Preoperative Breast Magnetic Resonance Imaging and Contralateral Breast Cancer Occurrence Among Older Women With Breast Cancer

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ABSTRACT

Purpose

Preoperative magnetic resonance imaging (MRI) detects occult contralateral breast cancers (CBCs) in women with breast cancer, but the impact of detection on long-term CBC events is unclear. We examined whether MRI use decreases the occurrence of CBCs and the detection of stages II to IV disease among women who develop a CBC.

Patients and Methods

Analyzing the SEER-Medicare database, we assessed overall, synchronous (< 6 months after primary cancer diagnosis), and subsequent (ie, metachronous) stage-specific CBC occurrences in women who were diagnosed with stages I and II breast cancer during 2004-2009 and who were observed through 2011.

Results

Among 38,971 women with breast cancer, 6,377 (16.4%) received preoperative MRI. After propensity score matching, and compared with women who did not undergo MRI, preoperative MRI use was significantly associated with a higher synchronous CBC detection rate (126.4 v 42.9 per 1,000 person-years, respectively; hazard ratio, 2.85; $P < .001$) but a lower subsequent CBC detection rate (3.3 v 4.5 per 1,000 person-years, respectively; hazard ratio, 0.68; $P = .002$). However, the 5-year cumulative incidence of CBC remained significantly higher among women undergoing MRI compared with those not undergoing MRI (7.2% v 4.0%, respectively; $P < .001$). The analyses of projected CBC events for 10,000 patients who receive MRI indicated that, after a 5-year follow-up, MRI use would detect an additional 192 in situ CBCs (95% CI, 125 to 279) and 120 stage I CBCs (95% CI, 62 to 193) but would not have a significant impact on stages II to IV CBC occurrences (~ 6; 95% CI, -21 to 47).

Conclusion

An increased synchronous CBC detection rate, attributable to MRI, was not offset by a decrease of subsequent CBC occurrence among older women with early-stage breast cancer, suggesting that preoperative MRI in women with breast cancer may lead to overdiagnosis.

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INTRODUCTION

Preoperative breast magnetic resonance imaging (MRI) has increased in use among women with newly diagnosed breast cancer in the United States^{1,2}; however, its routine use remains controversial.³⁻⁵ One MRI use is for screening of contralateral breast cancers (CBCs).⁶ By using MRI, occult CBCs may be detected and removed earlier in the hope of reducing the stage at which future CBCs may be diagnosed. A systematic review revealed that, compared with mammography and/or ultrasound, MRI had a 4.1% incremental CBC detection rate,⁷

yet the impact of MRI on long-term CBC outcomes remains unclear. For example, an individual person data meta-analysis suggested no benefit of preoperative MRI for preventing ipsilateral recurrence; however, this study did not investigate CBC events because of the unavailability of data.⁸

Experts have questioned the benefits of routine preoperative MRI, citing concerns about false-positive findings, cost, and psychologic stress.⁹⁻¹¹ In addition, adjuvant systemic therapy for primary cancer decreases the incidence of CBC.¹² Hence, early detection by MRI of clinically occult CBCs may not provide substantial clinical benefit. This is of particular concern for women

age ≥ 65 years who constitute one half of newly diagnosed breast cancer patients each year and have less time at risk for developing CBC than do younger women.¹³

Understanding the association between MRI and long-term CBC occurrence may elucidate the effectiveness of early detection that results from MRI use. Unlike with ipsilateral recurrence, where it can be difficult to differentiate between a true recurrence (prescribed therapies do not eliminate microscopic disease) and a coexisting, distinct locus of cancer elsewhere in the breast, examining CBC occurrence allows us to investigate the benefits of MRI in occult cancer detection. We hypothesized that MRI use would increase synchronous (within 6 months after primary diagnosis) CBC detection and decrease subsequent (ie, metachronous) CBC occurrence. In addition, we hypothesized that MRI use would be associated with detection of subsequent CBCs at an earlier stage.⁹ Finally, we examined whether MRI use is able to reduce overall advanced diseases.

PATIENTS AND METHODS

Data and Study Design

We used the SEER-Medicare database to identify patient demographics, primary tumor characteristics, occurrences and corresponding stages of CBC, and receipt of MRI. The SEER registries currently cover approximately 28% of the US population.¹⁴ We assessed the relationship between MRI use and CBC detection by applying propensity score matching, distinguishing between synchronous and subsequent CBCs. We used Markov models to estimate numbers of CBC events with and without MRI use. The Yale Human Investigation Committee determined that this study did not directly involve human participants and, therefore, did not require consent.

