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Associations of Preoperative Breast Magnetic Resonance Imaging with Subsequent Mastectomy and Breast Cancer Mortality

Shi-Yi Wang, MD, PhD[1,2], **Jessica B. Long, MPH**[2,3], **Brigid K. Killelea, MD**[2,4], **Suzanne B. Evans, MD**[2,5], **Kenneth B. Roberts, MD**[2,5], **Andrea L. Silber, MD**[2,6], **Amy J Davidoff, PhD**[2,7], **Tannaz Sedghi, MPH**[2], and **Cary P. Gross, MD**[2,3]

[1] Department of Chronic Disease Epidemiology, Yale University School of Public Health, New Haven, Connecticut

[2] Cancer Outcomes, Public Policy, and Effectiveness Research (COPPER) Center, Yale Cancer Center and Yale University School of Medicine, New Haven, Connecticut

[3] Section of General Internal Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut

[4] Department of Surgery, Yale University School of Medicine, New Haven, Connecticut

[5] Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut

[6] Section of Medical Oncology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut

[7] Department of Health Policy and Management, Yale University School of Public Health, New Haven, Connecticut

Abstract

Purpose—To examine associations between preoperative magnetic resonance imaging (MRI) use and clinical outcomes among women undergoing breast-conserving surgery (BCS) with or without radiotherapy for early-stage breast cancer.

Methods—We identified women from the Surveillance, Epidemiology, and End Results-Medicare dataset aged 67–94 diagnosed during 2004–2010 with stage I/II breast cancer who received BCS. We compared subsequent mastectomy and breast cancer mortality with vs. without preoperative MRI, using Cox regression and competing risks models. We further stratified by receipt of radiotherapy for subgroup analyses.

Corresponding author: Shi-Yi Wang, MD, PhD, Department of Chronic Disease Epidemiology, Yale School of Public Health, 60 College Street, P.O. Box 208034, New Haven, CT 06520, Phone number: 203-737-8096, shiyi.wang@yale.edu.

Compliance with Ethical Standards

Ethical approval: The Yale Human Investigation Committee determined that this study did not directly involve human subjects. Thus, tis article does not contain any studies with human participants or animals performed by any of the authors.

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Results—Our sample consisted of 24,379 beneficiaries, 4,691 (19.2%) of whom received preoperative MRI. Adjusted rates of subsequent mastectomy and breast cancer mortality were not significantly different with and without MRI: 3.2 vs. 4.1 per 1,000 person-years (adjusted hazard ratio [AHR], 0.92; 95% confidence interval [CI]: 0.70–1.19) and 5.3 vs. 8.7 per 1,000 person-years (AHR, 0.89; 95% CI: 0.73–1.08), respectively. In subgroup analyses, women receiving BCS plus radiotherapy had similar rates of subsequent mastectomy (AHR, 1.17; 95% CI: 0.84–1.61) and breast cancer mortality (AHR 1.00; 95% CI: 0.80–1.24) with vs. without MRI. However, among women receiving BCS alone, MRI use was associated with lower risks of subsequent mastectomy (AHR, 0.60; 95% CI: 0.37–0.98) and breast cancer mortality (AHR, 0.57; 95% CI: 0.36–0.92).

Conclusions—Preoperative MRI was associated with improved outcomes among older women with breast cancer receiving BCS alone, but not among those receiving BCS plus radiotherapy. Further research is needed to identify appropriate settings for which MRI may be helpful.

