surveillance with MRI (only 4.8% of incident cancers in non-carriers were stage IIA or higher). In addition, the benefits in terms of life-years saved will be much greater in young premenopausal women. It should be attempted through more advanced genetic testing and improved risk calculation models to identify those high-risk patients without a *BRCA1/2* mutation who will benefit most from intensified MRI-based surveillance. Another option would be to shift the intensified screening period in non-carriers to a later age, where breast cancer incidence will be higher (e.g., 40–60 years instead of the current period from 30 to 50 years). However, the risk of overdiagnosis due to the intensified surveillance in non-carriers will be higher in older women, especially when considering that around a third of cancers detected in this patient group through intensified surveillance with MRI will represent low-grade disease (either low-grade DCIS or low-grade invasive cancer).

Our study has some limitations. The main drawback is that stratification by risk group was based on *BRCA1/2* testing only as broader multi-gene panel testing was introduced in the GC-HBOC only toward the end of the recruitment period. It is therefore possible that the *BRCA1/2*-negative group in our study includes a small number of patients with other high- or moderate breast cancer risk genes, which may have influenced the breast cancer incidence in this risk group. Another limitation of our study is, that even though BI-RADS® scores were recorded for each imaging modality separately, the interpreting physician had access to all imaging studies performed during a particular screening round to

maximize screening performance. This may have introduced a bias slightly overestimating the detection performance of the individual surveillance modalities.

In summary, we were able to demonstrate that multimodal surveillance with MRI in high risk patients can successfully be implemented in clinical routine. In *BRCA1* carriers, surveillance with MRI is slightly less effective in preventing advanced stage breast cancer. Therefore, risk-reducing surgical options may play a bigger role in these women. CDRs and with this PPVs for subsequent screening rounds in young premenopausal high-risk women without a *BRCA1/2* mutation were lower than expected, shifting the balance towards negative side effects. This underlines the need for better risk assessment tools to identify those women, who will benefit most from surveillance with MRI.

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Compliance with ethical standards

Conflict of interest UB has received patent royalties from Hologic. EMF has received institutional research funding from GE Healthcare and Guerbet and has received speaker honoraria and travel expenses from GE Healthcare, Bayer Healthcare, and Guerbet. KR has received honoraria from AstraZeneca. DM has received speaker honoraria and institutional research funding from Philips. KWFS has received travel expenses from SuperSonic Imagine. KK has received honoraria from Roche, Pfizer, and AstraZeneca and has given expert testimony to and received travel expenses from Roche. MK holds stock or other ownership in Therawis Diagnostics and Meine Busenfreundin GmbH, has received honoraria from AstraZeneca, Celgene, Myriad Genetics, HRA, Stiftung Warentest, has held a consulting or advisory role with AstraZeneca and Celgene, has given expert testimony to Therawis Diagnostics, and has received travel expenses from Myriad Genetics and Celgene. All other authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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