

# Intensive Surveillance with Biannual Dynamic Contrast-Enhanced Magnetic Resonance Imaging Downstages Breast Cancer in *BRCA1* Mutation Carriers



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## Abstract

**Purpose:** To establish a cohort of high-risk women undergoing intensive surveillance for breast cancer.

**Experimental Design:** We performed dynamic contrast-enhanced MRI every 6 months in conjunction with annual mammography (MG). Eligible participants had a cumulative lifetime breast cancer risk  $\geq 20\%$  and/or tested positive for a pathogenic mutation in a known breast cancer susceptibility gene.

**Results:** Between 2004 and 2016, we prospectively enrolled 295 women, including 157 mutation carriers (75 *BRCA1*, 61 *BRCA2*); participants' mean age at entry was 43.3 years. Seventeen cancers were later diagnosed: 4 ductal carcinoma *in situ* (DCIS) and 13 early-stage invasive breast cancers. Fifteen cancers occurred in mutation carriers (11 *BRCA1*, 3 *BRCA2*, 1 *CDH1*). Median size of the invasive cancers was 0.61 cm. No

patients had lymph node metastasis at time of diagnosis, and no interval invasive cancers occurred. The sensitivity of biannual MRI alone was 88.2% and annual MG plus biannual MRI was 94.1%. The cancer detection rate of biannual MRI alone was 0.7% per 100 screening episodes, which is similar to the cancer detection rate of 0.7% per 100 screening episodes for annual MG plus biannual MRI. The number of recalls and biopsies needed to detect one cancer by biannual MRI were 2.8 and 1.7 in *BRCA1* carriers, 12.0 and 8.0 in *BRCA2* carriers, and 11.7 and 5.0 in non-*BRCA1/2* carriers, respectively.

**Conclusions:** Biannual MRI performed well for early detection of invasive breast cancer in genomically stratified high-risk women. No benefit was associated with annual MG screening plus biannual MRI screening.

See related commentary by Kuhl and Schrading, p. 1693

## Introduction

Among women at high genetic risk of breast cancer, current options for prevention and early detection include prophylactic mastectomy, prophylactic bilateral salpingo-oophorectomy

(BSO), chemoprevention, and heightened imaging surveillance (1–3). As an alternative to prophylactic mastectomy, intensive imaging surveillance using dynamic contrast-enhanced MRI is more sensitive than mammography (MG) alone and detects

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### Translational Relevance

This is the first report on a prospective cohort of genomically defined high-risk women undergoing screening with biannual dynamic contrast-enhanced MRI in conjunction with annual mammography. This novel screening approach performed well, especially for women at high genetic risk, by detecting invasive cancers at sizes  $\leq 1$  cm without nodal involvement and effectively avoiding interval invasive cancers with low recall rates. Annual mammography did not demonstrate a screening benefit when performed in conjunction with biannual MRI screening. Thus, with optimal genomic risk stratification, intensive surveillance using innovative biannual MRI imaging protocol has the potential to detect early-stage breast cancer, especially in women at risk of aggressive *BRCA1*-associated breast cancer.

breast cancer at an earlier stage, resulting in a more favorable prognosis (4–16). The American Cancer Society and other organizations have published guidelines that recommend annual MRI in conjunction with annual MG for a well-defined category of high-risk women including: carriers of damaging mutations in breast cancer susceptibility genes and their untested first-degree relatives, women with a lifetime breast cancer risk  $>20\%$  as defined by risk-prediction models, and women with prior history of chest radiation between the ages of 10 and 30 years (1, 17, 18). However, meta-analysis of the pivotal studies using this intense imaging surveillance demonstrated that a few of the participants were still diagnosed with tumors larger than 1 cm, with node-positive disease, and with interval invasive breast cancers (detected between rounds of stacked annual MRI/MG examinations; ref. 19).

While these guidelines appear to have changed clinical practice, there remain unanswered questions including optimal length of screening interval, ideal ages of initiation and completion of screening, the best combination of screening modalities, and limitations of risk-prediction models to identify ideal candidates for intensive surveillance. There is also concern for overdiagnosis of indolent ductal carcinoma *in situ* (DCIS) leading to overtreatment of women at moderate risk (20). The potential harms from MG in young women include radiation exposure for *BRCA1/2* carriers (21), anxiety associated with false-positive findings (22), and costs associated with additional procedures (23, 24). While potential risk from gadolinium exists, MRI poses no risk of radiation, has high specificity, and the aggressive behavior and natural history of *BRCA1/2*-associated breast cancers support the use of MRI as an effective alternative to prophylactic mastectomies (25–28). In this study, we established a novel imaging surveillance program to evaluate the performance of biannual MRI in conjunction with annual MG in genomically stratified, high-risk women. The results of this imaging-rich study provide a framework for optimizing MRI screening for early detection and cancer interception in women at high risk of inherited breast cancer.

