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ORIGINAL REPORT

Prospective Study of Breast Cancer Incidence in Women With a *BRCA1* or *BRCA2* Mutation Under Surveillance With and Without Magnetic Resonance Imaging

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ABSTRACT

Purpose
The sensitivity of magnetic resonance imaging (MRI) for breast cancer screening exceeds that of mammography. If MRI screening reduces mortality in women with a *BRCA1* or *BRCA2* mutation, it is expected that the incidence of advanced-stage breast cancers should be reduced in women undergoing MRI screening compared with those undergoing conventional screening.

Patients and Methods
We followed 1,275 women with a *BRCA1* or *BRCA2* mutation for a mean of 3.2 years. In total, 445 women were enrolled in an MRI screening trial in Toronto, Ontario, Canada, and 830 were in the comparison group. The cumulative incidences of ductal carcinoma in situ (DCIS), early-stage, and late-stage breast cancers were estimated at 6 years in the cohorts.

Results
There were 41 cases of breast cancer in the MRI-screened cohort (9.2%) and 76 cases in the comparison group (9.2%). The cumulative incidence of DCIS or stage I breast cancer at 6 years was 13.8% (95% CI, 9.1% to 18.5%) in the MRI-screened cohort and 7.2% (95% CI, 4.5% to 9.9%) in the comparison group ($P = .01$). The cumulative incidence of stages II to IV breast cancers was 1.9% (95% CI, 0.2% to 3.7%) in the MRI-screened cohort and 6.6% (95% CI, 3.8% to 9.3%) in the comparison group ($P = .02$). The adjusted hazard ratio for the development of stages II to IV breast cancer associated with MRI screening was 0.30 (95% CI, 0.12 to 0.72; $P = .008$).

Conclusion
Annual surveillance with MRI is associated with a significant reduction in the incidence of advanced-stage breast cancer in BRCA1 and BRCA2 carriers.

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INTRODUCTION

Women with a *BRCA1* or *BRCA2* mutation have a lifetime risk of breast cancer of up to 75%.[1] Recently, the American Cancer Society recommended that surveillance for women with a BRCA mutation include magnetic resonance imaging (MRI) of the breast, breast self-examination, clinical breast examination, and annual mammography.[2] This recommendation is based on the reports of our group and others wherein the sensitivity of MRI exceeded that of mammography.[3-6] To date, there has been no prospective study to determine whether annual MRI surveillance reduces mortality. However, if MRI screening were to lead to reduced mortality in women with a BRCA mutation, then the incidence of advanced breast cancers (eg, > 2 cm in diameter or node-positive) should be reduced in MRI-screened women compared with women at similar risk who undergo conventional surveillance.

To determine the extent to which an annual surveillance program that includes MRI screening is associated with a reduction in the incidence of advanced-stage breast cancer (stages II to IV), we followed a group of 445 women with a *BRCA1* or *BRCA2* mutation who underwent annual MRI screening and a comparison group of 830 mutation carriers who were screened with protocols that did not include MRI. We compared the incidences of noninvasive cancers, of small invasive cancers (stage I), and of large invasive cancers (stages II to IV) in the two groups.

PATIENTS AND METHODS

MRI-Screened Cohort

Between November 1997 and March 2007, 240 female BRCA1 and 205 BRCA2 mutation carriers between the ages of 25 and 65 years were recruited to the MRI study at the University of Toronto. Patients were referred from familial breast cancer clinics throughout Ontario. Women with a history of bilateral breast cancer or with metastatic disease were excluded. Women with a past history of unilateral breast cancer were eligible if the contralateral breast was intact. Participation in the study was offered to eligible women by the genetic counselor at the time of disclosure of a positive genetic test result. Informed consent was obtained from all patients. The study was approved by the institutional review boards of the participating institutions.

