Unilateral Breast Cancer: Screening of Contralateral Breast by Using Preoperative MR Imaging Reduces Incidence of Metachronous Cancer[1]

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Purpose: To investigate the clinical effect of a single magnetic resonance (MR) imaging screening examination of the contralateral breast at preoperative evaluation in women with unilateral breast cancer.

Materials and Methods: The institutional review board approved this study and waived informed consent. Among women with unilateral breast cancer who underwent curative surgery from 2004 to 2008, 1323 women (mean age, 46.8 years; range, 18–81 years) underwent mammography and ultrasonography (US) alone (comparison group) between January 2004 and December 2006; 1771 consecutive women (mean age, 48.2 years; range, 22–85 years) underwent mammography, US, and MR imaging (contralateral MR imaging–screened group) between January 2007 and December 2008. The incidence of synchronous cancer and the incidence of metachronous cancer in the contralateral breast were compared between groups. Multivariate Cox analysis was performed. Median follow-up was 56 months (range, 13–94 months).

Results: Twenty-five synchronous contralateral cancers (13 invasive cancers, 12 ductal carcinomas in situ; mean invasive size, 14 mm [range, 1–35 mm]; 92% [12 of 13] of invasive tumors were node negative) were additionally detected with MR imaging in the MR imaging–screened group. The cumulative incidence of contralateral breast cancer at 45 months was 0.5% (nine of 1771) (95% confidence interval [CI]: 0.23%, 0.96%) for the MR imaging–screened group and 1.4% (18 of 1323) (95% CI: 0.81%, 2.14%) for the comparison group (P = .02). Contralateral MR imaging screening (hazard ratio, 0.37; 95% CI: 0.15, 0.92; P = .03) and estrogen receptor negativity (hazard ratio, 3.98; 95% CI: 1.60, 9.92; P = .003) were associated with risk of contralateral cancer diagnosis in multivariate analysis.

Conclusion: A single MR imaging screening examination of the contralateral breast in women with unilateral breast cancer increased synchronous cancer detection and was associated with decreased diagnosis of metachronous contralateral cancer within 45 months.

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Women with unilateral breast cancer are at an increased risk for the development of contralateral breast cancers, with a 1%–5% incidence of synchronous cancer and a 3%–13% incidence of metachronous cancer (1–5). Moreover, women with bilateral breast cancer tend to have worse prognoses than do women with unilateral breast cancer (3,6,7). Indeed, study results (7) have shown that women who developed bilateral cancer within 5 years and at an age younger than 50 years had 5-year mortality rates that were 3.9 times higher than those of women with unilateral cancer.

Although mammography is the standard modality for breast cancer screening, and combined mammography and physical examination depict 1%–3% of contralateral breast cancers in 3% of patients at the time of initial diagnosis (7,8), not all cancers can be detected, particularly in women with dense breasts. Magnetic resonance (MR) imaging of the breast depicts contralateral cancers missed at mammography and physical examination in women with unilateral breast cancer; the rate of cancer detection within 12 months of the initial diagnosis of breast cancer is 3.1% (30 of 969) (9). Other investigators have also reported that MR imaging of the breast helps detect clinically and mammographically occult cancer in the contralateral breast at the time of a diagnosis of unilateral breast cancer (10,11).

However, results regarding whether preoperative MR imaging screening has a beneficial clinical effect have differed. In one study, Fischer and colleagues (12) reported an incidence of metachronous contralateral cancer of 1.7% among 121 patients who underwent preoperative MR imaging compared with an incidence of 4% among 225 patients who did not undergo MR imaging at the time of the initial diagnosis ($P < .001$). In contrast, Solin and colleagues (13) reported a 6% incidence of contralateral cancer at 8 years of follow-up in women who either had or had not undergone MR imaging. Because more institutions are opting to use MR imaging in the preoperative setting, further research providing more confirmatory information for clinicians is important.

Therefore, the purpose of this study was to investigate the clinical effect of a single MR imaging screening examination of the contralateral breast at preoperative MR imaging in women with unilateral breast cancer by comparing the incidence of synchronous cancer and the incidence of metachronous cancer in these women with rates in women who underwent conventional screening.

Advances in Knowledge

- A single preoperative MR imaging examination for the screening of the contralateral breast depicted 25 (1.4%) additional cancers among 1771 women with unilateral breast cancer compared with 1323 women who did not undergo MR imaging screening ($P < .001$).
- The cumulative incidence of metachronous contralateral breast cancer at 45-month follow-up was lower in women who underwent a single contralateral MR imaging screening examination (0.5% [nine of 1771]) than in women who did not undergo MR imaging screening (1.4% [18 of 1323]) ($P = .02$).
- A single preoperative MR imaging screening examination of the contralateral breast (hazard ratio, 0.37; 95% confidence interval [CI]: 0.15, 0.92; $P = .03$) and estrogen receptor negativity (hazard ratio, 3.98; 95% CI: 1.60, 9.92; $P = .003$) were significantly associated with a risk of a diagnosis of metachronous contralateral cancer at multivariate analysis.