## Materials and Methods

### Study population

Between 2004 and 2016, we established a prospective registry of women at high risk of breast cancer at The University of Chicago

Cancer Risk Clinic (NCT00989638). The targeted enrollment was 300 patients for the psychosocial prespecified endpoints of adherence and quality of life, but the screening registry would continue to enroll and follow an indefinite number of those at high-risk. To allow recruitment of women at different levels of risk, the eligibility criteria were as follows. Age was  $\geq 25$  years or, if  $<25$  years, was within 5 years of the youngest breast cancer diagnosis in the family. Women with prior history of cancer were eligible if at least one breast had not been previously irradiated for cancer. Finally, one or more of the following pertained: (i) carrier of a pathogenic mutation in breast cancer susceptibility genes as described in BROCA panel testing below; (ii) previous breast cancer at age  $<35$  years, with chemotherapy completed and disease free for at least two years; (iii) previous chest irradiation at age  $<30$  years; (iv) previous DCIS at age  $<35$  years and a mother or sister with breast cancer diagnosed  $<50$  years or a mother or sister with ovarian cancer at any age; (v) no previous breast cancer but with probability of being a *BRCA1* or *BRCA2* carrier of 20% or greater based on BRCAPRO analysis or  $\geq 25\%$  risk of being a mutation carrier by Couch model in addition to a lifetime breast cancer risk  $\geq 20\%$  by Gail or Claus model; (vi) of African ancestry with family history of breast cancer at age  $<40$  in a mother, sister, paternal aunt, or paternal grandmother. This final criterion was included to increase participation by African American women (29) who suffer a disproportionate burden of aggressive triple-negative breast cancer. Exclusion criteria were current pregnancy, history of kidney disease, presence of any implanted metallic foreign object, breast surgery within two weeks. The study was approved by The University of Chicago Institutional Review Board and in accordance with the precepts established by the Declaration of Helsinki. Written informed consent was obtained from all study participants.

### Screening protocol

Following initial evaluation by a physician and genetic counselor, the screening protocol consisted of biannual clinical breast examinations, biannual MRI using dedicated breast coil and techniques as described previously (30), and annual standard screening MG (Supplementary Fig. S1). Every screening episode was considered a screening round. The interval round was defined as the screening episode that was performed at the 6 months timepoint with MRI alone. Each imaging exam had independent reading per round. Whenever possible, clinical breast exam and MG were scheduled on the same day as the MRI. Dedicated breast radiologists using the ACR Breast Imaging Reporting and Data Systems (BI-RADS) independently interpreted the MRI and MG. MRI technique evolved during the study period and specifics are fully described in Supplementary Table S1. Upon completion of 5 years of study protocol, mutation carriers were offered the opportunity to continue screening indefinitely.

Actions to be taken following an abnormal imaging were prespecified as follows: (1) For BI-RADS score of 4 or 5 on MRI, a percutaneous biopsy was recommended; (ii) for BI-RADS score of 0 on MRI and/or BI-RADS scores of 0, 4, or 5 on MG, further investigation by imaging (e.g., ultrasonography, diagnostic MG, and/or unilateral MRI) was recommended and a biopsy was performed if clinically appropriate; (iii) MRI and MG tests with BI-RADS scores of 3 were discussed case-by-case, on an individual basis in a multidisciplinary setting. The majority of cases continued screening on a short-term 6-month follow-up exam in the same imaging modality as specified per protocol. In rare cases, an

ultra-short-term follow-up MRI was performed in 4 weeks and, based on the findings, participants continued screening per protocol.

### BROCA cancer gene panel

Genomic DNA isolated from blood was sequenced for 11 genes known to be associated with inherited predisposition to breast cancer: *ATM*, *BRCA1*, *BRCA2*, *TP53*, *PTEN*, *CDH1*, *PALB2*, *NBN*, *BRIP1*, *BARD1*, or *CHEK2*. Targeted capture and multiplexed sequencing to detect all classes of mutations in these genes were carried out using BROCA (31). For some subjects, commercial testing of one or more genes (usually *BRCA1* and *BRCA2*) had been undertaken previously. For these subjects, BROCA testing was carried out at the University of Washington or at Color Genomics (Burlingame, CA) without knowledge of the prior results. In all cases, mutations previously identified were confirmed. For all 11 genes, the current analysis includes only unambiguously damaging mutations, defined as truncations, exon deletions, and splice and missense mutations shown experimentally functional. Identified mutations were validated by Sanger sequencing and real-time PCR using TaqMan probes (Life Technologies).