Screening Protocol

Eligible women were invited to begin the screening protocol after 1 year had passed since their last mammogram. The protocol included evaluation by four screening modalities (clinical breast examination, mammography, screening ultrasound, and MRI) on a single day, annually, for 5 years. Ultrasound was discontinued in 2005. For women with a past history of breast cancer who had undergone breast-conserving surgery, bilateral breast screening was performed. For those who had undergone unilateral mastectomy, screening of the contralateral breast was performed. Each image was read and scored by a different radiologist who specialized in breast imaging. The protocol has been described in detail previously.[3]

MRI-Screened Group

Delayed contrast enhancement MRI was performed with a General Electric Signal 1.5 Tesla magnet (Milwaukee, WI), by using a bolus injection of 0.1 mmol/kg of gadolinium–diethylenetriamene pentaacetic acid (Omniscan; Amersham Health, Oakville, Ontario, Canada). The first 38 patients were scanned in the coronal plane and subsequent patients were scanned in the sagittal plane.[3] MRI results were scored according to the Breast Imaging-Reporting and Data System (BI-RADS) classification.[7] Assessment was performed primarily on the basis of morphology by using enhancement kinetics for indeterminate and presumed benign lesions. A biopsy was recommended if the clinical breast examination, the mammogram, the MRI examination, or the ultrasound was judged to be suggestive of cancer (BI-RADS categories 4 or 5 or equivalent). Core and excisional biopsies were performed under ultrasound, stereotactic, or MRI guidance.

The patients in the MRI-screened cohort were followed annually by questionnaire to determine whether breast cancer had been diagnosed since the last screening test. Patients in the MRI-screened cohort were followed for up to 6 years from the date of the first MRI examination. Eighty-one women in the MRI-screened cohort underwent a prophylactic mastectomy and left the study at that time (breast cancer was not detected in any of the women with a prophylactic mastectomy).

Comparison Group

The comparison group consisted of women who enrolled in a prospective cohort study of women who carried a *BRCA1* or *BRCA2* mutation at one of 13 centers in North America. The cohort was established in 1995 for the purpose of estimating the risks of cancer in women with a *BRCA1* or *BRCA2* mutation and identifying relevant risk factors. Women in the comparison group were $\geq$ 25 years old at study entry. All women in the comparison group completed a baseline questionnaire and at least one follow-up questionnaire. Women in the comparison group were ineligible if, previous to the baseline questionnaire, they had bilateral breast cancer or metastatic breast cancer or had had a prophylactic mastectomy. Women in the comparison group were also excluded if they had had a screening breast MRI before the date of the baseline questionnaire. Follow-up questionnaires were completed every 2 years. Of 944 potential patients, 830 women (88%) completed at least one follow-up questionnaire and were eligible for the study. Screening in the comparison group was not specified formally, but in all centers, annual clinical breast examination and mammography was recommended. Of the comparison group, 98.1% had at least one screening mammogram before the baseline questionnaire or during the follow-up period. In the follow-up questionnaire, the study participant was asked whether she had ever had a screening MRI or mammogram, and if so, the dates of the first and the most recent MRI and mammogram (dates of intervening mammograms were not collected). If the control participant developed breast cancer during the follow-up period, details were obtained regarding the means of detection of the breast cancer (self-examination, physician examination, mammogram, and so on) and a copy of the pathology report was requested and reviewed. Details of tumor size, nodal status, tumor grade, and estrogen receptor status were abstracted and recorded.

Statistical Analysis

We estimated the cumulative incidence of breast cancer in the MRI-screened women and in the comparison group, by using survival analysis under a competing risks model.[8] The cumulative cancer risk was estimated at 6 years from the date of the first MRI examination. Cumulative incidence was calculated for all breast cancers, for noninvasive breast cancers (ductal carcinoma in situ [DCIS]), for invasive breast cancers, for stage I breast cancers ($<$ 2 cm and node-negative) and for stages II to IV breast cancer ($>$ 2 cm or node-positive). In these analyses, the events were considered to be mutually exclusive, and a competing risks model was used (ie, for analyses of small cancers, a large cancer was considered to be a competing risk, and vice versa). All study participants were followed from study entry (date of first MRI or date of baseline questionnaire) until the earliest of (1) date of breast cancer diagnosis, (2) 6 years from the date of study entry, (3) date of prophylactic mastectomy (for women who had prophylactic mastectomy), (4) date of last follow-up, or (5) January 1, 2008. For patients with breast cancer, the date of diagnosis was the date on which the surgery was performed. Women in the comparison group who had a screening MRI outside of the study protocol were censored (as unaffected) at that time. The difference between the two curves was tested for statistical significance with the Pepe and Morris test,[9] by using a program from Pintilie.[8]