Implications for Patient Care

- Preoperative MR imaging screening of the contralateral breast in women with unilateral breast cancer reduces the incidence of metachronous cancer in the contralateral breast.
- Routine bilateral MR imaging of the breast should be considered for preoperative evaluation of women with unilateral breast cancer.

Materials and Methods

Screened Group and Comparison Group

The institutional review board of our institution approved this retrospective analysis, and the need to obtain informed consent was waived. Routine preoperative imaging evaluations for breast cancer surgery at our institution since 2004 have included bilateral mammography with bilateral whole-breast ultrasonography (US) and/or breast MR imaging. A search of the database in the radiology department identified 4011 consecutive women who had undergone surgery for breast cancer between January 2004 and December 2008. Of these 4011 patients, 3305 had undergone single-breast preoperative MR imaging. In 2007, bilateral breast MR imaging replaced unilateral MR imaging of the breast at our institution. Patients were excluded on the basis of the following criteria: known bilateral breast cancer according to clinical symptoms or mammography performed before preoperative imaging evaluation ($n = 58$), metastatic disease at presentation ($n = 49$), and no availability of 12-month follow-up data ($n = 104$). Finally, the data for the remaining 3094 patients were entered into the analysis (Fig 1).

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Abbreviations:
CI = confidence interval
DCIS = ductal carcinoma in situ
ER = estrogen receptor

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Conflicts of interest are listed at the end of this article.

Radiology

Figure 1

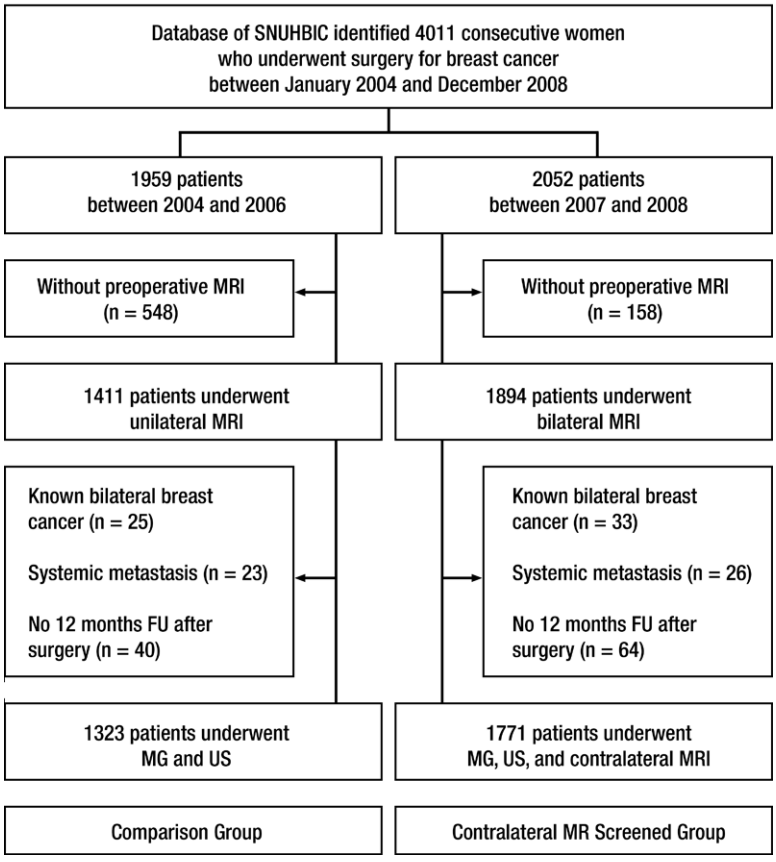

Figure 1: Flowchart of study population selection. *FU* = follow-up, *MG* = mammography, *SNUHBIC* = Seoul National University Hospital Breast Imaging Center.

In terms of contralateral breast screening, 1323 women (mean age, 46.8 years; range, 18–81 years) underwent mammography and US alone (comparison group) between January 2004 and December 2006, and 1771 consecutive women (mean age, 48.2 years; range, 22–85 years) underwent mammography, US, and MR imaging (contralateral MR imaging–screened group) between January 2007 and December 2008.