### Statistical analysis

A positive test was defined as BI-RADS score of 0, 4, or 5. Sensitivity, specificity, and predictive values of the imaging modalities were calculated. True positive findings were defined as pathologically proven invasive cancers or DCIS detected after positive screening. False negative findings were defined as symptomatic breast cancer presenting in between screening and incidental cancers detected following bilateral prophylactic mastectomy. False positive findings were defined as suspicious BI-RADS scores with a final benign diagnosis after further investigation. Finally, true negative findings included all normal studies (BI-RADS scores 1 or 2). BI-RADS 3 scores were either followed every 6 months per protocol or ultimately biopsied. Receiver operating characteristic (ROC) analysis was conducted on the ordinal BI-RADS scores on MRI or MG. Area under ROC curve (AUC) was estimated and compared between screening modalities using a permutation test (10,000 permutations). Follow-up was calculated from the date of the study entry until the date of the last planned screening exam, detection of breast cancer, bilateral prophylactic mastectomy, or death, whichever came first. Breast cancer incidence rate was calculated per 100 person-years at risk. Biopsy rate and recall rate, which is the number of individuals asked to return for follow-up imaging or additional procedures after an anomaly is found on an imaging study, were calculated. In the calculation of sensitivity, the analysis was per patient. In the calculation of specificity, the analysis was per screen. We assumed repeat observations in the same patients were independent. We also used a bootstrapping method to account for the possible correlation within patients. We found that the 95% confidence intervals (CI) for specificity from the two methods were almost the same, suggesting that the repeat observations are independent. Thus, this finding suggests that the radiologists evaluate the "current" screening image without considering results from previous (negative) screening image. Log-rank test and Cox proportional hazard model were used to explore factors related to breast cancer risk. All statistical analyses were conducted using STATA (v.15, Stata Corp).

**Table 1.** Characteristics of study participants

Characteristic	Number	%
All participants	295	100%
Age at entry, in years, mean ( $\pm$ SD)	43.3 ( $\pm$ 11.0)	
Germline deleterious mutation		
<i>BRCA1</i> <sup>a</sup>	75	25.4%
<i>BRCA2</i> <sup>b</sup>	61	20.7%
<i>CDH1</i>	4	1.4%
<i>PALB2</i>	3	1.0%
<i>TP53</i>	1	0.3%
<i>ATM</i> <sup>c</sup>	2	0.7%
<i>NBN</i>	1	0.3%
<i>BRIP1</i> <sup>b</sup>	1	0.3%
<i>PTEN</i>	1	0.3%
<i>CHEK2</i>	10	3.4%
All tested genes wild-type	130	44.1%
Not tested	8	2.7%
Ancestry		
Caucasian	252	85.4%
African American	34	11.5%
Hispanic	5	1.7%
Asian	4	1.4%
Menopausal status		
Premenopausal	140	47.5%
Postmenopausal		
Bilateral salpingo-oophorectomy (BSO)	94	31.9%
No BSO	41	13.9%
Missing	20	6.8%
Mammographic breast density		
Extremely or heterogeneously dense	167	56.6%
Moderate or low density	125	42.4%
Missing	3	1.0%
Prior cancer history		
Breast cancer	54	18.3%
Ovarian cancer	4	1.4%
Breast and ovarian cancer	6	2.0%
Neither	231	78.3%

<sup>a</sup>One patient has mutations in both *BRCA1* and *ATM* genes.

<sup>b</sup>One patient has mutations in both *BRCA2* and *BRIP1* genes.