The Cox proportional hazards model was used to estimate the relative reduction in the risk of stages II to IV breast cancer associated with membership in the MRI-screened cohort. The survival curves were compared for the assumption of proportional hazards by using the Supremum test, implemented in SAS (SAS Institute, Cary, NC). The assumption of proportionality was not rejected for any comparison (at $P = .05$). The hazard ratio (HR) was adjusted for age at entry, mutation (*BRCA1 v BRCA2*), oophorectomy (yes/no), parity (0, 1, 2, 3+), past history of breast cancer (yes/no), hormone replacement therapy use (ever/never), and oral contraceptive use (ever/never). The HR was computed for all participants and then computed separately for the *BRCA1*- and *BRCA2*-positive subgroups. There were two women in the comparison group with breast cancer for whom insufficient information was available to determine stage, and these two women were excluded from the subgroup analyses.

RESULTS

We followed 1,275 women with a *BRCA1* or *BRCA2* mutation for a mean of 3.2 years (median, 3.0 years) for incident breast cancers. Of these, 445 women were enrolled in the MRI screening trial in Toronto, Ontario, Canada (MRI-screened cohort) and 830 women in the comparison group underwent conventional screening elsewhere in Canada or in the United States. The mean age of members of the MRI-screened cohort at study entry was 43.4 years (range, 25 to 65 years), and the mean age of the women in the comparison group was 45.5 years (range, 25 to 65 years). Baseline characteristics are presented in Table 1.

In the MRI-screened cohort, 139 of the women (31.2%) completed five screens, 114 women (25.6%) withdrew from the study before completing the fifth screen, and 205 women (46.0%) continued to undergo screening. Eighty-one women in the MRI-screened cohort and 149 women in the comparison group left the study because they had a prophylactic mastectomy. None of the controls had a screening

Table 1. Characteristics of Study Patients

Characteristic	MRI Cohort (n = 445) No.	%	Comparison Group (n = 830) No.	%	*P*
Mutation status					
BRCA1	240	54	539	65	
BRCA2	205	46	283	34	
BRCA1 and BRCA2	0		8	1	< .001
Previous cancer					
Breast	87	20	301	44	< .001
Ovary	33	7	117	14	< .001
None	330	74	440	53	
Menopausal status					
Premenopausal	242	54	363	44	
Postmenopausal	197	44	464	56	.001
Unknown	6	1.4	3	0.3	
Age, years					.001
Mean	43.4		45.5		
Range	25-65		25-65		
Year of entry					
Mean	2002		2000		
Range	1996-2007		1994-2006		
Length of follow-up, years					
Median	3.0		3.0		.7
Mean	3.0		3.3		.06
Parity					.001
Mean	2.2		1.8		
Nulliparous	87	20	175	21	.5
Oophorectomy (yes)	267	60	402	48	< .001
Hormone replacement therapy	113	25	218	26	.7
Tamoxifen	58	13	213	26	< .001

Abbreviation: MRI, magnetic resonance imaging.

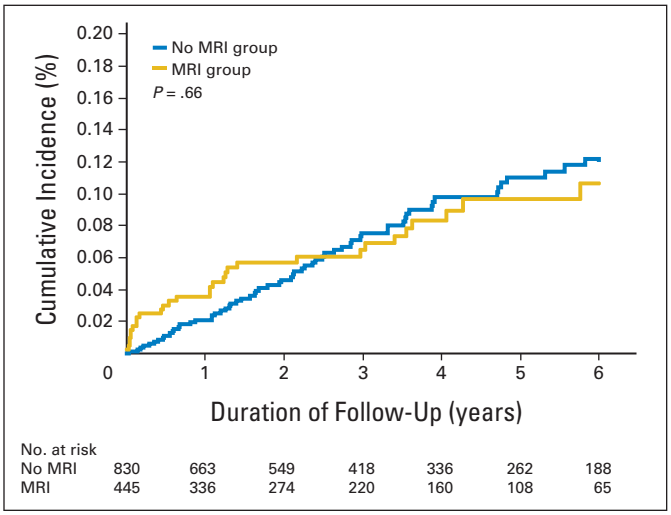

Fig 1. Cumulative incidence of invasive breast cancer in magnetic resonance imaging (MRI) –screened cohort and comparison group.

MRI at or before the time of study entry; however, 188 women in the comparison group (23%) had an MRI during the follow-up period and were censored at that time.