Introduction

Routine use of preoperative MRI remains controversial.[1–3] Prior reports indicate that MRI detects approximately 15% additional unsuspected ipsilateral malignancies among patients with breast cancer.[4,5] Because of MRI's superior detection capability, and the assumption that MRI will improve surgical care by helping plan the extent of resection of the tumor, preoperative MRI has been widely applied in clinical practice.[6,7] However, there is increasing evidence that MRI is associated with an increased probability of receiving a mastectomy and does not decrease re-excision rates or contralateral breast cancer incidence.[7–11]

Studies examining the long-term effects on local recurrence attributed to MRI have only recently started to emerge. Using data from one randomized controlled trial and three observational studies, a meta-analysis concluded that preoperative MRI did not reduce the risk of local recurrence.[12] In this review, however, approximately 9% of the patients had ductal carcinoma in situ (DCIS), and 10% had received a mastectomy. Additionally, the results based on these studies, conducted in institutions with advanced imaging capabilities, may not be generalizable to the real world. Understanding the effectiveness of preoperative breast MRI in the general practice setting might allow physicians to tailor their recommendations appropriately.

Another important knowledge gap exists regarding whether the impact of MRI use on clinical outcomes differs between the two groups receiving and not receiving adjuvant radiotherapy (RT). Because RT is able to control not only occult lesions but also the residual burden of disease in the tumor bed, MRI use might not improve outcomes for patients who are going to receive RT. That is, the occult lesions, if undetected, could be eradicated by RT, which renders MRI valueless for those who received RT. In contrast, for patients who elect to forgo RT, MRI use may facilitate surgical plans, such as removing occult lesions or having a wider excision; these actions might reduce ipsilateral breast cancer recurrence and improve clinical outcomes. Understanding whether MRI would be able to yield additional risk stratification is especially important for the older population because RT could be

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omitted for older women with favorable tumor characteristics.[13,14] MRI might be beneficial by identifying high-risk patients for whom adjuvant RT is needed.

Accordingly, we examined the relation between MRI use and clinical outcomes among female Medicare beneficiaries undergoing breast-conserving surgery (BCS). Specifically, we identified patients in the Surveillance, Epidemiology, and End Results (SEER)–Medicare database who received BCS with or without RT. We compared clinical strategies involving breast MRI vs. no MRI with respect to the likelihood of long-term mastectomy rate and breast cancer specific mortality. We also explored whether there would be benefits attributed to MRI use in women not receiving RT and therefore separately stratified and analyzed two subsets by RT receipt.

Methods

Data and study design

The SEER registries currently cover approximately 30% of the United States population.[15] We utilized SEER data to identify baseline patient sociodemographic and tumor characteristics. We used Medicare claims to identify receipt of MRI, type of treatment (surgery, radiotherapy, and chemotherapy), comorbidities, and providers' characteristics. The Yale Human Investigation Committee determined that this study did not directly involve human subjects.

Patients

We identified all women with stages I/II breast cancer diagnosed during 2004–2010 and who were 67 to 94 years old at the time of diagnosis. We limited our sample to women who received BCS within 9 months of cancer diagnosis, had tumor histology consistent with epithelial origin, had known tumor laterality, and had been enrolled in Medicare Parts A and B 24 months before diagnosis through earliest of death or end of follow-up in December 2014. Patients were excluded if they were male, or diagnosed at death or autopsy, they had any cancer condition identified from claims in the 3 to 24 months prior to diagnosis, or their income or education by zip code was unknown. Survival follow-up started at 9 months after diagnosis (the required timeframe for receipt of breast conserving surgery), so we excluded women who died within 9 months after cancer diagnosis.

Exposure and outcome ascertainment

We identified breast MRI use according to the Healthcare Common Procedure Coding System codes 76093–94, 77058–59, and C8903-C8908. We included MRI use between 90 days pre-diagnosis through the date of the first breast surgery. Outcomes of interest included treated recurrence (measured by receiving mastectomy during follow-up period)[16–18] and breast cancer specific mortality. We identified patients who received mastectomy after 9 months of initial diagnosis through December 2014 as reported by Medicare claims. Breast cancer specific mortality through December 2014 was derived from the SEER program.