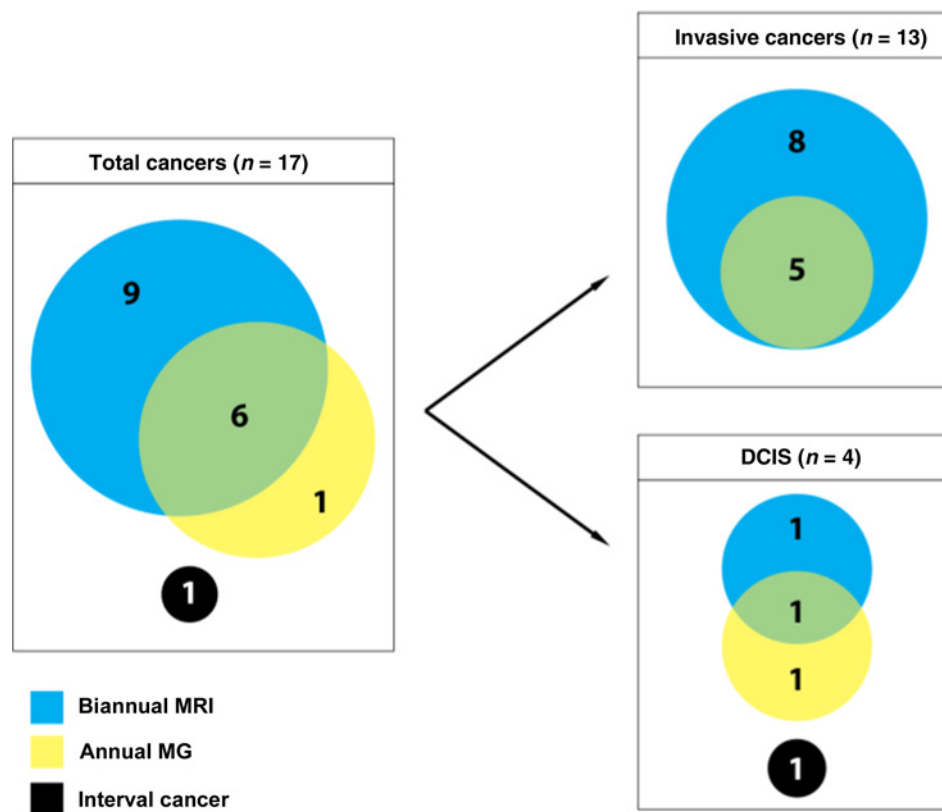
## Results

The prospective cohort study was open to enrollment in 2004 and closed to accrual in December 2016. Of 305 subjects consented, 10 were removed from further analysis because they never completed the first round of screening. Clinical characteristics of the remaining 295 study participants are listed in Table 1. The mean age at entry was 43.3 ( $\pm$ 11) years; 45.8% were postmenopausal and 31.9% had prior history of BSO. Sixty women (20.3%) had personal history of breast cancer. Genomic analysis was completed using BROCA panel or clinical testing in 258 participants (87.5%), 29 participants (9.8%) had testing for known familial mutation or complete *BRCA1* and *BRCA2* testing, and only 8 (2.7%) were not tested because they did not give a blood sample. A total of 157 (53.2%; including two patients with mutations in two genes) carried a pathogenic mutation in at least one breast cancer susceptibility gene: 75 *BRCA1*, 61 *BRCA2*, 10 *CHEK2*, 4 *CDH1*, 3 *PALB2*, 2 *ATM*, 1 *TP53*, 1 *PTEN*, 1 *NBN*, and 1 *BRIP1*. Spectrum of pathogenic mutations is listed in Supplementary Table S2.

Over the study period, 2,111 MRI and 1,223 MG were performed, representing a mean of 7.3 MRI and 4.3 MG examinations per subject. The number of screening episodes per subject ranged from 1 to 21. There were no statistically significant differences in number of screening episodes between mutation carriers, patients with previous breast cancer, and other women. Of the 1,223

**Figure 1.**

Characteristics of cancers diagnosed by imaging modality. Abbreviations: MG, mammography; MRI, dynamic contrast-enhanced magnetic resonance imaging.



annual MG, 83.5% were done on the same day as MRI. Compliance rates for each screening round are shown in Supplementary Fig. S2. Of subjects who had the opportunity to finish 5 years of screening, 41% did so. Change in insurance coverage, opting to have bilateral prophylactic mastectomy, moving out of town/ changing care providers, and pregnancy were the top reasons why women left the study (Supplementary Table S3).

#### Performance of the screening modalities

Thirteen early-stage invasive breast and four DCIS were diagnosed. Fifteen of the total occurred in patients with mutations (11 *BRCA1*, 3 *BRCA2*, 1 *CDH1*). Eight invasive cancers and 1 DCIS were detected only by MRI, 1 DCIS was detected only by MG, and 5 invasive cancers and one DCIS were detected by both modalities (Fig. 1). Of the 9 cancers detected only by MRI, three were detected on examinations when both MRI and MG were performed and 6 were detected on interval rounds when only MRI was used. MRI missed one high-grade DCIS in a *BRCA1* mutation carrier measuring 0.5 cm that was seen on MG and one intermediate grade DCIS measuring 1.7 cm that was found incidentally (4 months after MRI and 2 months before next scheduled MRI/MG visit) in a prophylactic mastectomy specimen from a 36-year-old *BRCA2* mutation carrier.

Sensitivity, specificity, and predictive values of MRI and MG alone or combined are summarized in Table 2. The sensitivity of biannual MRI screening alone was 88.2% (95% CI: 63.6%–98.5%). This was similar to the sensitivity for biannual MRI + annual MG screening modalities combined (94.1%, 95% CI: 71.3%–99.9%) and greater than that for annual MG screening

alone (41.2%, 95% CI: 18.4%–67.1%). The specificity for biannual MRI alone, annual MG studies alone, and biannual MRI + annual MG screening modalities combined were 96.8% (95% CI: 95.9%–97.5%), 97.8% (95% CI: 96.8%–98.5%), and 96.1% (95% CI: 95.2%–96.9%), respectively. The cancer detection rate of biannual MRI alone was 0.7% per 100 screening episodes (95% CI: 0.4%–1.2%), which is similar to the cancer detection rate of 0.7% per 100 screening episodes (95% CI: 0.4%–1.2%) for annual MG + biannual MRI.

ROC curves according to BI-RADS scores were generated to evaluate the diagnostic performance of the imaging modalities (Fig. 2). The AUC was 0.687 for annual MG alone, 0.904 for biannual MRI alone, and 0.941 for both modalities combined. There was no statistical difference in AUC between biannual MRI alone and biannual MRI + annual MG modalities combined ( $P = 0.53$ ), and the AUC for biannual MRI alone was statistically higher than that for annual MG ( $P = 0.0052$ ).

