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Bae, Min
Sung, Janice
Bernard-Davila, Blanca
et al.

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Original Research

Survival Outcomes of Screening with Breast MRI in Women at Elevated Risk of Breast Cancer

Min Sun Bae, MD, Janice S. Sung, MD, Blanca Bernard-Davila, MPH, MS, Elizabeth J. Sutton, MD, Christopher E. Comstock, MD, Elizabeth A. Morris, MD*

Memorial Sloan Kettering Cancer Center, Department of Radiology, New York, NY (M.S.B., J.S.S., B.B-D., E.J.S., C.E.C., E.A.M.)

*Address correspondence to E.A.M. (e-mail: morrise@mskcc.org)

Abstract

Objective: To determine survival outcomes in women with breast cancer detected at combined screening with breast MRI and mammography versus screening mammography alone.
Methods: This is an institutional review board-approved retrospective study, and the need for informed consent was waived. A total of 3002 women with an increased risk of breast cancer were screened between 2001 and 2004. Of the 3002 women, 1534 (51.1%) had 2780 combined screenings (MRI and mammography) and 1468 (48.9%) had 4811 mammography-only screenings. The X^2 test and the Kaplan-Meier method were used to compare cancer detection rates and survival rates.
Results: The overall cancer detection rate was significantly higher in the MRI plus mammography group compared with the mammography-only group (1.4% [40 of 2780] vs 0.5% [23 of 4811]; $P < 0.001$). No interval cancers occurred in the MRI plus mammography group, whereas 9 interval cancers were found in the mammography-only group. During a median follow-up of 10.9 years (range: 0.7 to 15.2), a total of 11 recurrences and 5 deaths occurred. Of the 11 recurrences, 6 were in the MRI plus mammography group and 5 were in the mammography-only group. All five deaths occurred in the mammography-only group. Disease-free survival showed no statistically significant difference between the two groups ($P = 0.32$). However, overall survival was significantly improved in the MRI plus mammography group ($P = 0.002$).
Conclusion: Combined screening with MRI and mammography in women at elevated risk of breast cancer improves cancer detection and overall survival.

Key words: screening; MRI; mammography; survival breast cancer.

Introduction

Breast cancer is the most common cancer and the second leading cause of cancer deaths among women in the United States. Although mortality from breast cancer has declined over the past two decades, an estimated 41 760 women in the United States will die from the disease in 2019 (1). The decline in breast cancer mortality is mostly attributable to early detection with screening mammography and improved treatment (2). Mammography is the only imaging modality proven to reduce mortality from breast cancer and is an effective screening test in women with an average breast cancer risk (3–5). However, the sensitivity of mammography is decreased in women at high risk for breast cancer and in women with dense breasts (6–10). The current American Cancer Society (ACS) and National Comprehensive Cancer Network (NCCN) guidelines recommend annual combined screening with breast MRI and mammography for high-risk women. The guidelines include women who are BRCA1 or BRCA2 mutation carriers, women with first-degree relatives with BRCA or other cancer susceptibility mutations, women who have a greater than 20% to 25%

Key Messages

- Screening with MRI plus mammography improves detection of early breast cancer in women at elevated risk of breast cancer.
- Overall survival of breast cancer patients was significantly improved in the MRI plus mammography group compared with the mammography-only group.
- Disease-free survival showed no significant difference between the two groups.

lifetime risk for breast cancer, and women who had chest irradiation between the ages of 10 and 30 years (11, 12). Recent evidence from retrospective studies supports the use of MRI to screen women with a personal history of breast cancer or lobular carcinoma in situ (LCIS), but current guidelines by the ACS and NCCN recommend neither for nor against screening MRI in this patient population (11–15).