Patients

We identified all women with stages I and II breast cancer diagnosed during 2004 to 2009 who were age 67 to 94 years at the time of diagnosis and who were observed through 2011. We limited our sample to women whose tumor laterality was known. To avoid contamination effects, we excluded women who had received MRI between the date of first breast surgery and 180 days after cancer diagnosis. We also excluded synchronous stage IV CBC because of difficulty in determining whether metastasis was a result of primary breast cancer or CBC. The step-wise ascertainment of our cohort is given in Appendix Table A1 (online only).

Intervention and Outcome Ascertainment

We identified use of breast MRI by using Healthcare Common Procedure Coding System codes and defined preoperative MRI as receipt of at least one MRI screening from 90 days prediagnosis through the date of first breast surgery. Because MRI is a diagnostic test and does not change outcomes, per se, preoperative MRI is the intervention of interest as well as any changes in surgical treatment after imaging. To ascertain outcomes, we used SEER sequence numbers to identify CBC occurrences after primary breast cancer diagnosis, which are categorized as in situ plus invasive, or total, in situ, and invasive breast cancer. We also identified the corresponding stage for invasive breast cancer. For each CBC event identified, we used an a priori cutoff point of 6 months to separate synchronous CBCs from subsequent CBCs.^{15,16} We censored CBC occurrences at the date of death or December 1, 2011, whichever occurred first.

Covariate Selection

Patient characteristics included age at diagnosis, year of diagnosis, race, marital status, SEER registry, metro status of residence, comorbidity, number of outpatient clinic visits, US Census-based estimates of income

and education at the zip code level,¹⁷ and Elixhauser comorbidity conditions.¹⁸ Tumor characteristics included stage, grade, size, histology, estrogen receptor (ER) and progesterone receptor status, and number of positive lymph nodes as reported by SEER.

Statistical Analysis

We used propensity score matching to adjust for baseline characteristics and account for potential treatment selection bias. Using logistic regression, including all patient and tumor characteristics, we estimated the probability of receiving screening with MRI (Appendix Table A2). We used a 2:1 ratio for nearest neighbor matching within 0.2 standard deviations of the logit of the estimated propensity score without replacement.¹⁹ Balance diagnostics were assessed by comparing prevalence of baseline characteristics using standardized differences, expressed as a percentage.²⁰ Prior research has suggested that 2:1 matching can improve precision²¹ and that a standardized difference of ≥ 10 indicates a meaningful imbalance in the baseline covariate.²²

In the matched sample, we used a Cox proportional hazards regression model to describe the association between MRI and time to CBC occurrence. We applied competing risk models to account for women who died of any cause. The model is clustered by matched sets to allow for correlation between matched pairs of patients by receipt of MRI. In particular, we analyzed synchronous and subsequent CBCs individually. For synchronous CBC analyses, patients with subsequent CBC were included because they were at risk for synchronous CBC occurrence. On the basis of our definition, time to synchronous CBC was truncated at 6 months. For analyses of time to subsequent CBC occurrence, patients with synchronous CBCs were censored prior to 6 months. We assessed the proportional hazards assumption using the Kolmogorov-type supremum test, and observed cumulative martingale residuals.²³ We estimated the cumulative risk of CBC occurrence ≤ 5 years after primary breast cancer diagnosis for the MRI and non-MRI groups.

We developed Markov models to project the number of synchronous and subsequent CBCs during a 5-year follow-up by receipt of MRI. Markov model Health states consisted of no CBC occurrence and four absorbing states, including death and in situ, stage I, and stages II to IV CBCs. Transition probabilities were derived from stage-specific CBC incidence rates and the background mortality of the propensity-score matched sample by using a cycle length of 6 months to separate synchronous and subsequent CBCs. We validated our Markov model by comparing CBC events between model estimation and the observed numbers, and used 95% CIs of hazard ratios (HRs) to project plausible ranges. We used TreeAge (TreeAge Software, Williamstown, MA) to perform Markov model projections and SAS (SAS/STAT User's Guide, Version 9.4; SAS Institute, Cary, NC) for all other analyses. Tests were two sided with an α of .05. Acknowledging that MRI use may lead to more aggressive treatments and extensive follow-up, we reported the prevalence of adjuvant chemotherapy/imaging tests according to MRI use (Appendix Tables A3-A4). We conducted three sensitivity analyses controlling for adjuvant chemotherapy or follow-up MRI, or excluding patients receiving contralateral prophylactic mastectomy among the propensity-score matched sample.