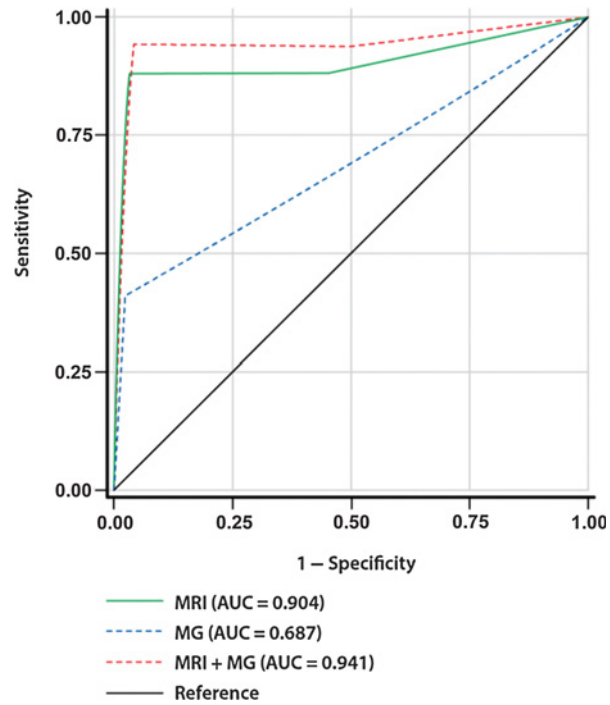
#### Clinicopathologic features of the screen-detected cancers

Thirteen invasive breast cancers and three DCIS were detected with screening (Table 3). All the 13 invasive cancers were detected by MRI and were  $\leq 1$  cm with a median size of 0.6 (range 0.1–1.0 cm; excluding patients receiving neoadjuvant therapy). No patients had axillary lymph node involvement. Of note, all three screening-detected, high-grade DCIS were diagnosed in *BRCA1* mutation carriers. Of the 13 invasive cancers, all but one had associated DCIS and 4 were triple-negative breast cancer. Eleven were detected in mutation carriers (8 *BRCA1*, 2 *BRCA2*, and 1 *CDH1*). Except for a *CDH1* mutation carrier who developed

**Table 2.** Performance by screening imaging modality and mutation status

	All subjects (n = 295)				BRCA1 carriers (n = 75)				BRCA2 carriers (n = 61)				Other women (n = 159)			
	MG	MRI	MG + MRI		MG	MRI	MG + MRI		MG	MRI	MG + MRI		MG	MRI	MG + MRI	
Number of screening episodes	1,223	2,111	2,209		320	557	572		276	516	536		627	1,038	1,101	
Sensitivity, % (95% CI)	41.2 (18.4-67.1)	88.2 (63.3-98.5)	94.1 (71.3-99.9)		45.5 (16.7-76.6)	90.9 (58.7-99.8)	100 (71.5-100)		33.3 (0.8-90.6)	66.7 (9.4-99.2)	66.7 (9.4-99.1)		33.3 (0.8-90.6)	100 (29-100)	100 (29.2-100)	
Specificity, % (95% CI)	97.8 (96.8-98.5)	96.8 (95.9-97.5)	96.1 (95.2-96.9)		98.4 (96.3-99.5)	96.9 (95.1-98.2)	96.6 (94.8-97.9)		97.1 (94.3-98.7)	95.9 (93.8-97.4)	95.1 (92.9-96.8)		97.8 (96.3-98.8)	97.1 (95.9-98.0)	96.3 (95.0-97.3)	
Positive predictive value, % (95% CI)	20.6 (8.7-37.9)	18.1 (10.5-28.0)	15.7 (9.2-24.2)		50 (18.7-81.3)	37 (19.4-57.6)	36.7 (20.0-56.1)		11.1 (0.3-48.2)	8.7 (1.1-28.0)	7.1 (0.9-23.5)		6.7 (0.2-31.9)	9.1 (1.9-24.3)	6.8 (1.4-18.6)	
Negative predictive value, % (95% CI)	99.2 (98.5-99.6)	99.9 (99.6-100.0)	99.95 (99.7-100.0)		98.1 (95.8-99.3)	99.8 (99.0-100.0)	100 (99.3-100.0)		99.3 (97.3-99.9)	99.8 (98.9-100.0)	99.8 (98.9-100.0)		99.8 (98.8-100.0)	100 (99.6-100.0)	100 (99.7-100.0)	
Number of recalls	34	87	106		10	28	31		9	24	29		15	35	46	
Number of biopsies	19	48	54		7	17	18		6	16	18		6	15	18	
Number of breast cancer detected	7	15	16		5	10	11		1	2	2		1	3	3	
Recall rate, per 100 screening episodes	2.8%	4.1%	4.8%		3.1%	5.0%	5.4%		3.3%	4.7%	5.4%		2.4%	3.4%	4.2%	
Biopsy rate, per 100 screening episodes	1.6%	2.3%	2.4%		2.2%	3.1%	3.1%		2.2%	3.1%	3.4%		1.0%	1.4%	1.6%	
Breast cancer detection rate, per 100 screening episodes	0.6%	0.7%	0.7%		1.6%	1.8%	1.9%		0.4%	0.4%	0.4%		0.2%	0.3%	0.3%	
Number of recalls needed to detect one cancer	4.9	5.8	6.6		2.0	2.8	2.8		9.0	12.0	14.5		15.0	11.7	15.3	
Number of biopsies needed to detect one cancer	2.7	3.2	3.4		1.4	1.7	1.6		6.0	8.0	9.0		6.0	5.0	6.0	

Abbreviations: MG, annual mammography alone; MG + MRI, annual mammography combined with biannual dynamic contrast-enhanced magnetic resonance imaging; MRI, biannual dynamic contrast-enhanced magnetic resonance imaging alone.