A meta-analysis of 11 prospective studies of a total 4983 high-risk women reported that the sensitivity was 39% for screening mammography alone, 77% for screening MRI alone, and 94% for combined screening with MRI and mammography (16, 17). Despite the high sensitivity that can be achieved by adding MRI to mammography, it is unknown whether the combined screening reduces breast cancer mortality. Knowing if a screening test reduces deaths from cancer can be one of the most important outcomes (18); however, there is little evidence supporting that supplemental screening with MRI improves survival. The purpose of this study was to determine survival outcomes in women with breast cancer detected at combined screening with breast MRI and mammography versus screening mammography alone.

Methods

Study Design and Population

This is a retrospective, cohort analysis study comparing survival outcomes of patients with breast cancer, according to whether they underwent screening with breast MRI and mammography or a mammography-only screening between January 2001 and December 2004. Our institutional review board approved this study, which is Health Insurance Portability and Accountability Act compliant, and the need for informed consent was waived. We included consecutive women who were undergoing screening breast MRI and/or screening mammography between 2001 and 2004. Women were included in the database if they had one or more risk factors for breast cancer, including a BRCA1 or BRCA2 mutation (n = 19), a strong family history of breast cancer but no mutation in BRCA genes (n = 230), an untested first-degree relative with breast cancer (n = 1572), a personal history of breast cancer (n = 1023), a history of mantle irradiation for Hodgkin lymphoma (n = 17), or a history of LCIS (n = 160). A total of 3021 women who met inclusion criteria underwent breast cancer screening between 2001 and 2004. All women had at least a one-year follow-up after the last round of screening to confirm the absence of cancer. Women undergoing screening MRI alone were excluded from the study (n = 19). The study cohort consisted of 3002 women, 1534 in the MRI plus mammography group and 1468 in the mammography-only group.

Image Acquisition and Interpretation

MRI was performed with the patient in the prone position with a 1.5-T commercially available system (Sigma; GE Medical Systems, Milwaukee, WI) by using a dedicated surface breast coil. Imaging sequences included a localizing sequence followed by a sagittal T2-weighted sequence (repetition time/echo time [TR/TE], 4000 msec/85 msec). Sagittal T1-weighted three-dimensional fast spoiled gradient echo (TR/TE, 17 msec/2.4 msec; flip angle, 35°; bandwidth, 31.25 MHz) sequences were then performed before and three times after a rapid bolus injection of 0.1 mmol/L of gadopentetate dimeglumine (Magnevist; Berlex, Wayne, NJ) per kilogram of body weight. Images were obtained for an acquisition time per volumetric acquisition of less than 2 minutes each. Total imaging time per breast, including three enhanced acquisitions, was approximately 15 minutes. Section thickness was 2 mm without a gap, using a matrix of 256 × 192 and a field of view of 16–18 cm. After the examination, the precontrast T1 images were subtracted from the first postcontrast T1 images on a pixel-by-pixel basis.

Two-view mammograms, plus additional views and spot magnification views where appropriate, were performed with digital mammography units (Senographe 2000D; GE Medical Systems, Milwaukee, WI). Breast density was evaluated according to the BI-RADS density grades (19, 20). For each MRI or mammographic examination, results were assigned according to the BI-RADS assessment categories (19, 20). MRI interpretations were performed in conjunction with the clinical history and other available breast imaging studies. All imaging studies were interpreted by dedicated breast imaging radiologists (4 radiologists, with 6 to 15 years of experience).