RESULTS

The sample consisted of 38,971 women with breast cancer (mean age, 76.4 years), including 6,737 women (16.4%) who received preoperative MRI (Table 1). Women who received MRI tended to be younger, white, married, have higher median income, and have fewer comorbidities. After propensity score matching, baseline characteristics between those who received MRI and those who did not were well balanced, with standardized differences less than 10, the exception being those living in zip codes in which less than 30% of the

Table 1. Selected Characteristics of Early Breast Cancer Patients by MRI Status in Original Sample and Propensity-Score Matched Cohort

Characteristic	Original Sample			Propensity-Score Matched Cohort		
	MRI (n = 6,377), %	No MRI (n = 32,594), %	Standardized Difference*	MRI (n = 6,377), %	No MRI (n = 12,754), %	Standardized Difference*
Age, years						
67-69	25.9	15.2	26.5	25.9	22.1	8.9
70-74	33.7	25.6	18.0	33.7	32.2	3.3
75-79	22.8	25.0	-5.2	22.8	25.0	-5.1
80-84	12.7	20.3	-20.7	12.7	14.9	-6.5
≥ 85	5.0	13.9	-31.0	5.0	5.9	-4.3
Race						
White	92.1	89.2	10.0	92.1	91.8	1.0
Black	3.7	6.9	-14.3	3.7	4.1	-2.0
Other	4.2	3.9	1.4	4.2	4.1	0.5
Adults with ≤ high school education by zip code, %						
< 30	40.4	23.8	36.2	40.4	34.2	13.0
30 to < 40	18.4	16.1	5.9	18.4	18.8	-1.2
40 to < 50	16.3	17.1	-2.2	16.3	17.5	-3.3
50 to < 60	13.5	17.9	-12.3	13.5	15.5	-5.7
≥ 60	11.5	25.1	-35.6	11.5	14.0	-7.6
Elixhauser comorbidity						
None	52.4	42.8	19.2	52.4	49.6	5.5
1-2	37.8	39.7	-3.9	37.8	39.1	-2.6
≥ 3	9.8	17.4	-22.4	9.8	11.3	-4.8
Stage						
I	63.5	63.1	0.8	63.5	63.7	-0.3
II	36.5	36.9	-0.8	36.5	36.3	0.3
Grade						
Well differentiated	27.9	26.3	3.7	27.9	27.1	1.9
Moderately differentiated	46.4	43.8	5.2	46.4	45.6	1.6
Poorly differentiated	20.9	23.9	-7.3	20.9	22.3	-3.4
Undifferentiated	0.5	0.8	-4.3	0.5	0.5	-0.5
Unknown	4.3	5.2	-4.0	4.3	4.5	-0.9
Tumor size, cm						
< 2.0	69.6	66.6	6.6	69.6	69.3	0.8
2.0-5.0	28.4	31.6	-6.8	28.4	28.9	-1.1
> 5.0	1.6	1.6	0.4	1.6	1.6	0.7
Missing	0.3	0.3	0.3	0.3	0.3	0.3
No. of positive lymph nodes						
No positive nodes/unknown	76.8	70.8	13.8	76.8	76.5	0.7
≥ 1 positive nodes	18.7	17.0	4.6	18.7	18.4	1.0
No nodes examined	4.4	12.2	-28.5	4.4	5.1	-3.2
Hormone Receptors						
ER+ or PR+	84.5	80.9	9.3	84.5	83.5	2.6
ER- and PR-	12.0	12.7	-2.1	12.0	12.5	-1.6
Missing	3.5	6.4	-13.2	3.5	4.0	-2.4

NOTE. All data are given as percentage. Additional variables in propensity-score matching included marital status, median income, residence status, histology (ductal, lobular, or other), SEER registries, year of diagnosis, and number of physician outpatient visits prior to breast cancer diagnosis.

Abbreviations: ER, estrogen receptor; MRI, magnetic resonance imaging; PR, progesterone receptor.

*Standardized difference is the mean difference divided by the pooled standard deviation.

population had a high school education or less (standardized difference, 13.0).

Overall CBC Occurrence

In the propensity-score matched cohort (73,489 person-years of follow-up time; median follow-up, 43 and 46 months for the MRI and non-MRI groups, respectively), we found that women who underwent MRI had a higher rate of overall CBC occurrence during the follow-up period than did women who did not undergo MRI (18.9 ν 9.2 per 1,000 person-years, respectively; HR, 2.01; 95% CI, 1.81 to 2.23; Table 2). The Kolmogorov-type supremum test indicated that overall CBC occurrence did not violate the assumption of proportional hazard but that subsequent CBC occurrence validated the assumption. We therefore reported synchronous and subsequent CBCs separately.