Breast MR Imaging Protocol

All bilateral breast MR imaging examinations were performed with a 1.5-T system (Signa; GE Medical Systems, Milwaukee, Wis). The following sequences were performed: sagittal fat-suppressed T2-weighted fast spin-echo MR imaging (repetition time msec/echo time msec, variable from 5500 to 7150/82; matrix, 256 × 160; field of view, 200 × 200 mm; section thickness, 1.5 mm; no gap) and dynamic contrast material–enhanced MR imaging, including one precontrast and five postcontrast bilateral sagittal sequences performed with a fat-suppressed T1-weighted three-dimensional fast spoiled gradient-echo imaging (6.5/2.5; matrix, 256 × 160; flip angle, 10°; field of view, 200 × 200 mm; section thickness, 1.5 mm; no gap). The interval between breast MR imaging and surgery ranged from 1 to 7 days (mean, 2 days).

One day before surgery for breast cancer, one of two radiologists (W.K.M. and N.C., with 10 and 6 years of experience in breast imaging, respectively), performed US and interpreted the results of mammography and MR imaging of the breast along with clinical and physical examination findings. According to the predefined protocol, the radiologists prospectively recorded symptoms and signs, the histopathologic findings at previous core-needle biopsy, the imaging findings, and the final assessment category for each imaging modality on the basis of the Breast Imaging Reporting and Data System in the radiologic reports on the picture archiving and communicating system. The final assessment category was separately classified for each breast. If any suspicious findings were newly identified during the preoperative image evaluation, the detection method (screening mammography, US, or MR imaging) was recorded and image-guided needle localization was performed for histologic confirmation on the morning of surgery.

Postoperative Care and Follow-up

After breast cancer surgery was performed, radiation treatment, adjuvant systemic therapy, or adjuvant hormonal treatment was administered according to the characteristics of each patient and her tumor. The same standard of clinical treatment was used by the same clinicians in our institution throughout the study period. The patients in both the contralateral MR imaging–screened group and the comparison group were examined annually with mammography and bilateral whole-breast US for the surveillance of locoregional recurrence or contralateral breast cancer. The median duration of follow-up for the 1771 patients who underwent MR imaging screening of the contralateral breast was 45 months (range, 18–61 months). The median follow-up duration for the 1323 patients who did not undergo MR imaging screening of the contralateral breast was 65 months (range, 13–94 months). The median duration of follow-up for all patients was 56 months (range, 13–94 months). Synchronous contralateral breast cancer was defined as contralateral cancer diagnosed within 6 months of the first primary cancer. Metachronous contralateral cancer was defined as any contralateral cancer found after 6 months of the first primary cancer.

Data and Statistical Analysis

The differences between the clinicopathologic features and incidence of

synchronous cancer between the patients with and those without contralateral MR imaging screening were estimated with the Fisher exact test. Histopathologic information, including tumor size, axillary nodal status, histologic grade, estrogen receptor (ER) expressional status, and progesterone receptor expressional status, was obtained from histopathologic reports. Human epidermal growth factor receptor 2 status was not analyzed in our study because testing for this receptor by using fluorescence in situ hybridization was not routinely performed in patients with newly diagnosed breast cancer in our institution during the study period.

To adjust different follow-up periods between the two groups, we estimated the cumulative incidence of a diagnosis of contralateral breast cancer in the contralateral MR imaging–screened group and in the comparison group at 45 months by using a Kaplan-Meier survival analysis. The time period between breast surgery for the index cancer and a histopathologic diagnosis of invasive cancer or ductal carcinoma in situ (DCIS) in the contralateral breast was calculated, and the frequencies of detected cancers within 24 months were compared between the two groups with a Fisher exact test. The log-rank test was used to compare the differences in cumulative incidence of contralateral breast cancer between the two groups. In the univariate analysis, when the *P* value was less than .2 in association with a contralateral breast cancer diagnosis according to baseline characteristics, an adjusted analysis was performed with the multivariate Cox proportional hazards model. A *P* value of less than .05 was considered to indicate a statistically significant finding. The 95% confidence intervals (CIs) were calculated by using the method of Clopper and Pearson. Statistical analyses were performed by using statistical software (SPSS, version 16.0; SPSS, Chicago, Ill).

Results

There were no significant differences in mean patient age, pathologic tumor stage, pathologic stage of axillary lymph nodes, hormonal receptor status, or adjuvant systemic therapy between the two groups of patients (Table 1). The contralateral MR imaging–screened group underwent breast-conserving surgery slightly more often (67.9% [1202 of 1771 patients]) than did the comparison group (64.2% [850 of 1323 patients]) (*P* = .04).