Data Collection

Data collected for this study included the age at screening, number of screening rounds, risk factors (genetic or family history of breast cancer, personal history of breast cancer, history of mantle irradiation, or history of LCIS), and breast density. We defined women with a genetic history of breast cancer as having a BRCA1 or BRCA2 mutation or a strong family history of breast cancer but no mutation in BRCA genes. For women diagnosed with breast cancer, pathologic confirmation was obtained. The database contained the age at diagnosis, histologic tumor type (invasive or ductal carcinoma in situ [DCIS]), tumor size, tumor grade (histologic grade or, if not available, nuclear grade), nodal status, lymphovascular invasion, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). The cancer stage was recorded according to the TNM staging system of the American Joint Committee on Cancer (AJCC) (21). Immunohistochemical analyses for ER, PR, and HER2 were performed by using the American Society of Clinical Oncology and College of American Pathologists guidelines (22, 23). For HER2 classification, the fluorescent in situ hybridization (FISH) result was used when an immunohistochemistry result was 2+. Human epidermal growth factor receptor 2 gene amplification by FISH or a 3+ immunohistochemistry result was considered HER2 positive. For molecular subtype classification, patients were classified in three subtypes: hormone receptor (HR) positive (ER positive and/or PR positive), HER2 (ER negative, PR negative, and HER2 positive), and triple negative (ER negative, PR negative, and HER2 negative). Data on patient survival were collected using the following variables: date of diagnosis, date of last follow-up, type and date of recurrence, vital status, and date of death. Disease-free survival was defined as the time from the date of diagnosis to the date of recurrence or the date of the last follow-up. Overall

survival was defined as the time from the date of the last known vital status or date of death.

Statistical Analysis

The cancer detection rate was calculated as the ratio between the number of cancers and the number of screening rounds, and stratified by tumor type (invasive or DCIS), age at diagnosis (< 50 or ≥ 50 years), or risk groups (genetic history, family history, or personal history); a Poisson distribution was assumed to calculate the 95% confidence intervals (CIs). We did not examine the cancer detection rate among women with a history of mantle irradiation or LCIS because of small numbers (MRI plus mammography, n = 3; mammography-only, n = 2). Cancer detection rates were compared between the MRI plus mammography and mammography-only groups using the X^2 test. Interval cancers were defined as cancers diagnosed between screening rounds or within 1 year after the completion of screening (24).

Patient and tumor characteristics were compared between the two groups using X^2 tests and *t* tests, when appropriate. The data set was divided into pairs of subgroups using the following criteria: breast density, nondense (BI-RADS A and B) versus dense (BI-RADS C and D); cancer stage, early (stages 0 and I) versus advanced (stages II to IV); tumor grade, low-intermediate versus high. The disease-free and overall survival rates were analyzed with the Kaplan-Meier method and tested with the log-rank test. SAS statistical software version 9.3 (SAS Institute, Cary, NC) was used for the analyses. All statistical tests were two sided, and $P < 0.05$ was considered statistically significant.

Results

Study Population

Of the 3002 women, 1534 (51.1%) had 2780 combined screenings (average screening rounds, 1.8), and 1468 (48.9%) had 4811 mammography-only screenings (average screening rounds, 3.3). At the time of screening, the majority of women in both groups were between the ages of 40 and 60 years, although the mean age was younger in the MRI plus mammography group compared to the mammography-only group (49 years and 57 years, respectively; $P < 0.001$; Table 1). Women in the MRI plus mammography group were significantly more likely to have dense breasts (83.8% [1285 of 1534] vs 59.1% [867 of 1468]; $P < 0.001$). In addition, the distribution of risk factors was statistically significantly different between the two groups ($P < 0.001$). The vast majority of women in the mammography-only group had a family history of breast cancer, while the proportions of women with a genetic history or personal history of breast cancer were higher in the MRI plus mammography group (genetic history, 13.8% [212 of 1534] vs 2.2% [33 of 1468]; personal history, 56.7% [869 of 1534] vs 10.1% [148 of 1468]).

Cancer Detection Rates

There were 63 breast cancers in 63 women; 40 cancers were detected in the MRI plus mammography group and 23 cancers were detected in the mammography-only group. No interval cancers occurred in the MRI plus mammography group, while 9 interval cancers were found in the mammography-only group. The overall cancer detection rate was significantly higher in the MRI plus mammography group compared with the mammography-only group (1.4%; 95% CI, 1.0% to 2.0% vs 0.5%; 95% CI, 0.3% to 0.7%; $P < 0.001$; Table 2).