Synchronous CBC Occurrence

In the matched sample, there were 375 synchronous CBCs (5.9%) among women who received MRI compared with 263 synchronous CBCs (2.1%) in women who did not receive MRI. Compared with women who did not undergo MRI, women who received MRI had a higher rate of both synchronous in situ CBC (47.9 ν 12.9 per 1,000 person-years, respectively; HR, 3.66; 95% CI, 2.92 to 4.58) and invasive CBC (78.6 ν 30.0 per 1,000 person-years, respectively; HR, 2.52; 95% CI, 2.16 to 2.93; Fig 1 and Table 2). Women who underwent MRI were also more likely than women who did not to have synchronous invasive CBCs that were stage I disease (57.3 ν 18.9 per 1,000 person-years, respectively; HR, 2.92; 95% CI, 2.42 to 3.52) and stages II to IV diseases (18.2 ν 10.4 per 1,000 person-years, respectively; HR, 1.67; 95% CI, 1.25 to 2.22).

Subsequent CBC Occurrence

MRI use was significantly associated with a lower subsequent CBC occurrence (3.3 ν 4.5 per 1,000 person-years for MRI group ν non-MRI group, respectively; HR, 0.68; 95% CI, 0.53 to 0.86; Table 2). The relationship between MRI use and subsequent CBC occurrence varied by tumor invasiveness. The MRI group had a significantly higher rate of subsequent in situ CBC than did the non-MRI group (1.8 ν 1.1 per 1,000 person-years, respectively; HR, 1.59; 95% CI, 1.11 to 2.27; Fig 1) but a lower rate of subsequent invasive CBC than the non-MRI group (1.6 ν 3.4 per 1,000 person-years, respectively; HR, 0.39; 95% CI, 0.27 to 0.55). Compared with the non-MRI group, MRI use was associated with a lower rate of subsequent stage I CBC (1.2 ν 2.3 per 1,000 person-years, respectively; HR, 0.43; 95% CI, 0.29 to 0.64) and stages II to IV CBC (0.3 ν 0.9 per 1,000 person-years, respectively; HR, 0.28; 95% CI, 0.12 to 0.64). Acknowledging that there were 19 individuals with invasive CBC, but missing values for cancer stage, we conducted a sensitivity analysis assuming stage I for the MRI group and stages II to IV for the non-MRI group. Our results were not substantially changed by inputting missing values of cancer stage in favor of MRI. Sensitivity analyses accounting for chemotherapy, contralateral prophylactic mastectomy, or follow-up MRI use also reached similar results.

A large proportion of CBC events, especially for women who received MRI, occurred in the first 6 months (ie, synchronous; Fig 2), as indicated by the increase in cumulative CBC incidence.

Even after 5 years of follow-up, cumulative CBC incidence (both in situ and invasive) for the MRI group (7.2%) was almost two times that of the non-MRI group (4.0%; $P < .001$). Similarly, the 5-year cumulative incidence of invasive CBC remained significantly higher among women undergoing MRI (4.3%) than among women not undergoing MRI (2.9%; $P < .001$).

Simulation

Outcomes predicted by the Markov models were similar to empirical data in terms of actual number of CBC events. On the basis of our models (Fig 3 and Appendix Table A5), for every 10,000 women who underwent MRI, there would be a net increase of 377 synchronous CBCs (95% CI, 264 to 517) and a net decrease of 58 subsequent CBCs (95% CI, -98 to 2) at the end of a 5-year follow-up compared with those not undergoing MRI. Overall, after a 5-year follow-up, MRI use would be associated with detection of an additional 192 in situ CBC occurrences (95% CI: 125 to 279) and 120 stage I CBC occurrences (95% CI, 62 to 193), but would not have a significant impact on stages II to IV CBC occurrences (~ 6 ; 95% CI, -21 to 47). Using total CBC occurrence in the MRI group as the denominator, 45.3% of CBCs detected in the MRI group were overdiagnosed.