At the time of the preoperative evaluation, the number of

Table 1

Characteristics of Patients in Contralateral Breast MR Imaging–screened and Comparison Groups at Preoperative Evaluation

Characteristic	Contralateral MR Imaging–screened Group (*n* = 1771)	Comparison Group (*n* = 1323)	*P* Value
Patient age at diagnosis (y)*	48.2 ± 9.7 (22–85)	46.8 ± 9.0 (18–81)	.17
Breast composition			.48
Extremely dense	327 (18.5)	245 (18.5)	
Heterogeneously dense	961 (54.3)	686 (51.9)	
Scattered fibroglandular	411 (23.2)	330 (24.9)	
Almost entirely fatty	72 (4.1)	62 (4.7)	
Type of cancer (index cancer)			.39
Invasive	1501 (84.8)	1136 (85.9)	
DCIS	270 (15.2)	187 (14.1)	
Pathologic T stage			.84
Tis	270 (15.2)	187 (14.1)	
T1	831 (46.9)	631 (47.7)	
T2	603 (34.0)	457 (34.5)	
T3	67 (3.8)	48 (3.6)	
No. of metastatic axillary lymph nodes†			.84
0	953 (63.5)	727 (64.0)	
1–3	371 (24.7)	279 (24.6)	
4–9	124 (8.3)	85 (7.5)	
≥10	53 (3.5)	45 (4.0)	
ER status†			.06
Positive	926 (61.7)	744 (65.5)	
Negative	566 (37.7)	381 (33.5)	
Testing not performed or unknown	9 (0.6)	11 (1.0)	
Progesterone receptor status†			.06
Positive	828 (55.2)	671 (59.1)	
Negative	664 (44.2)	454 (40.0)	
Testing not performed or unknown	9 (0.6)	11 (1.0)	
Adjuvant systemic therapy†			.13
Chemotherapy only	401 (26.7)	279 (24.6)	
Hormones only	287 (19.1)	190 (16.7)	
Chemotherapy and hormones	753 (50.2)	615 (54.1)	
None	60 (4.0)	52 (4.6)	
Adjuvant tamoxifen‡			.78
No	123 (45.6)	82 (43.9)	
Yes	147 (54.4)	105 (56.2)	
Prior surgery type for index cancer			.04
Mastectomy	569 (32.1)	473 (35.8)	
Breast-conserving surgery	1202 (67.9)	850 (64.2)	

Note.—Unless otherwise noted, data are numbers of patients, with percentages in parentheses.

* Data are means ± standard deviations, with ranges in parentheses.

† Limited to patients with invasive carcinoma only (*n* = 2637).

‡ Limited to patients with DCIS only (*n* = 457).

Table 2

Synchronous Cancers in Contralateral Breast according to Detection Method

Characteristic	Contralateral MR Imaging–screened Group (n = 1771)	Comparison Group (n = 1323)	P Value
Cancers detected at preoperative mammography and US	21/1771 (1.2)	18/1323 (1.4)	.62
Type of cancer			
Invasive	10/21 (48)	7/18 (39)	
DCIS	11/21 (52)	11/18 (62)	
Size of tumor (invasive) (mm)*			
0–5	1/10 (10)	0	
6–10	1/10 (10)	1/7 (14)	
11–20	5/10 (50)	2/7 (29)	
≥21	3/10 (30)	4/7 (57)	
Mean†	20 (3– 49)	18 (7–23)	
Nodal status*			
Negative	9/10 (90)	7/7 (100)	
Positive	1/10 (10)	0	
Cancers detected at preoperative MR imaging	25/1771 (1.4)	0	<.001
Type of cancer			
Invasive	13/25 (52)	…	
DCIS	12/25 (48)	…	
Size of tumor (invasive) (mm)‡		…	
0–5	2/13 (15)	…	
6–10	6/13 (46)	…	
11–20	4/13 (31)	…	
≥21	1/13 (8)	…	
Mean†	14 (1–35)	…	
Nodal status‡			
Negative	12/13 (92)	…	
Positive	1/13 (8)	…	

Note.—Unless otherwise noted, data are numbers of patients, with percentages in parentheses.

* Limited to patients with synchronous invasive cancer detected at mammography and US only (n = 17).

† Data in parentheses are ranges.

‡ Limited to patients with synchronous invasive cancer detected at MR imaging only (n = 13).

contralateral breast cancers detected at mammography and US were similar between the two groups (1.2% [21 of 1771] vs 1.4% [18 of 1323]; P = .62) (Table 2). Of the 39 synchronous contralateral cancers detected at preoperative mammography and US, 56% (22 of 39) were DCIS and 44% (17 of 39) were invasive. The mean sizes of invasive tumors were similar between the two groups (20 mm [range, 3–49 mm] vs 18 mm [range, 7–23 mm]; P = .75). The majority (94% [16 of 17]) of these invasive tumors were node negative.