**Figure 2.**

ROC curves for MRI and MG. The difference of the diagnostic performance employing ROC analysis between MRI (AUC = 0.904) and MG + MRI (AUC = 0.941) was not statistically significant ( $P = 0.53$ ). The AUC for MRI was statistically higher than that AUC for MG ( $P = 0.0052$ ). AUC, area under the ROC curve; MG, annual mammography alone; MRI + MG, biannual dynamic contrast-enhanced magnetic resonance imaging + annual mammography; MRI, biannual dynamic contrast-enhanced magnetic resonance imaging alone; ROC, receiver operating characteristic.

a low-grade invasive lobular carcinoma with associated lobular carcinoma *in situ* (LCIS), all other invasive cancers were ductal and moderate to high grade.

**Recall and biopsy rates**

Ninety-one women had 106 recalls, of which 19 were following MG alone, 72 following MRI alone, and 15 following combined imaging modalities. The recall rates per 100 screening episodes were 4.1% for MRI, 2.8% for MG, and 4.8% for combined modalities. For BI-RADS 3, only four examinations were repeated with an ultra-short-term MRI and then followed on study every 6 months per protocol. In total, 54 biopsies were performed (Table 2; Supplementary Fig. S3) and 5.8 recalls and 3.4 biopsies were needed to diagnose one cancer. Of note, for *BRCA1* mutation carriers, the screening yield was excellent with 2.8 recalls and 1.7 biopsies to detect one cancer using biannual MRI. This is in contrast to 12.0 recalls and 8.0 biopsies for one cancer detected in *BRCA2* mutation carriers, and 11.7 recalls and 5.0 biopsies for one cancer detected in other women.

**Breast cancer incidence rates**

Over a median follow-up of 3.1 years, the overall breast cancer incidence rate was 1.42 per 100 person-years (Fig. 3A, 95% CI: 0.83-2.27). Eleven of the 75 *BRCA1* mutation carriers developed breast cancers, yielding an incidence rate of 3.65 per 100 person-years (95% CI: 1.82-6.53) that was significantly

Table 3. Characteristics of breast cancers detected

ID	Mutant gene	Prior breast cancer	BSO	Age breast ca dx	Cancer type	Grade	ER	PR	HER2	MRI lesion (cm)	Invasive tumor (cm)	Positive nodes	Stage	Detection modality	Detection round
1	BRCA1	None	Yes	42	DCIS only	3	nd	nd	nd	0.9 (MF)		0/4	Stage 0	Both	1st screening round
2	BRCA1	None	Yes	55	IDC	3	pos	neg	neg	0.4	0.3	0/4	Stage 1	Both	1st screening round
3	BRCA1	CL	No	27	IDC + DCIS	3	pos	neg	nd	1.2	0.1	0/2	Stage 1	MRI	1st screening round
4	None	IL	No	37	IDC + DCIS	3	pos	pos	neg	0.9	1.0	0/1	Stage 1	MRI	1st screening round
5	BRCA1	CL	Yes	46	DCIS only	3	nd	nd	nd	0.3		0/1	Stage 0	MRI	MRI interval round
6	BRCA1	CL	Yes	43	IDC + DCIS	2	neg	neg	neg	0.7	0.7	0/5	Stage 1	MRI	MRI interval round
7	None	CL	Yes	59	IDC + DCIS	2	pos	pos	neg	0.6	0.6	0/4	Stage 1	MRI	MRI interval round
8	BRCA1	CL	Yes	43	IDC + DCIS	2	pos	pos	neg	1.0	NAC (0.9)	0/3	Stage 1	MRI	MRI + MG round
9	BRCA1	None	Yes	51	DCIS only	3	nd	nd	nd			0/4	Stage 0	MG	MRI + MG round
10	CDH1	None	No	75	ILC + LCIS	1	pos	neg	neg	1.6	0.8	0/1	Stage 1	Both	MRI + MG round
11	BRCA2	CL	Yes	66	IDC + DCIS	3	neg	neg	neg	1.1	NAC (0)	0/3	Stage 1	Both	MRI + MG round
12	BRCA1	IL	Yes	61	IDC + DCIS	3	pos	pos	neg	0.9	0.8	0/2	Stage 1	MRI	MRI interval round
13	BRCA1	None	No	43	IDC + DCIS	3	pos	neg	neg	1.2	0.9	0/2	Stage 1	MRI	MRI interval round
14	BRCA1	CL	Yes	50	IDC + DCIS	3	neg	neg	neg	1.3	0.4	0/2	Stage 1	Both	MRI + MG round
15	BRCA2	None	Yes	48	IDC + DCIS	3	pos	pos	neg	0.9	0.6	0/4	Stage 1	MRI	MRI interval round
16	BRCA1	None	Yes	55	IDC + DCIS	3	neg	neg	neg	0.8	0.5	0/2	Stage 1	Both	MRI + MG round
17	BRCA2	None	Yes	36	DCIS only	2	pos	pos	nd			0/0	Stage 0	None	PMS