DISCUSSION

Our study has two notable findings regarding the impact of MRI use on CBC outcomes. First, an increase in synchronous CBC detection that was attributable to MRI use was not offset by a similar decrease in subsequent CBC occurrence. This suggests that MRI use may lead to overdiagnosis of CBC among Medicare beneficiaries, as most of the CBCs not detected by MRI did not become clinically evident. Several factors may explain our finding of overdiagnosis: for example, evidence that systemic therapy decreases CBC has been well documented.¹² Other potential explanations include a disease reservoir for ductal carcinoma in situ (not all in situ CBCs become a clinical problem),²⁴⁻²⁷ spontaneous regression for a portion of women with breast cancer,²⁸ or an aging population. In the case of ductal carcinoma in situ, two studies found that only 28%-39% of patients who received only biopsy progressed to invasive carcinoma after a 15-year follow-up.^{26,27} For older women, a shorter life expectancy provides less time to be at risk for CBCs after a primary cancer diagnosis, and breast cancer tends to be more indolent with advancing patient age.^{29,30}

Second, MRI use did not decrease the overall number of stages II to IV CBC occurrences. Conceptually, the main benefit of early detection by MRI is to prevent future advanced diseases, the prognoses of which are deleterious. In our study, we observed a shift from invasive to in situ subsequent CBCs related to MRI use; however, the incidence of subsequent stages II to IV CBC is relatively low compared with that of synchronous stages II to IV CBC. Furthermore, patients who underwent preoperative MRI were more likely to receive a follow-up MRI, which leads to diagnosis at an earlier stage of subsequent CBCs; thus, our analyses would be biased toward the MRI group, with fewer stages II to IV CBC occurrences. Nonetheless, we still demonstrated that preoperative MRI use did not decrease the overall number of stages II to IV CBC occurrences. MRI use, therefore, resulted in a greater rate of detection of

Table 2. CBC Incidence by MRI Status in Propensity-Score Matched Cohort

No. of CBC Occurrences	CBC Incidence per 1,000 Person-Years		HR (95% CI)	P
	MRI	No MRI		
Overall CBC (n = 19,131)				
In situ + invasive	18.9	9.2	2.01 (1.81 to 2.23)	< .001
In situ	7.6	2.6	2.91 (2.42 to 3.51)	< .001
Invasive	11.3	6.6	1.66 (1.46 to 1.89)	< .001
Synchronous CBC* (n = 19,131)				
In situ + invasive	126.4	42.9	2.85 (2.52 to 3.23)	< .001
In situ	47.9	12.9	3.66 (2.92 to 4.58)	< .001
Invasive	78.6	30.0	2.52 (2.16 to 2.93)	< .001
Subsequent CBC† (n = 18,400)				
In situ + invasive	3.3	4.5	0.68 (0.53 to 0.86)	.002
In situ	1.8	1.2	1.59 (1.11 to 2.27)	.012
Invasive	1.6	3.4	0.39 (0.27 to 0.55)	< .001

Abbreviations: CBC, contralateral breast cancer; HR, hazard ratio; MRI, magnetic resonance imaging.

*Less than 6 months after primary cancer diagnosis.

†Six months or greater after primary cancer diagnosis.

synchronous in situ and stage I invasive CBCs but did not prevent commensurate subsequent stages II to IV CBC occurrence.

Previous studies examining the benefits of MRI on long-term CBC outcomes were more limited in scope.³¹⁻³⁵ One study reported a significantly lower subsequent CBC rate for those who received MRI compared with those who did not (1.7% v 4.0%, respectively)³¹; however, the study did not adjust for baseline characteristics between the two groups, such as significant imbalances in tumor size and systematic therapy use.^{36,37} Using data from the same institution, two studies reported that MRI decreased subsequent CBC occurrence,^{32,33} but did not compare the trade-offs with synchronous CBC detection. Two additional studies did not find significant differences in CBC occurrence for women who received MRI versus those who did not (6% v 6% and 2.2% v 1.3%, respectively)^{34,35}; however, these studies did not separately examine synchronous and

subsequent CBCs, and had small sample sizes that likely lacked sufficient power to detect observed differences. Our study included approximately 6,500 women receiving MRI and selected matched controls from a pool of over 30,000 women not undergoing MRI, allowing us to clarify the effect of MRI use on short-term synchronous CBC versus subsequent CBC occurrences.

In addition to the advantage of the sample size of our study, using SEER data for our analyses conferred several benefits. First, CBC occurrence and stage information was derived directly from the SEER database and was not based on any algorithm. The information in SEER has previously been used to evaluate CBC occurrence.^{38,39} Distinguishing between in situ, stage I, and stages II to IV CBCs provides important information for patients and clinicians. In addition, because ours is a [population-based study](#), our results are representative of real-world clinical practice among

Fig 1. Stage- and time-specific incidence rate of CBC by MRI status. Each bar indicates a stage-specific incidence rate of CBC occurrence by MRI status and within 6 months versus after 6 months of primary breast cancer diagnosis. CBC, contralateral breast cancer; MRI, magnetic resonance imaging.