Cancer detection rates were significantly higher in the MRI plus mammography group for women with a family history of breast cancer (2.0%; 95% CI, 1.0% to 3.6% vs 0.3%; 95% CI, 0.2% to 0.5%; $P < 0.001$), for women age ≥ 50 years (1.6%; 95% CI, 1.0% to 2.4% vs 0.4%; 95% CI, 0.2% to 0.7%; $P < 0.001$), for women age < 50 years (1.3%; 95% CI, 0.8% to 2.1% vs 0.6%; 95% CI, 0.2% to 1.1%; $P = 0.034$), for invasive cancers (1.0%; 95% CI, 0.6% to 1.4% vs 0.4%; 95% CI, 0.2% to 0.6%; $P = 0.001$), and for DCIS (0.5%; 95% CI, 0.2% to 0.8% vs 0.1%; 95% CI, 0% to 0.2%; $P = 0.002$). The highest detection rate was observed among women with a genetic history of breast cancer, although not statistically significant (2.5%; 95% CI, 1.2% to 4.6% vs 2.0%; 95% CI, 0.2% to 7.1%; $P > 0.99$). No significant difference was found among women with a personal history of breast cancer (0.9%; 95% CI, 0.5% to 1.5% vs 1.2%; 95% CI, 0.5% to 2.7%; $P = 0.61$).

Table 1. Characteristics of the Study Population

Characteristic	MRI Plus Mammography (n = 1534)	Mammography-Only (n = 1468)	*P*
Age at screening (y)			<0.001
<40	239 (15.6)	68 (4.6)	
40–49	562 (36.6)	358 (24.4)	
50–59	498 (32.5)	477 (32.5)	
60–69	198 (12.9)	326 (22.2)	
≥70	37 (2.4)	239 (16.3)	
Breast density			<0.001
Nondense (BI-RADS A or B)	249 (16.2)	601 (40.9)	
Dense (BI-RADS C or D)	1285 (83.8)	867 (59.1)	
Risk factor			<0.001
Genetic history	212 (13.8)	33 (2.2)	
Family history	325 (21.2)	1239 (84.4)	
Personal history	869 (56.7)	148 (10.1)	
History of mantle irradiation	11 (0.7)	6 (0.4)	
History of LCIS	117 (7.6)	42 (2.9)	

Data are numbers of women, with percentages in parentheses.
Abbreviation: LCIS, lobular carcinoma in situ.

Patient and Tumor Characteristics

The age at diagnosis was significantly younger in the MRI plus mammography group compared to the mammography-only group (mean age, 52 years and 55 years, respectively; $P < 0.001$). The pathologic tumor sizes differed significantly between the two groups ($P < 0.001$). The mean tumor size was 0.7 cm in the MRI plus mammography group and 1.4 cm in the mammography-only group ($P = 0.001$). In the MRI plus mammography group, 73.1% (19 of 26) of invasive tumors were 1 cm or smaller compared to 29.4% (5 of 17) in the mammography-only group. None of invasive tumors in the MRI plus mammography group were larger than 2 cm compared to 11.8% (2 of 17) in the mammography-only group.

The interval cancer rate was significantly higher in the mammography-only group (40.9% [9 of 22] vs 0% [0 of 38]; $P < 0.001$). Of the 9 interval cancers, 8 (88.9%) were invasive cancers and 1 (11.1%) was DCIS (Table S1). Two interval cancers showed axillary lymph node metastasis and one other presented with distant metastasis. No statistically significant differences were observed in other characteristics. Detailed data on the 60 cancers are listed in Table S2.

Survival Outcomes

Of the 63 patients with breast cancer, 3 (4.8%) were followed for less than 5 years after the diagnosis. Thus, the remaining 60 patients were included in the survival analysis. The median follow-up time