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Covariate creation and selection

Patient characteristics included age at diagnosis, race, year of diagnosis, marital status, SEER registry, metropolitan status of residence, concurrent enrollment in Medicaid in the year before diagnosis, comorbidity, and as proxies for primary care access and utilization: flu vaccination and the number of outpatient clinic visits on separate days within 3 to 24 months before cancer diagnosis.[19] SEER-Medicare also provides census-based estimates of median household income and percentage of adults with a high school education or less at the zip code level. We used Elixhauser comorbidity conditions, adapting the approach that requires a diagnosis code to appear on either one inpatient claim or ≥2 outpatient claims greater than 30 days apart in order for a condition to be considered present.[20] We also incorporated a disability index, a claims-based indicator for services commonly needed by patients with poor functional performance status.[21] Tumor characteristics included stage, grade, size, histology, estrogen receptor (ER) and progesterone receptor (PR) status, and number of positive lymph nodes involved, as reported by SEER. We determined RT, chemotherapy, or anti-HER2 therapy status, respectively defined as RT, chemotherapy, or trastuzumab use that occurred between diagnosis and 9 months after definitive breast cancer surgery using Medicare claims data. To increase specificity, patients needed to have ≥1 claims for brachytherapy or ≥4 claims of external beam radiation therapy or intensity modulated radiation therapy to be considered RT recipients.[22] Provider characteristics included the breast surgeon's Medicare patient volume, teaching hospital status, and whether the surgery was received at a National Cancer Institute (NCI)–designated comprehensive cancer center.

Statistical analysis

We used χ^2 tests to evaluate the association between MRI use and demographic, tumor, treatment, and provider characteristics. We estimated the cumulative risk of treated recurrence and breast cancer specific mortality for the entire cohort by MRI use, as well as for additional subsets with and without RT. Differences in the survival functions were tested using the log-rank test.

We used Cox proportional hazards models to assess the association between MRI use and treated recurrence and breast cancer specific mortality. A series of models were fitted to examine the bivariate association between our outcomes of interest and MRI use, as well as other potential confounders. Multivariable models were fitted to estimate the hazard ratio (HR) for MRI use, adjusted for potential confounding variables found to be associated with outcomes (p-value <.20) in bivariate analyses. Log-cumulative hazard plots verified the validity of the proportional hazards assumption. Death from any cause and a contralateral breast cancer diagnosis were modeled as competing events for the treated recurrence analysis, while death from causes other than breast cancer were modeled as competing events for the breast cancer mortality analysis. We included an interaction term between RT and MRI use, and conducted subgroup analyses stratified by RT status. As a secondary analysis, we examined the associations between MRI use and outcomes among a low-risk group. Using the inclusion criteria of the Cancer and Leukemia Group B C9343 trial, we selected patients ages 70 and older with low-risk tumor characteristics (T1N0M0 and ER-positive) from our sample. Acknowledging that patients might have a second lumpectomy

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and/or RT instead of mastectomy for a recurrence event, we conducted two sensitivity analyses where treated recurrence was measured 9 months after cancer diagnosis by the treatments of 1) mastectomy or BCS; and 2) mastectomy, BCS, or RT. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). Tests were two-sided with an alpha value of .05.

Results

The sample consisted of 24,379 women with breast cancer (mean age 74 and 77 years among beneficiaries receiving and not receiving MRI, respectively), including 4,691 (19.2%) who received preoperative MRI (Table 1 and Appendix Table 1). The median follow-up time was 5.6 years. Women who received MRI tended to be younger, white, married, and have higher median incomes, fewer comorbidities and a better disability index (p<.001 for all). There was no significant difference between the two groups in terms of tumor stage or tumor size (p=.50 and .07, respectively); however, women who received MRI were more likely to have well- or moderately-differentiated and positive ER or PR breast cancer, yet were less likely to have lymph nodes unexamined (p<.001 for all). Women who received MRI were more likely to receive RT, chemotherapy, and anti-HER2 therapy (p<.001 for all).