Fig 2. Cumulative incidence of CBC by breast MRI, propensity-score matched cohort. (A) Cumulative incidence of in situ plus invasive CBC occurrence. (B) Cumulative incidence of invasive CBC occurrence. The difference in CBC occurrence was significant (log-rank $P < .001$ for both A and B). The vertical line indicates the cutoff point (6 months) between synchronous and subsequent occurrences. Gray and blue areas represent 95% CIs. CBC, contralateral breast cancer; MRI, magnetic resonance imaging.

the elderly in the United States. In practice, differences between the MRI and non-MRI groups likely extend beyond the baseline of preoperative MRI use (Appendix Tables A3 and A4).

One concern is that differences in follow-up imaging between the two groups may impact our findings. However, a close examination of differences in cumulative CBC occurrence between women who do and do not receive MRI supports our conclusions: within only 6 months, cumulative CBC occurrence in women who received preoperative MRI was already higher (5.9%) than cumulative CBC occurrence over the full 5-year follow-up period for those who did not (4.0%), indicating that the preoperative MRI is associated with an increased rate of detection of CBC.

This study had several limitations. First, our analyses were restricted to older patients with median follow-up times of

45 months. Our results may not apply to younger women who have longer life expectancies, who have more aggressive cancers, or who are more likely to receive preoperative MRI. In addition, approximately 85% of our study population had ER-positive breast cancer. These patients generally receive 5 years of endocrine therapy, which likely decreased subsequent CBC occurrence. However, an excess of CBC occurrence paralleled results demonstrated in ipsilateral breast cancer recurrence wherein the detection of additional cancers exceeded rates of local recurrence,⁴⁰ highlighting the potential of overdiagnosis. This is true in younger populations and suggests that our findings are not a result of indolent cancers and death from other causes. Nonetheless, future research focusing on the younger population, with longer follow-up time and with patients with ER-negative breast cancer, is

Fig 3. Number of CBC cases at the end of 5-year follow-up among 10,000 women by receipt of MRI. Use of preoperative MRI was significantly associated with an increase of overall in situ or stage I CBC occurrence, but was not significantly associated with a decrease of overall stages II to IV CBC occurrence. We assumed that the incident rates of subsequent stage-specific CBC were consistent over 5 years. Error bars represent estimates of the differences between two groups undergoing and not undergoing MRI, using the upper and lower limits of 95% CIs of the hazard ratios and the incidence rates of synchronous and subsequent stage-specific CBC occurrence of the non-MRI group. CBC, contralateral breast cancer; MRI, magnetic resonance imaging

necessary. Second, we did not examine ipsilateral recurrence because SEER does not routinely collect ipsilateral recurrence information. Future research should investigate whether MRI use reduces ipsilateral recurrences. Third, although SEER represents the gold-standard for population-based assessment of cancer incidence and has been used to study CBC occurrence previously, the SEER registries may have missed CBC cases or may have incorrectly specified CBC stages. It is unlikely, however, that CBC events reported in the SEER database would differ by baseline MRI status, and, therefore, our results are unlikely to be biased. Fourth, this study focused on CBC staging, but not CBC grade and biologic markers, which are also important determinants of prognosis.⁴¹ Finally, our study is not a randomized trial. While we applied a propensity-score matching method to reduce selection bias, we were unable to control for unobserved factors, such as breast density and family history, which may influence preoperative MRI use and CBC occurrences.

Our study assessed the benefit of MRI use on both synchronous CBC and subsequent CBC occurrence. We found that preoperative breast MRI use was associated with a shift in stage at diagnosis for subsequent CBC events—an increase of subsequent in situ CBC occurrence but a decrease in subsequent invasive CBC occurrence. However, the decrease in subsequent CBC events did not counteract a large net increase in synchronous CBC detection

that was attributed to MRI use. Given that we have found no evidence of reduced overall advanced CBC events, patients and physicians must carefully the balance risks and benefits of preoperative MRI use.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org

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GLOSSARY TERMS

magnetic resonance imaging: a procedure in which radio waves and a powerful magnet linked to a computer are used to create detailed pictures of areas inside the body. These pictures can show the difference between normal and diseased tissue.