After an average of 3.1 years of follow-up, there were 41 cases of breast cancer (DCIS or invasive) diagnosed in 445 women in the MRI cohort. After an average of 3.3 years of follow-up, there were 76 cases of breast cancer diagnosed in the 830 women in the control group.

The cumulative incidence of DCIS at 6 years was 5.1% (95% CI, 1.2% to 9.0%) for the MRI-screened cohort and 1.6% (95% CI, 0.2% to 2.3%; $P = .63$) for the comparison group. Of the 10 cases of DCIS that were diagnosed in the MRI cohort, four were in *BRCA1* carriers and six were in *BRCA2* carriers. Of the nine cases of DCIS that were diagnosed in the comparison group, seven were in *BRCA1* carriers and two were in *BRCA2* carriers.

The cumulative incidence of invasive breast cancer at 6 years was 10.6% (95% CI, 6.5% to 14.7%) for the MRI-screened cohort and 12.2% (95% CI, 9.3% to 15.1%) for the comparison group ($P = .7$; Fig 1). However, the cancers in the MRI-screened cohort were detected earlier, on average, than those in the comparison group; an excess of cancers was observed in the MRI-screened group initially, but after 3 years of follow-up, the cumulative incidence in the two groups was similar (Fig 1).

Because the purpose of MRI screening is to identify breast cancer at an early stage (eg, noninvasive or small [< 2 cm] and node-negative), we estimated the risks of early-stage breast cancers (DCIS or stage I) and of advanced-stage breast cancer (stages II to IV) in the two cohorts. The cumulative incidence of DCIS or stage I breast cancer at 6 years was significantly higher for the MRI-screened cohort (13.8%; 95% CI, 9.1% to 18.5%) than it was for the comparison group (7.2%; 95% CI, 4.5% to 9.9%; $P = .01$; Fig 2). In contrast, the cumulative incidence of stages II to IV breast cancers at 6 years was lower for the MRI-screened cohort (1.9%; 95% CI, 0.2% to 3.7%) than it was for the comparison group (6.6%; 95% CI, 3.8% to 9.3%; $P = .02$; Fig 3).

Of the 41 women in the MRI-screened cohort who were diagnosed with breast cancer, 40 were diagnosed by using MRI screening and one was diagnosed by self-examination as an interval cancer. Of the 76 women in the control group who were diagnosed with breast cancer, 25 (33%) were diagnosed through screening (24 by mammogram and one by ultrasound), 38 were diagnosed through physical

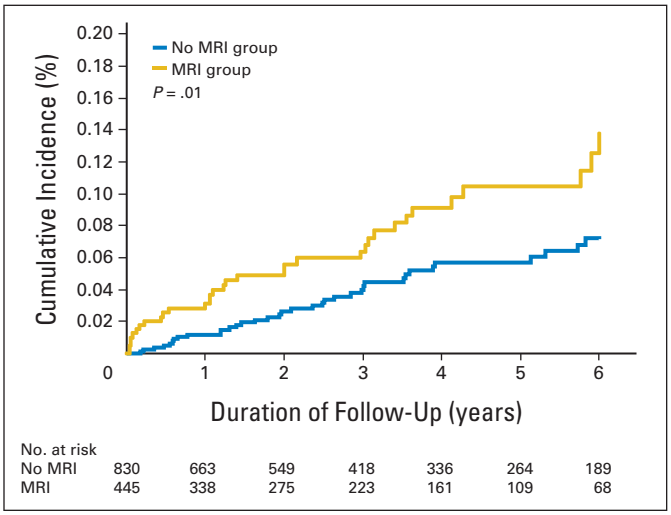

Fig 2. Cumulative incidence of early-stage (stages 0 to I) breast cancer in magnetic resonance imaging (MRI) –screened cohort and comparison group (competing risk model).