Abbreviations: BSO, bilateral salpingo-oophorectomy; ca dx, cancer diagnosis; CL, contralateral; ER, estrogen receptor; HER2, HER2 receptor; IDC, invasive ductal cancer; ILC, invasive lobular cancer; IP, ipsilateral; LCIS, lobular carcinoma *in situ*; MF, multifocal (9 mm biggest); MG, mammography; MRI, dynamic contrast-enhanced magnet resonance imaging; NAC, neoadjuvant chemotherapy; nd, not done; neg, negative; PMS, prophylactic mastectomy specimen; pos, positive; PR, progesterone receptor.

higher than that in women without *BRCA1* mutations (Fig. 3B,  $P = 0.0005$ ). Women with prior history of breast cancer had higher risk of breast cancer than those without (Fig. 3C,  $P = 0.0004$ ). In the multivariable Cox model of the two factors, both factors were predictors for breast cancer occurrence; specifically, the adjusted HR for *BRCA1* was 4.86 (95% CI: 1.76–13.45) and the adjusted HR for prior breast cancer was 4.74 (95% CI: 1.76–12.78).

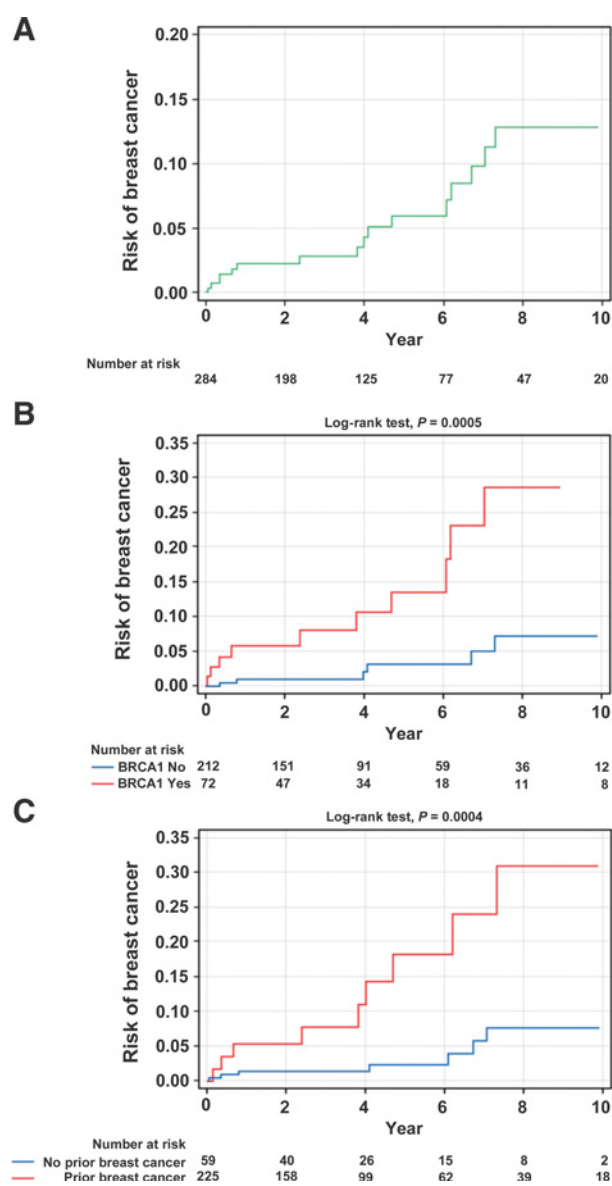
## Discussion

This is the first report on a prospective cohort of genetically defined high-risk women undergoing intensive surveillance with MRI every 6 months in conjunction with clinical breast examinations and annual MG. Thirteen invasive cancers and four DCIS were diagnosed, predominantly in *BRCA1* mutation carriers (65%). Although sensitivity and specificity of this novel approach were similar to previous studies using annual MRI and MG surveillance, this study differs in that all invasive cancers were detected at sizes  $\leq 1$  cm with zero nodal involvement and no interval invasive cancers. Most significantly, this prospective study demonstrates for the first time that aggressive *BRCA1*-associated breast cancers can be downstaged using MRI every 6 months without subjecting women to excessive recalls or biopsies. There were too few cancers in *BRCA2* mutation carriers to make definitive conclusions about benefit of biannual MRI.