population-based study: a study in which the patients are drawn from a defined population in a manner that is representative of the source population studied. Such a design can avoid bias arising from the selective factors that guide affected individuals to a particular medical facility, allowing for greater generalizability of the findings.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Preoperative Breast Magnetic Resonance Imaging and Contralateral Breast Cancer Occurrence Among Older Women With Breast Cancer

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Appendix

Table A1. Stepwise Ascertainment of Study Cohort

No. Remaining	No. Excluded	Description
65,805		Female, age 67-94 with early stage breast cancer diagnosed 2004-2009, and epithelial origin
	146	Unknown month of diagnosis, died prior to reported diagnosis, diagnosis from autopsy or death report, or unknown tumor laterality
	11,985	No claims 24 months before to 12 months after diagnosis
	6,342	Did not receive surgery within 9 months of diagnosis
	1,125	Second cancer diagnosis (nonbreast) during the period from initial diagnosis to 12 months postsurgery
	6,252	Not enrolled in Medicare Parts A and B fee-for-service through 12 months after surgery or death if died before 12 months postsurgery elapsed
	360	Had Medicare claims for cancer Elixhauser conditions 24-3 months prior to cancer diagnosis in SEER or unknown zip code level income or education history
	624	Received MRI between surgery and 6 months after diagnosis, but not between diagnosis and surgery or had synchronous stage IV CBC
38,971		FULL SAMPLE
	19,840	Not identified as control
19,131		MATCHED SAMPLE

Breast MRI and CBC Occurrence

Table A2. Logistic Regression Model: Predictors of Breast MRI Use (N = 38,971)

Characteristic	OR (95% CI)
Age	
67-69	Reference
70-74	0.76 (0.70 to 0.82)
75-79	0.53 (0.49 to 0.58)
80-84	0.36 (0.32 to 0.40)
85+	0.22 (0.19 to 0.25)
Race	
White	Reference
Black	0.77 (0.66 to 0.90)
Other	0.94 (0.80 to 1.09)
Marital Status	
Married	Reference
Unmarried	0.86 (0.80 to 0.91)
Other	1.10 (0.94 to 1.29)
Zip Code Median Income	
< \$33,000	Reference
\$33,000-40,000	1.12 (0.99 to 1.27)
\$40,000-50,000	1.24 (1.09 to 1.40)
\$50,000-63,000	1.33 (1.16 to 1.52)
≥ \$63,000	1.60 (1.38 to 1.86)
Zip Code Percentage Adults with ≤ High School Education	
< 30%	Reference
30 to < 40%	0.73 (0.67 to 0.80)
40 to < 50%	0.67 (0.60 to 0.74)
50 to < 60%	0.66 (0.59 to 0.74)
≥ 60%	0.53 (0.46 to 0.61)
Residence	
Metropolitan	Reference
Urban	0.65 (0.56 to 0.76)
Less urban	0.92 (0.79 to 1.07)
Rural	1.36 (1.03 to 1.79)
Elixhauser Comorbidity	
None	Reference
1-2	0.78 (0.73 to 0.83)
≥ 3	0.49 (0.44 to 0.55)
Stage	
I	Reference
II	1.09 (0.96 to 1.24)
Grade	
Well differentiated	Reference
Moderately differentiated	1.00 (0.93 to 1.08)
Poorly differentiated	0.88 (0.80 to 0.97)
Undifferentiated	0.83 (0.55 to 1.25)
Unknown	0.95 (0.82 to 1.11)
Tumor Size	
< 2.0 cm	Reference
2.0-5.0 cm	0.91 (0.82 to 1.02)
> 5.0 cm	1.18 (0.90 to 1.54)
Missing	1.21 (0.67 to 2.16)
Number Positive Lymph Nodes	
No positive nodes/unknown	Reference
1+ positive nodes	1.09 (0.97 to 1.22)
No nodes examined	0.54 (0.47 to 0.62)
Hormone Receptors	
ER+ or PR+	Reference
ER- and PR-	1.16 (1.05 to 1.28)
Missing	0.79 (0.68 to 0.93)
Histology	
Ductal	Reference
Lobular	1.76 (1.64 to 1.89)
Other	0.87 (0.76 to 0.99)
Year of Diagnosis	
2004	Reference
2005	1.62 (1.40 to 1.87)
2006	2.59 (2.26 to 2.97)
2007	5.09 (4.47 to 5.80)

(continued in next column)

Table A2. Logistic Regression Model: Predictors of Breast MRI Use (N = 38,971) (continued)