The treated recurrence incidence rate in patients who received MRI was 3.2 per 1,000 person-years, compared to 4.1 per 1,000 person-years in patients who did not receive MRI (Table 2 and Figure 1A). In multivariate analysis, breast MRI use was not significantly associated with a lower risk of treated recurrence (HR: 0.92; 95% CI: 0.70–1.19; p=.51). Although the interaction between RT and MRI use was not statistically significant (p-value=.137), the association between MRI use and treated recurrence appeared to differ according to RT status (Figure 1B). Adjusted HRs of treated recurrence rates were 1.17 (95% CI: 0.84–1.61; p=.35) for the RT group and 0.60 (95% CI: 0.37–0.98; p=.04) for the non-RT group, respectively.

Breast cancer specific mortality in patients who received MRI was 5.3 per 1,000 person-years, compared to 8.7 per 1,000 person-years in patients who did not receive MRI (Table 2 and Figure 2A). In multivariate analysis, MRI use was not significantly associated with a lower breast cancer mortality (HR: 0.89; 95% CI: 0.73–1.08; p=.23; Table 2). As was the case with the analysis of mastectomy, the interaction between RT and MRI use was statistically insignificant (p-value=.15), yet stratified analyses showed differences between the RT and non-RT groups. Among patients who received RT, breast cancer mortality rates were 5.2 and 7.1 per 1,000 person-year for patients who did and did not receive MRI, respectively (Table 2 and Figure 2B), and the adjusted HR of breast cancer mortality was 1.00 (95% CI: 0.80–1.24; p=.99). Among those in the non-RT group, breast cancer mortality rates were 5.5 and 14.9 for patients who did and did not receive MRI, respectively; and the adjusted HR of breast cancer mortality was 0.57 (95% CI: 0.36–0.92; p=.02).

After limiting our sample to C9343 eligible patients, results of main analyses were qualitatively similar to the findings we reported above (Appendix Table 2). In the stratified analyses, however, the AHRs of MRI on treated recurrence or breast cancer mortality were

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no longer statistically significant among patients who did not receive RT. Sensitivity analyses using subsequent mastectomy, BCS, or RT as treated recurrence showed no benefits attributed to MRI use (Appendix Table 3).

Discussion

More than 20% of older women with early stage breast cancer received preoperative breast MRI in the United States in 2007.[7,10] Advocates for preoperative MRI use argue that MRI use facilitates surgical planning to achieve better ipsilateral disease control. However, limited evidence has indicated that MRI use does not reduce the risk of local or distant recurrence.[12] Analyzing 3,180 affected breasts among 3,169 patients across four studies, prior research found an insignificant effect of MRI use on local recurrence free survival (adjusted HR 0.88 with 95% CI 0.52–1.51).[12] Unfortunately, this individual patient data meta-analysis did not include radiation therapy and systematic therapy in the multivariate analysis because of large p-values in the univariate analyses. Our study strengthens their findings because our study is population-based with adjustment for RT and systematic treatment. The absence of a reduction in breast cancer mortality attributed to MRI use further confirm MRI use does not improve clinical outcomes.

Our findings build upon prior work in important aspects. First, our analyses, stratified by MRI use and receipt of RT, are particularly intriguing because they suggest that MRI use may be beneficial for the non-RT group. While previous research combined data from four studies, the sample size was small for subjects who did not receive RT (60 and 78 for patients who received BCS alone with and without receiving MRI, respectively).[12] Our study included 5,840 patients who received BCS alone, and 815 of them also received MRI; our larger sample size could thus advance knowledge regarding this issue. Our stratified analyses indicate that additional MRI use does not provide benefits for patients who receive RT but may be beneficial for patients who did not receive RT. The exact reason for this is unclear. Women who undergo MRI may receive a wider excision and/or additional surgery which could lead to a lower burden of residual tumor in the ipsilateral breast. Additionally, there may be other confounders associated with the use of MRI. For example, women who decline both RT and MRI options may be therapeutic minimalists, who may be more likely to decline endocrine therapy or follow-up surveillance imaging, leading to eventual distant metastasis and elevated breast cancer specific mortality. Given the nature of subgroup analyses, the results here should be interpreted as hypothesis generating only, rather than hypothesis testing. Further research examining the associations between MRI use and clinical outcomes among patients who receive BCS without RT is warranted.