Table 2. Cancer Detection Rates by Tumor Type, Age Group, and Risk Group

	MRI Plus Mammography			Mammography-Only			
Measure	No.	Rate*	95% CI*	No.	Rate*	95% CI*	*P*
Overall	40/2780	1.4	1.0 to 2.0	23/4811	0.5	0.3 to 0.7	<0.001
Tumor type							
Invasive	27/2780	1.0	0.6 to 1.4	18/4811	0.4	0.2 to 0.6	0.001
DCIS	13/2780	0.5	0.2 to 0.8	5/4811	0.1	0.0 to 0.2	0.002
Age group (y)							
<50	20/1499	1.3	0.8 to 2.1	8/1410	0.6	0.2 to 1.1	0.034
≥50	20/1281	1.6	1.0 to 2.4	15/3401	0.4	0.2 to 0.7	<0.001
Risk group							
Genetic history	10/395	2.5	1.2 to 4.6	2/99	2.0	0.2 to 7.1	>0.99
Family history	11/550	2.0	1.0 to 3.6	12/4052	0.3	0.2 to 0.5	<0.001
Personal history	15/1592	0.9	0.5 to 1.5	6/489	1.2	0.5 to 2.7	0.61

Abbreviations: CI, confidence interval; DCIS, ductal carcinoma in situ.
*Data are percentages.

Table 3. Clinical Characteristics of Patients with Breast Cancer Recurrence

Patient No.	Risk Factor	Screening Group	Age (y)	Histology	Stage	TNM	Type of Event	Follow-Up Interval (y)
1	FH	MRI + mammography	42	IDC	I	T1aN0M0	Contralateral cancer	1.7
2	GH	MRI + mammography	49	ILC	I	T1cN0M0	Contralateral cancer	3.4
3	LCIS	MRI + mammography	48	DCIS	0	TisN0M0	Contralateral cancer	0.7
4	LCIS	MRI + mammography	53	DCIS	0	TisN0M0	Local recurrence	3.9
5	LCIS	MRI + mammography	45	DCIS	0	TisN0M0	Local recurrence	7.6
6	FH	MRI + mammography	39	IDC	I	T1cN0M0	Contralateral cancer	11.6
7	PH	Mammography-only	45	IDC	III	T4N0M0	Distant metastasis	8.0
8	FH	Mammography-only	60	IDC	I	T1bN0M0	Distant metastasis	1.4
9	FH	Mammography-only	45	IDC	I	T1cN0M0	Contralateral cancer	1.9
10	GH	Mammography-only	51	IDC	I	T1aN0M0	Contralateral cancer	2.3
11	LCIS	Mammography-only	87	IDC	I	T1cN0M0	Local recurrence	3.0

Abbreviations: DCIS, ductal carcinoma in situ; FH, family history of breast cancer; GH, genetic history of breast cancer; IDC, invasive ductal cancer; ILC, invasive lobular cancer; LCIS, lobular carcinoma in situ; PH, personal history of breast cancer.

Table 4. Clinical Characteristics of Patients who Died in the Mammography-Only Group

Patient No.	Risk Factor	Age (y)	Mode of Detection	Histology	Stage	TNM	Cause of Death	Follow-Up Interval (y)
1	PH	45	Interval cancer	IDC	III	T4N0M0	Breast cancer	9.4
2	FH	60	Mammography	IDC	I	T1bN0M0	Breast cancer	7.9
3	PH	60	Mammography	IDC	II	T2N1M0	Unknown	9.6
4	GH	51	Mammography	IDC	I	T1aN0M0	Breast cancer	3.4
5	PH	78	Interval cancer	IDC	IV	TXNXM1	Breast cancer	2.3

Abbreviations: FH, family history of breast cancer; GH, genetic history of breast cancer; IDC, invasive ductal cancer; PH, personal history of breast cancer.

was 10.9 years (range, 0.7 to 15.2 years). Eleven of 60 (18.3%) patients with breast cancer developed a recurrence: 6 of 38 (15.8%) in the MRI plus mammography group and 5 of 22 (22.7%) in the mammography-only group (Table 3). Two patients developed distant metastases, and all 5 deaths occurred in the mammography-only group (Table 4). The Kaplan-Meier estimate for overall survival was significantly increased in the MRI plus mammography group compared with the mammography-only group ($P < 0.002$; Figure 1). Disease-free survival showed no significant difference between the two groups ($P = 0.32$).