In the contralateral MR imaging–screened group, biopsy of the contralateral breast was recommended for 49 (2.7%) of 1771 women because of a lesion detected at preoperative MR imaging. Excision after needle localization during curative surgery was performed for all lesions, and 25 contralateral breast cancers were additionally detected at MR imaging in the contralateral MR imaging–screened group compared with the comparison group (1.4% [25 of 1771] vs 0% [0 of 1323]; P < .001). The positive predictive value of biopsy in the group that underwent contralateral MR imaging screening was 51% (25 of 49); 24 lesions were benign. These lesions consisted of fibrocystic changes (n = 13), intraductal papillomas (n = 4), fibroadenomas (n = 5), adenosis (n = 1), and florid ductal epithelial hyperplasia (n = 1). In addition to biopsies, short-term follow-up MR imaging was recommended for 8.8% (156 of 1771) of women who underwent contralateral MR imaging screening. Of the 25 synchronous contralateral cancers detected at MR imaging, 48% (12 of 25) were DCIS and 52% (13 of 25) were invasive (Table 2). The mean size of invasive tumors was 14 mm (range, 1–35 mm). All tumors, except for one invasive tumor, were node negative (pN0, n = 12; pN1, n = 1). The mean size for DCIS was 14 mm (range, 1–31 mm).

With regard to metachronous contralateral breast cancers, after a median follow-up of 45 months (range, 18–61 months), 11 cancers (0.6% [11 of 1771]) were diagnosed in the contralateral MR imaging–screened group. After a median follow-up of 65 months (range, 13–94 months), 25 cancers (1.9% [25 of 1323]) were diagnosed in the comparison group.

The cumulative incidence of contralateral cancer diagnosis at 45 months was 0.5% (nine of 1771; 95% CI: 0.23%, 0.96%) for the contralateral MR imaging–screened group and 1.4% (18 of 1323; 95% CI: 0.81%, 2.14%) for the comparison group (P = .02) (Table 3; Fig 2). Of the nine metachronous cancers in the contralateral MR imaging–screened group, five (56%) were DCIS and four (44%) were invasive. Of the 18 metachronous cancers in the comparison group, six (33%) were DCIS and 12 (67%) were invasive (56% and 33%, respectively; P = .41). The mean sizes of the detected invasive cancers in both groups did not significantly differ (1.3 and 2.0 cm, respectively; P = .31). The mean intervals to detection of metachronous cancers in both groups were not significantly different (33 and 27 months, respectively; P = .16). However, cancers detected within 24 months were significantly more common in the comparison group than in the contralateral MR imaging–screened group (55.6% [10 of 18] vs 11.1% [one of nine]; P = .04). The majority of metachronous

cancers were clinically asymptomatic and were detected during postoperative surveillance with mammography and US in both groups (89% [eight of nine] and 89% [16 of 18], respectively). All lymph nodes were negative for contralateral cancers in the contralateral MR imaging–screened group. Nine (75%) of the 12 invasive cancers in the comparison group were node negative. Contralateral axillary recurrence without a diagnosis of in-breast cancer developed in 0.1% (two of 1771) of the patients in the contralateral MR imaging–screened group and in 0.3% (four of 1323) of the patients in the comparison group.

We also assessed the diagnosis of metachronous contralateral breast cancer according to clinicopathologic factors, including method of screening, age, type of cancer, index tumor size, lymph node status, histologic grade, ER status, progesterone receptor status, adjuvant systemic therapy, and type of surgery (Table 4). Among these factors, index tumor size, lymph node status, ER status, and method of screening factors showed *P* values of less than .2 at univariate analysis and were therefore included in the multivariate analysis with the Cox proportional hazard model. Because ER status and progesterone receptor status were highly correlated, only ER status was included for the multivariate analysis. Finally, the multivariate Cox analysis revealed that contralateral MR imaging screening (hazard ratio, 0.37; 95% CI: 0.15, 0.92; $P = .03$) and ER negativity (hazard ratio, 3.98; 95% CI: 1.60, 9.92; $P = .003$) were significant independent predictors of a diagnosis of metachronous contralateral cancer (Table 5).

Table 3

Metachronous Cancers in Contralateral Breast Identified in Contralateral MR Imaging–screened and Comparison Groups

Characteristic	Contralateral MR Imaging–screened Group ($n = 1771$)	Comparison Group ($n = 1323$)	*P* Value
Total	9/1771 (0.5)	18/1323 (1.4)	.02*
Type of cancer			.41
Invasive	4/9 (44)	12/18 (67)	
DCIS	5/9 (56)	6/18 (33)	
Size of tumor (invasive) (mm)†			.31
0–5	1/4 (25)	0	
6–10	1/4 (25)	2/12 (17)	
11–20	1/4 (25)	6/12 (50)	
≥21	1/4 (25)	4/12 (33)	
Mean‡	13 (5–23)	20 (10–55)	
Nodal status†			.08
Negative	4/4 (100)	9/12 (75)	
Positive	0	3/12 (25)	
Detection method			
Mammography and US	8/9 (90)	16/18 (89)	
Palpable symptoms	1/9 (11)	2/18 (11)	

Note.—Unless otherwise noted, data are numbers of patients, with percentages in parentheses.