Characteristic	OR (95% CI)
2008	7.73 (6.80 to 8.78)
2009	8.64 (7.60 to 9.82)
SEER Registry	
San Francisco	0.35 (0.29 to 0.43)
Connecticut	1.09 (0.96 to 1.24)
Detroit	0.59 (0.51 to 0.69)
Hawaii	0.11 (0.06 to 0.19)
Iowa	0.41 (0.34 to 0.48)
New Mexico	2.46 (2.04 to 2.96)
Seattle	1.77 (1.57 to 1.99)
Utah	0.63 (0.52 to 0.78)
Atlanta	0.60 (0.50 to 0.73)
San Jose	0.34 (0.27 to 0.43)
Los Angeles	1.30 (1.16 to 1.46)
Rural Georgia	0.44 (0.20 to 0.99)
Greater California	Reference
Kentucky	0.31 (0.26 to 0.37)
Louisiana	0.58 (0.50 to 0.68)
New Jersey	0.98 (0.88 to 1.08)
Greater Georgia	0.39 (0.33 to 0.45)
Physician Visits (24-3 months prediagnosis)	
< 6 visits	Reference
6-10 visits	1.19 (1.09 to 1.30)
11-17 visits	1.26 (1.15 to 1.38)
> 17 visits	1.38 (1.25 to 1.52)

Abbreviations: ER, estrogen receptor; MRI, magnetic resonance imaging; OR, odds ratio; PR, progesterone receptor.

Table A3. Adjuvant Chemotherapy Use According to Preoperative MRI Use

Chemotherapy	Propensity-Matched Cohort (1 MRI: 2 No MRI)				χ^2 P value
	MRI (N = 6,377)		No MRI (N = 12,574)		
	N	%	N	%	
Yes	1,401	22.0%	2,342	18.4%	< .001
No	4,977	78.0%	10,414	81.6%	

NOTE. Chemotherapy treatment between cancer diagnosis and 9 months after breast surgery, according to Medicare claims.

Abbreviation: MRI, magnetic resonance imaging.

Table A4. Follow-Up Imaging Tests According Preoperative MRI Use

	Time After Initial Diagnosis (Years)				
	1-2	2-3	3-4	4-5	5-6
Number at Risk					
Preoperative MRI	5,959	5,743	3,987	2,517	1,358
No preoperative MRI	12,240	11,658	8,528	5,747	3,357
Subsequent MRI					
Preoperative MRI*	13%	9%	7%	5%	5%
No preoperative MRI*	3%	2%	2%	2%	1%
P value	< .001	< .001	< .001	< .001	< .001
Subsequent ultrasound					
Preoperative MRI	22%	16%	14%	12%	10%
No preoperative MRI	15%	11%	9%	7%	7%
P value	< .001	< .001	< .001	< .001	< .001
Subsequent mammography					
Preoperative MRI	86%	75%	69%	60%	55%
No preoperative MRI	83%	73%	67%	60%	54%
P value	< .001	.009	.13	.88	.85
Subsequent imaging (MRI, ultrasound or mammography)					
Preoperative MRI	88%	77%	70%	62%	56%
No preoperative MRI	84%	74%	68%	61%	55%
P value	< .001	< .001	.022	.52	.54

Abbreviation: MRI, magnetic resonance imaging.

*Over the study period, approximately 23.3% of patients who had preoperative MRI had subsequent MRI; whereas 6.0% of patients who did not have preoperative MRI had subsequent MRI.

Breast MRI and CBC Occurrence

Table A5. Estimates of CBC Occurrence and Corresponding Stages at the End of 5-Year Follow-Up Among 10,000 Early-Stage Patients According to Receipt of MRI

	MRI	No MRI	Difference Between Two Groups*
Synchronous CBC	586	209	377 (264 to 517)
In situ	231	64	167 (121 to 224)
Stage I	270	94	176 (130 to 230)
Stage II–IV	86	52	34 (13 to 62)
Subsequent CBC	122	181	–58 (–98 to 2)
In situ	73	47	25 (4 to 54)
Stage I	39	95	–56 (–68 to –37)
Stage II–IV	10	38	–28 (–34 to –15)
Overall CBC	709	390	319 (166 to 519)
In situ	304	111	192 (125 to 279)
Stage I	309	188	120 (62 to 193)
Stage II–IV	96	90	6 (–21 to 47)

NOTE. Minor discrepancies may exist due to rounding.

Abbreviations: CBC, contralateral breast cancer; MRI, magnetic resonance imaging.

*Women who did not receive breast MRI were the reference group; parentheses indicated the estimations using the upper and lower limits of 95% confidence intervals of the hazard ratios.