Discussion

The results of this retrospective cohort study demonstrate that combined screening with breast MRI and mammography improves the overall survival rate compared to screening mammography alone in high-risk women diagnosed with breast cancer. No distant metastases and deaths were found in the MRI plus mammography group. Our findings are not consistent with a previous study, which showed no overall survival difference in women undergoing combined screening versus screening mammography alone (25). This might be caused by differences in study populations, methodology, and cancer treatment. Contrary to the prior

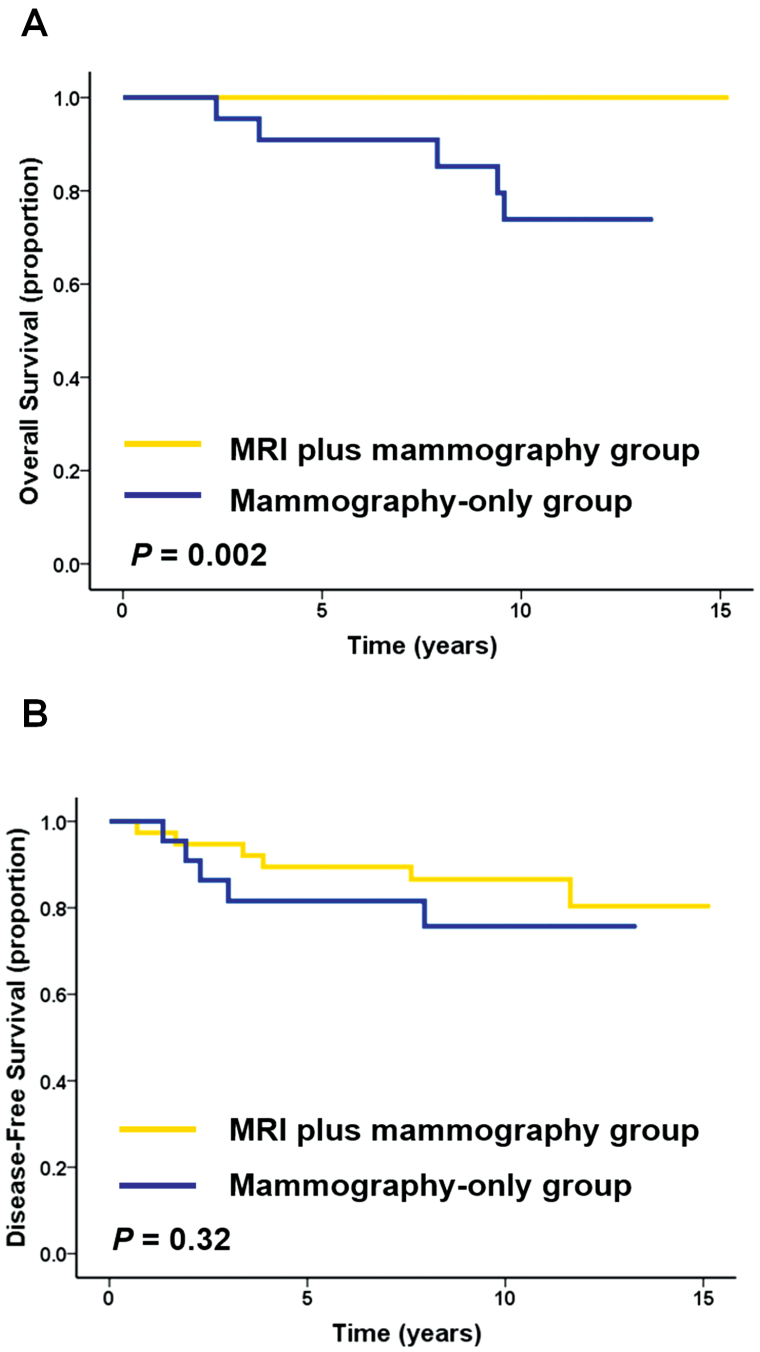

Figure 1. Kaplan-Meier curves for (**A**) overall survival ($P = 0.002$) and (**B**) disease-free survival ($P = 0.32$) between the MRI plus mammography and mammography-only groups.

study, our patient groups were diagnosed and treated during the same time period. Improved metastasis-free and overall survival in the MRI screening versus no screening groups have been reported (25, 26).