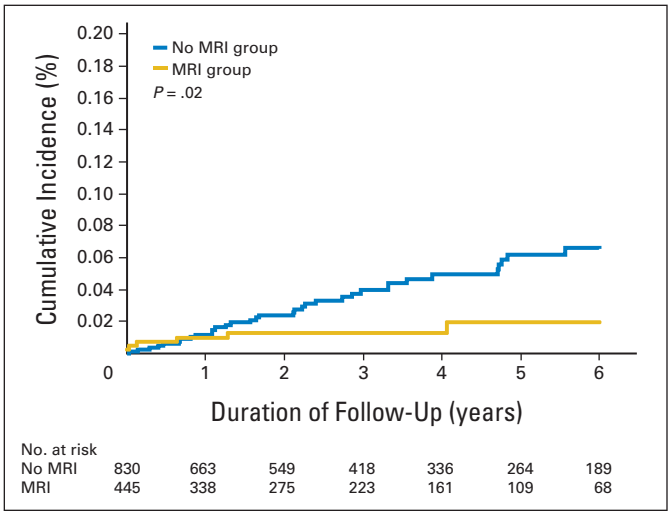

Fig 3. Cumulative incidence of stages II to IV breast cancer in magnetic resonance imaging (MRI) –screened cohort and comparison group (competing risk model).

examination (32 by self-examination and six by physician examination), and two were diagnosed through prophylactic mastectomy. Of the 38 women in the comparison group diagnosed with breast cancer through physical examination, all 38 had at least one prior screening mammogram.

On average, the invasive tumors detected in the MRI-screened cohort were smaller than those in the control group (0.9 *v* 1.8 cm; $P < .001$). Only one (3%) of 31 tumors in the MRI-screened cohort was > 2 cm versus 17 (29%) of 59 cancers in the comparison group ($P = .004$). Among the 31 women with invasive cancer diagnosed in the MRI-screened cohort, 14 were diagnosed at the first screen (prevalent cancers), and 17 were diagnosed at subsequent screens (incident cancers). The mean size of the prevalent cancers was 1.1 cm and the mean size of the incident cancers was 0.8 cm ($P = .3$ for difference). The tumors in the MRI-screened group and unscreened group were equally likely to be estrogen receptor–positive (Table 2).

To estimate the relative reduction in the risk of stages II to IV breast cancer (node-positive or > 2 cm) associated with being in the MRI-screened cohort, the Cox proportional hazards model was used. After adjustment for age at entry, oophorectomy, parity, past history of breast cancer, tamoxifen use, oral contraceptive use, and hormone replacement therapy use, the adjusted HR for the development of (any) breast cancer associated with membership in the MRI-screened cohort was 0.88 (95% CI, 0.59 to 1.3). The adjusted HR for the development of stages II to IV breast cancer associated with membership in the MRI-screened cohort was 0.30 (95% CI, 0.12 to 0.72; Table 3). The HR was 0.40 (95% CI, 0.14 to 1.2) for BRCA1 carriers and 0.15 (95% CI, 0.03 to 0.75) for BRCA2 carriers. Among the 31 women diagnosed with invasive breast cancer in the MRI-screened group, the mean tumor size was 1.0 cm for the BRCA1 carriers and 0.8 cm for the BRCA2 carriers.

DISCUSSION

In our prospective study of 1,275 women with a BRCA1 or BRCA2 mutation, participation in an annual MRI screening program was associated with a statistically significant reduction of 70% in the incidence of large or node-positive invasive breast cancers (stages II to IV) in the 6-year period following the initiation of screening. Because the cumulative incidence of all invasive breast cancer was similar in the two groups, we attribute the reduction in the risk of advanced breast cancers to the benefit of MRI screening rather than to chance or to an imbalance in the two subgroups at baseline.

Table 2. Characteristics of Breast Cancers Identified in MRI-Screened Cohort and Comparison Group

Characteristic	MRI Cohort (n = 41) No.	%	Comparison Group (n = 77) No.	%	*P*
Age at diagnosis, years					.9
Mean	48.1		48.3		
Range	32-67		27-70		
Type of cancer					
Invasive	31	76	67	88	
DCIS	10	24	9	12	.08
Size of tumor (invasive), mm					
0-5	9	29	5	8	
6-10	14	45	16	27	
11-20	7	23	21	36	
21+	1	3	17	29	.002
Missing	0		8		
Mean	0.9		1.8		< .001
Range	0.1-3.0		0.1-7.0		
Nodal status (invasive)					
Negative	26	87	39	60	
Positive	4	13	26	40	.009
Node-negative and < 2 cm	35	85	40	54	
Node-positive or ≥ 2 cm	6	15	34	46	.004
Missing	1		2		
ER status (invasive)					
Positive	14		19		.83
Negative	16		24		
Equivocal	0		1		
Unknown	1		20		

Abbreviations: MRI, magnetic resonance imaging; DCIS, ductal carcinoma in situ; ER, estrogen receptor.