Diagnosing breast cancer at an early and treatable stage is crucial for improving outcomes for young women with breast cancer due to inherited mutations (26). In this imaging-rich study, from 3,334 imaging studies (2,111 MRI and 1,223 MG), 16 cancers were detected with screening. Of the 8 invasive cancers detected only by MRI, three were detected on examinations when both MRI and MG were performed, and 5 were detected on interval rounds when only MRI was used. Considering the aggressive biology of inherited breast cancers, these five invasive cancers likely represent cancers that would have been diagnosed at more advanced stages if MRI were used annually. Previous studies of combined annual MRI and MG in high-risk patients with long-term follow-up, specifically in *BRCA1* and *BRCA2* carriers, detected breast cancers at more advanced stages, including approximately 15% cancers with nodal involvement and 5% interval cancers (4–7, 14, 19). Few studies have evaluated a biannual screening approach. A retrospective single institution chart review report of alternating yearly MRI with MG in 73 *BRCA1/2* carriers detected 10 invasive cancers of which 70% were  $>1$  cm and 10% showed lymph node involvement (15). Furthermore, considering the lack of added value of annual MG to MRI alone in surveillance of high-risk women demonstrated in our study and others (16, 19, 27, 32, 33), as well as the concerns about the risk of radiation-induced breast cancer in young women (21), the routine use of MG screening for women at high genetic risk undergoing MRI screening warrants reconsideration, particularly for *BRCA* mutation carriers under 40 years old.

The strengths of the study include its prospective design, genomic stratification of participants using panel sequencing, and long-term follow-up (34, 35). More than half of the participants were carriers of highly penetrant mutations in breast cancer susceptibility genes. The recall rate of 4.1% (87/2,111) for MRI was lower than recall rates of 10%–28% reported in high-risk women undergoing annual surveillance with MRI in previous studies (5, 36–39) and reached the current target rate of  $<7\%$  recommended by the National Health Service Breast Cancer





**Figure 3.** Breast cancer incidence rate per 100 person-years in all subjects (A), by *BRCA1* status (B), and by prior breast cancer status (C). Because 11 subjects had only baseline image, 284 subjects were included in the incidence rate calculation.

Screening Program in the United Kingdom (38, 40). Our study demonstrated that, with radiology reader expertise, careful clinical decision-making, and improved MRI technology, it is possible to achieve high positive predictive value and low recall rates. Most significant is the exceedingly high cancer yield in *BRCA1* mutation carriers where we only needed 1.7 biopsies to diagnose 1 cancer in comparison to 8.0 and 5.0 biopsies for *BRCA2* carriers and non-*BRCA* mutation carriers, respectively. Thus, similar sensitivity/specificity, a higher positive predictive value, and a lower false-positive biopsy rate in women with mutations in *BRCA1* compared with other groups, suggest that this screening strategy may be more beneficial to *BRCA1* mutation carriers. Finally, while this screening study was not designed to provide information about

overall survival, it did meet highly relevant surrogate end points of lack of interval invasive cancers and downstaging of aggressive tumors.

Study limitations include the relatively small number of events, as well as its nonrandomized and single-institution design. Nonetheless, this genomic and imaging biomarker-rich study provides the framework for optimizing screening for early detection and cancer interception in high-risk populations. More than half of the incident cancers occurred in women with prior diagnosis of breast cancer, but this is because genetic testing now often occurs after a diagnosis of cancer and these women are at risk for second primary cancers. These women are also highly motivated for secondary prevention opportunities to improve overall outcomes. The study also included participants who tested negative for any pathogenic mutation but had >20% lifetime risk. These participants had a lower incidence rate of breast cancer than *BRCA1* and *BRCA2* mutation carriers, highlighting that better risk prediction models for women at different levels of risk, models that are molecular subtype-specific, are needed for future prevention and early detection studies (41–43).

In summary, this is the first prospective study to show that aggressive breast cancer in high-risk patients can be downstaged using biannual MRI in genomically stratified high-risk women. In the setting of appropriate risk stratification using BROCA panel, MRI every 6 months performed exceedingly well in *BRCA1* carriers and women with prior breast cancer. Yearly MG did not increase the yield of invasive cancer diagnoses and could probably be eliminated in future studies. MG is known to lead to unnecessary biopsies and overdiagnosis of indolent lesions and DCIS (44). The goal of intensive imaging surveillance should be to downstage aggressive breast cancer as a first step toward improving overall outcomes for mutation carriers (45). In the United Kingdom, screening recommendations for young *BRCA* mutation carriers (<40 years) does not include MG (46). The ongoing WISDOM Trial in the United States is specifically designed to address overdiagnosis and overtreatment of indolent breast cancers by developing a population-based approach to risk stratification (20). Emerging technologies such as ultrafast and abbreviated MRI protocols and use of less contrast material have the potential to further improve performance and reduce overall costs of screening for patients at the highest risk of aggressive breast cancer without losing specificity and sensitivity (43, 47). Finally, with improved understanding of penetrance of pathogenic mutations in breast cancer susceptibility genes such as *BRCA1* and *BRCA2*, the cost-effectiveness of population screening to identify all mutation carriers, preferably by age 30 years, as well as the benefit of intensive surveillance coupled with primary prevention protocols deserve further evaluation.

**Disclosure of Potential Conflicts of Interest**

T. Walsh is a consultant/advisory board member for Color Genomics. D. Sheth reports receiving commercial research grants from Guerbet. E. Obeid reports receiving commercial research grants from Merck and Genentech, and is a consultant/advisory board member for Incyte and Pfizer. O.I. Olopade holds ownership interest (including patents) in CancerIQ. No potential conflicts of interest were disclosed by the other authors.

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