* Log-rank test was performed for comparison of cumulative incidence of contralateral breast cancer between patients with and those without MR imaging screening at 45 months.

† Limited to patients with metachronous invasive cancer only ($n = 16$).

‡ Data in parentheses are ranges.

Discussion

In our study, we found that the incidence of synchronous contralateral cancer was higher (4% [25 of 1771] vs 0 [0 of 1323]; $P < .001$) and that the incidence of metachronous contralateral cancer was lower (0.5% [nine of 1771] vs 1.4% [18 of 1323]; $P = .02$) in women who underwent a single contralateral breast MR imaging screening examination compared with those who did not. In addition, a particularly notable result of the multivariate Cox analysis was that contralateral MR imaging screening (hazard ratio, 0.37; $P = .03$) was an independent factor associated with a decreased incidence of metachronous cancer, in addition to ER positivity.

The strengths of our study include its completeness of historical control with consecutive patients, the large study population, and interpretation of both conventional and MR imaging findings provided by experienced radiologists (6–10 years of experience at study entry). It is generally considered a primary limitation of any historical control group that evolution in diagnosis and management of breast cancer over time can potentially confound the outcomes. However, during our study period, the same surgeons and radiologists performed the same standard of clinical treatment as well as imaging evaluations. Thus, if it did exist, a learning curve effect on the interpretation of MR imaging findings or a difference in the care of patients with breast cancer between the two groups would have been minimal. A randomized, comparative, two-group trial stratifying for family history and the use of adjuvant therapy would provide the most accurate data on the clinical efficacy of MR imaging screening of the contralateral breast. However, given the low incidence of contralateral breast cancer, it is unlikely to become a research priority (14). Therefore, our study, with a large sample size and well-characterized patient groups followed for 4 years, should help clarify the clinical effect of MR imaging of the breast.

Our results contrast with those noted in a report by Solin et al (13), who found no differences between groups with and those without breast MR imaging (6% and 6%, respectively; $P = .39$). We attribute this difference to their use of a nonrandomized, contemporaneous control group (rather

Figure 2

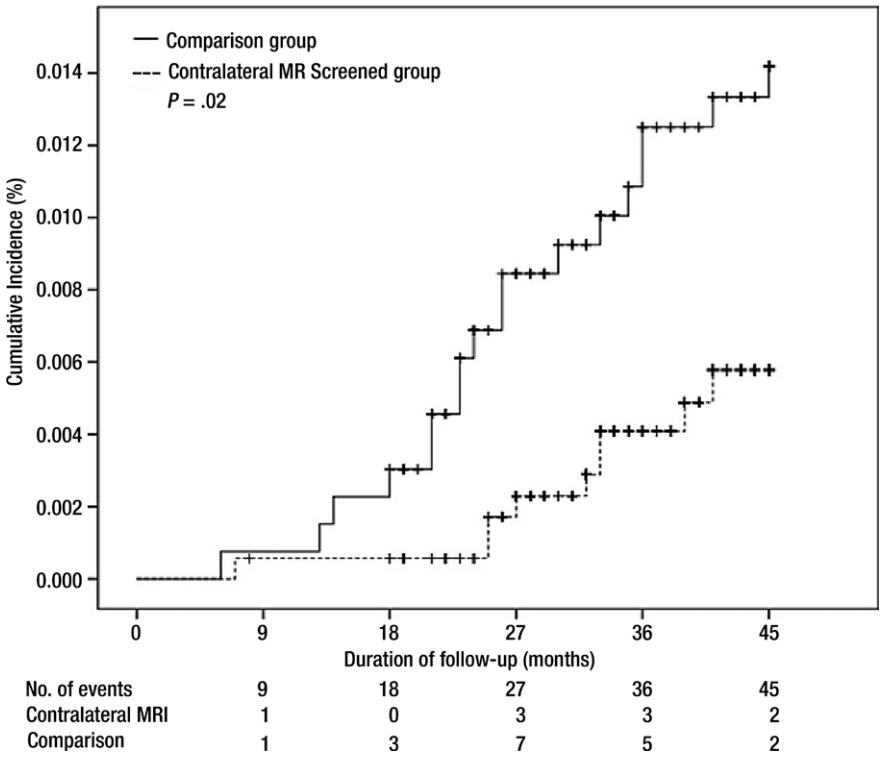

Figure 2: Graph shows cumulative incidence of contralateral breast cancer in the contralateral MR imaging–screened group and the comparison group ($P = .02$, log-rank test). The numbers of contralateral breast cancer events at each time point are shown below the graph.

than a historical control group, as used in our study), thereby allowing for the possibility of selection bias. Furthermore, MR imaging of the breast was more commonly performed in younger patients in their study, a feature that might have been associated with more occurrences of subsequent metachronous cancer. In contrast, in our study, both the MR imaging–screened and historical comparison groups had undergone preoperative breast MR imaging, and, indeed, there was no age difference between the two groups.