Table 3. Hazard Ratios Associated With Membership in the MRI-Screened Group

Type of Cancer	Hazard Ratio	95% CI	*P*
DCIS	1.71	0.61 to 4.80	.31
Invasive cancer	0.79	0.50 to 1.24	.30
Small invasive cancers (< 2 cm and node-negative)	1.33	0.75 to 2.36	.33
Advanced invasive cancers (> 2 cm or node-positive)	0.30	0.12 to 0.72	.008

NOTE. The hazard ratios were adjusted for age at entry, oophorectomy (yes/no), parity (0, 1, 2, 3+), past history of breast cancer (yes/no), mutation (BRCA1/BRCA2), hormone replacement therapy use (ever/never), and oral contraceptive use (ever/never).

Abbreviation: MRI, magnetic resonance imaging; DCIS, ductal carcinoma in situ.

We saw a greater incidence of DCIS in the MRI-screened cohort than in the comparison group. To some extent, the detection of DCIS should lead to a reduction in the number of invasive cancers; however, in this study, because the cumulative incidence of invasive cancers was similar in the two groups, the reduction in advanced cancers is more likely to be due to the identification of small invasive cancers than to the detection of preinvasive lesions. In addition, among the women screened with MRI, the number of cases of DCIS detected (10) was much smaller than the number of invasive cancers detected (31). Only a small fraction of cases of DCIS are expected to progress to invasive cancer over a 6-year period (< 10%), and the potential for preventing invasive cancer by diagnosing and treating DCIS may be limited in a short period of follow-up.

To the best of our knowledge, ours is the first study to compare an MRI-screened cohort of BRCA carriers with a control group. The women in the comparison group were advised to undergo routine annual mammography; nevertheless, the majority of cancers in the comparison group were detected by physical examination. Previous prospective studies report similar results.[8-13] Only one of 31 invasive cancers in the MRI cohort was diagnosed as an interval cancer compared with 38 of 77 cancers in the comparison group ($P < .001$).

Previously, we and others[4, 5,14,15] have shown MRI to be more sensitive than mammography, and we now show that the improvement in sensitivity results in a significant reduction in the incidence of advanced breast cancers. It will be necessary to follow this and similar cohorts to show that this reduction leads to a reduction in breast cancer– associated mortality. We found the protective effect of MRI screening on advanced breast cancer to be greater for *BRCA2* carriers (HR, 0.15; 95% CI, 0.03 to 0.75) than for *BRCA1* carriers (HR, 0.40; 95% CI, 0.14 to 1.2). The observed difference may be due to chance, or it may reflect a faster rate of growth in the *BRCA1* carriers than in *BRCA2* carriers.[16] The *BRCA1* cancers were diagnosed, on average, at a larger size than were the *BRCA2*-associated cancers (1.0 *v* 0.8 cm). It is possible that the ideal interval between screens should be shorter for *BRCA1*-positive women than for *BRCA2*-positive women.

There are several limitations to our study. The screening protocol was not assigned at random. All women in the comparison group were recommended to have annual mammographic screening, but a standardized screening protocol was not in place. The MRI-screened women were all from Toronto, and the women in the comparison group were from throughout North America. Members of the MRI-screened cohort were followed annually, whereas members of the comparison group completed follow-up questionnaires every 2 years. The differences in the baseline characteristics (eg, year of birth, menopausal status, *BRCA1 v BRCA2*, previous breast cancer, and hormone use) of the two groups were adjusted for in the multivariate analysis. There may be other imbalances in the two groups in terms of residence (urban *v* rural), socioeconomic status, and education. However, there is no compelling reason to believe that these differences influenced the risks of advanced cancers in the two subgroups. Furthermore, the proportions of women in the two groups who experienced an invasive breast cancer were similar, but a marked difference was seen in the incidence of advanced breast cancers. The protective effect was large, and the adjusted HR was statistically significant (HR, 0.30; 95% CI, 0.12 to 0.72; $P = .008$).

In conclusion, annual screening with MRI is associated with a significant reduction in the incidence of stages II to IV invasive breast cancers. Future studies designed to estimate the reduction of breast cancer–specific mortality are warranted.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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