There are no randomized controlled trials evaluating the effect of screening breast MRI on survival rates. Although the randomized trial is an optimal study design, it would take years to complete if mortality is the end point, and it would need to enroll a large number of women to obtain statistical significance (27). Therefore, we compared the survival outcomes of patients in our screening program who were diagnosed with breast cancer.

Our results confirm findings shown in other previously published studies on high-risk women (6–9, 17, 24). The cancer detection rate for combined screening with MRI and mammography was significantly higher than that for mammography alone (1.4%; 95% CI, 1.0% to 2.0% vs 0.5%; 95% CI, 0.3% to 0.7%; $P < 0.001$). As expected, we found the highest cancer detection rate in the MRI plus mammography group among women with a genetic history of breast cancer (2.5%; 95% CI, 1.2% to 4.6%). Our cancer detection rate is similar to the cancer detection rate reported by prospective studies on women with genetic or familial high risk, ranging from 1.6% to 3.0% (27–29). Moreover, irrespective of age or tumor type, cancer detection rates were increased in the MRI plus mammography group. However, the increased detection rate was not observed among women with a personal history of breast cancer. It should be noted that differences existed in the two screening groups for baseline characteristics such as risk factors. These differences may reflect some variations in the cancer detection rate.

None of the interval cancers in our study occurred in women screened with MRI and mammography. This is consistent with previous studies, with interval cancers being reduced by supplemental screening with breast MRI or ultrasound (30–32). It has been reported that interval cancers have a larger tumor size, higher grade, and higher stage compared with screen-detected cancers (33). In our study, the mean pathology size of invasive tumors was smaller in the MRI plus mammography group (0.7 cm vs 1.4 cm; $P = 0.001$), and one stage IV cancer in the mammography-only group was an interval cancer. Other studies found a higher hazard rate of breast cancer death in interval cancers than in screen-detected cancers (34, 35). In one study, using data from multiple randomized controlled trials, patients with interval cancer had a 39% greater hazard of breast cancer death than patients with screen-detected cancers (35).

Our study has some limitations. Because the study was designed to compare the outcomes of different screening strategies, the baseline characteristics differed between the two groups. However, we wanted to evaluate whether a survival benefit exists in patients who underwent screening with MRI plus mammography versus mammography alone. In addition, the study populations included patients who were diagnosed with breast cancer before 2006, when screening breast MRI was not routinely recommended in women at increased risk. Another limitation was that it was a single-institution retrospective study. Additional multi-institutional studies on larger populations would be beneficial. The feasibility of conducting a randomized screening trial on survival is low, and it is unlikely that one can accrue such a study since there is strong data regarding early detection. Finally, we did not explore lead time bias and how it might account for survival benefit in this study.

In conclusion, combined screening with MRI and mammography improved cancer detection in women at elevated risk of breast cancer and the overall survival rate in women diagnosed with breast cancer compared to screening mammography alone. However, the combination of MRI and mammography did not improve disease-free survival. Given the benefits of MRI in reducing interval cancers, detecting smaller cancers, and improving overall survival, we believe that more women could benefit from MRI screening. Existing recommendations for breast MRI screening should be reassessed and possibly expanded.

Supplementary material

Supplementary material is available at the *Journal of Breast Imaging* online.

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Conflict of interest statement

J.S.S. has received research grants from Hologic and GE Healthcare. C.E.C. has received research grants from ECOG-ACRIN (5UG1CA189828-05) and an honorarium for speaking at a symposium sponsored by Bayer Healthcare Pharmaceuticals. E.A.M. has received a grant from GRAIL. All other authors have no conflicts of interest to declare.

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