Moreover, Solin et al included only patients with early stage breast cancer who had undergone breast conservation treatment rather than consecutive patients. Thus, in their study, if MR imaging had depicted both ipsilateral extensive disease and synchronous contralateral cancers not detected at mammography, the patients would have undergone total mastectomy for primary cancer and ultimately would have been excluded from the study, leading to underestimation of the clinical effect of MR imaging of the breast. In our study, we included consecutive patients encountered in real clinical practice, with those who had undergone mastectomy accounting for 34% (1042 of 3094) of the entire study population and in whom 26% (seven of 27) of the subsequent metachronous cancers occurred. It has been suggested that some cancers detected at MR imaging screening might not have been clinically apparent and might not have affected patient survival. In our study, MR imaging screening seemed to depict some preclinical contralateral diseases earlier and render them synchronous bilateral cancers; these cancers would otherwise have emerged for discovery and classification as metachronous contralateral breast cancers, considering the incidence of synchronous contralateral cancers (2.6% vs 1.4%) and of metachronous contralateral cancers (0.5% vs 1.4%) in the contralateral MR imaging–screened and comparison groups. Furthermore, adjuvant chemotherapy and tamoxifen have been shown to decrease the subsequent rate of metachronous contralateral cancer by 20% and 62%, respectively (15). However, a study that included 6550 patients with bilateral breast cancer found profound differences in prognosis between women with synchronous and those with metachronous bilateral breast cancers. The authors attributed the results to the dual effect of adjuvant chemotherapy, which selectively prevented the occurrence of favorable cancers, thereby leading to more aggressive cancers surfacing clinically (7). Another study that consisted of 723 patients with metachronous contralateral breast cancers found that a less than 3-year interval to second cancers was a strong poor prognostic factor in distant disease-free survival (16). Therefore, we believe that earlier detection of occult contralateral cancers at MR imaging screening, which reduces subsequent metachronous cancers within 45 months, could potentially prevent the appearance of an adjuvant therapy–resistant phenotype after treatment. This hypothesis is consistent with that of a recent article on the genetics and evolutionary biology of cancer cells (17), which suggested the importance of early detection of and intervention in cancers before genetic diversification and extensive dissemination due to chemotherapy.

In our study, 48% (12 of 25) of the cancers identified at contralateral MR imaging screening were DCIS and 52% were invasive cancers. All of the invasive cancers but one were stage pT1 and node negative. This finding is compatible with those of a previous meta-analysis of MR imaging screening of the contralateral breast (11). In that meta-analysis, which included 3252 women with newly diagnosed breast cancer, 35.1% of MR imaging–detected

Table 4

Univariate Analysis of Clinical and Histologic Characteristics Related to Metachronous Contralateral Breast Cancer Diagnosis

	Contralateral MR Imaging–screened Group (n = 1771)		Comparison Group (n = 1323)		All Patients (n = 3094)			
Characteristic	No. of Patients	No. of Events	No. of Patients	No. of Events	No. of Patients	No. of Events	Hazard Ratio*	*P* Value
Patient group								.03
Comparison	…	…	…	…	…	…	1	
Contralateral MR imaging screening	…	…	…	…	…	…	0.39 (0.18, 0.89)	
Patient age (y)								.95
<40	337	1 (0.3)	225	4 (1.8)	562	5 (0.9)	1	
≥40	1434	8 (0.6)	1098	14 (1.3)	2532	22 (0.9)	1.03 (0.39, 2.72)	
Type of cancer								.29
Invasive	1501	7 (0.5)	1136	14 (1.2)	2637	21 (0.8)	1	
DCIS	270	2 (0.7)	187	4 (2.1)	457	6 (1.3)	1.63 (0.66, 4.04)	
Tumor size (cm)†								.16
<4	1344	7 (0.5)	1026	10 (1.0)	2370	17 (0.7)	1	
≥4	157	0	110	4 (3.6)	267	4 (1.5)	2.17 (0.73, 6.45)	
Nodal status†								.13
Negative	953	6 (0.6)	727	5 (0.7)	1680	11 (0.7)	1	
Positive	548	1 (0.2)	409	9 (2.2)	957	10 (1.0)	1.80 (0.84, 3.88)	
Histologic grade‡								.73
I Or II	663	3 (0.5)	578	7 (1.2)	1241	10 (0.8)	1	
III	660	4 (0.6)	488	7 (1.4)	1148	11 (1.0)	1.16 (0.49, 2.73)	
ER status§								.005
Positive	926	2 (0.2)	744	6 (0.8)	1670	8 (0.5)	1	
Negative	566	5 (0.9)	381	8 (2.1)	947	13 (1.4)	3.65 (1.47, 9.04)	
Progesterone receptor status‖								.01
Positive	671	6 (0.89)	828	1 (0.12)	1499	7 (0.47)	1	
Negative	454	8 (1.76)	664	6 (0.90)	1118	14 (1.25)	3.48 (1.35, 8.97)	
Adjuvant systemic therapy†								.24
No	60	1 (1.7)	52	1 (1.9)	112	2 (1.8)	1	
Yes	1441	6 (0.4)	1084	13 (1.2)	2525	19 (0.8)	0.42 (0.10, 1.80)	
Type of surgery								.43
Mastectomy	569	1 (0.2)	473	6 (1.3)	1042	7 (0.7)	1	
Breast-conserving surgery	1202	8 (0.7)	850	12 (1.4)	2052	20 (1.0)	1.43 (0.60, 3.38)	

Note.—Unless otherwise specified, data in parentheses are percentages.

* Data in parentheses are 95% CIs.

† Limited to patients with invasive cancer only (n = 2637).

‡ Histologic grade was not assessed or was unknown in 9.4% (248 of 2637) of patients with invasive cancer.

§ ER status was not assessed or was unknown in 0.7% (20 of 2637) of patients with invasive cancer.

‖ Progesterone receptor status was not assessed or was unknown in 0.7% (20 of 2637) of patients with invasive cancer.

contralateral cancers were DCIS, and the majority (81% [17 of 21]) of invasive cancers were node negative. Invasive cancers not seen at mammography or US can be expected to manifest as interval cancers with worse prognoses. In addition, evidence suggests that DCIS tends to progress to invasive disease if left untreated (18,19), and approximately 30% of women with untreated DCIS develop ipsilateral invasive breast cancer at long-term follow-up; of these, more than half develop distant metastases (20,21).

The main barrier to the utility of MR imaging screening, despite its 88%–100% sensitivity in cancer detection, is its low specificity (22,23). Results of several studies (24–26) have shown that MR imaging screening in a high-risk population results in higher sensitivity for cancer detection than do conventional modalities. We observed a 51% (25 of 49) positive predictive value for biopsies prompted by findings at breast MR imaging, a rate that may be considered as falling within an accepted range in clinical practice.

Our study had several limitations. First, this study was a retrospective, nonrandomized study from a single institution, and the two groups in our

Table 5

Multivariate Analysis of Risk Factors Related to Metachronous Contralateral Breast Cancer

Variable	Hazard Ratio (95% CI)	*P* Value
Method of screening		.03
Comparison group	1	
Contralateral MR imaging–screened group	0.37 (0.15, 0.92)	
Tumor size (cm)		.30
<4	1	
≥4	1.82 (0.59, 5.58)	
Nodal status		.24
Negative	1	
Positive	1.71 (0.71, 4.15)	
ER status		.003
Positive	1	
Negative	3.98 (1.60, 9.92)	

Note.—Data in parentheses are 95% CIs.

study were not treated during the same period. Although the same standard treatment was used throughout the study period, breast-conserving surgery was performed slightly more often in the contralateral MR imaging–screened group. However, we believe that a lesser extent of surgery for index cancer in the MR imaging–screened group might have little effect on our results for incidence of metachronous contralateral breast cancer. Second, the 0.9% (27 of 3094) incidence of metachronous contralateral cancer in our study is relatively low, considering the 3.8% (4657 of 123757) incidence of metachronous cancer in a large Swedish cohort (7). However, this difference may be in part due to ethnic factors, because Asian women tend to have a lower incidence of breast cancer and typically have greater breast density (27,28). In addition, our study population had already undergone mammography and US, and this may have been another factor leading to a lower proportion of cancers detected at MR imaging. Third, the median duration of follow-up (56 months; range, 13–94 months) for our study population was relatively short, and we did not analyze survival outcome. Our results showing that preoperative contralateral MR imaging screening reduces metachronous contralateral cancer might represent a form of lead-time bias, meaning that the earlier detection of cancer at screening does not always lead to improvement in survival.

In conclusion, a single MR imaging screening examination of the contralateral breast at preoperative evaluation in women with unilateral breast cancer reduces the incidence of metachronous contralateral cancer within 45 months, potentially leading to a reduction in mortality from breast cancer.

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