Second, for patients who had favorable tumor characteristics and were eligible for the C9343 trial, MRI use did not significantly decrease treated recurrence or breast cancer mortality, regardless of RT status. Among patients who did not receive RT, however, the estimated effect size (i.e.; the adjusted HR of 0.75 or 0.70 for treated recurrence and breast cancer mortality, respectively; Appendix Table 2 is substantial. Based on our findings, we estimated the risk of ipsilateral recurrence for patients with residual disease after surgery (had either additional lesions undetected or residual disease in the tumor bed), a counterfactual scenario as these MRI-detected lesions would be surgically removed. We provided a schematic

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depiction of our sample (Figure 3), in which patients not receiving MRI can be putatively divided further into two groups with and without residual lesions. Given that the C9343 trial enrolled patients before 2000 during a time where MRI was rarely used, its finding of a 4% 5-year local recurrence probability could apply to patients who did not receive MRI, consisting of patients with and without additional lesions. Given the adjusted HR of 0.75 attributed to MRI use, the 5-year risk of local recurrence for patients who did not have additional lesions is 3.0%. Using the estimate from systematic literature reviews that MRI detects 15% additional lesions, the risk of local recurrence for patients who had residual lesions undetected and did not receive RT is estimated at 9.7%, calculated by 3.0% * 85% (i.e., 100% minus 15%; patients without additional lesions) + 9.7% * 15% (patients with additional lesions) = 4.0% (entire no-RT-no-MRI group). Although this calculation involves a lot of assumptions, MRI use might yield additional risk stratification for patients who did not receive RT, and identify patients who are not candidates for omitting RT. We also raise a concern that for existing and future trials withholding radiotherapy in women with breast cancer undergoing BCS, the use of preoperative MRI must be known and controlled for as an eligibility or stratification factor.

In the current era of evidence- and value-based practice as well as patient-centered care with shared decision-making processes, our results could help providers and patients rethink the utility of MRI. This is especially important for older women with breast cancer, as BCS alone may be an appropriate option. We suggest that physicians and patients discuss individual treatment preferences first, based on the findings of conventional imaging. If patients want to minimize risks of local recurrence with a decision favoring a mastectomy or BCS plus RT over BCS alone, it is important for physicians to express that preoperative MRI use does not provide additional benefits and may not be medically necessary. If physicians and patients are making a decision between BCS with or without RT, further studies are needed to determine if preoperative MRI may help identify patients for whom BCS without RT may not be appropriate. Examining patient preferences and treatment decision-making as well as cost-effectiveness between MRI use and RT are topics of interest for future investigation.

We acknowledge the limitations of our study. First and foremost, as a retrospective observational study, causal inferences cannot be made from the results of our study. While we included a moderately comprehensive set of controlling variables in analyses, we were unable to control for unobservable factors, which may influence our outcomes. As Table 1 indicated, several patient, tumor, and treatment characteristics were more favorable in the MRI group, compared with the non-MRI group, indicating potential selection bias favoring the MRI group. Even so, we still found no benefits attributed to MRI use. Therefore, it is unlikely that MRI use is associated with improved outcomes, especially for those who underwent RT. In contrast, the observed benefits of MRI use in the non-RT group might be driven by selection bias. For instance, the AHR of breast cancer specific mortality was 0.57, similar to the effect size of chemotherapy.[23] Such huge benefits seemed implausible, indicating selection bias and residual confounding. Further studies are needed to examine the impact of MRI use among patients who undergo BCS without RT.

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Second, we did not have recurrence information and therefore only used subsequent mastectomy as a proxy of treated recurrence. It is possible that patients who received preoperative MRI and BCS (with and without RT) may tend to avoid mastectomy. Thus, they might receive additional BCS if they had a local recurrence event. However, our sensitivity analyses including BCS as treated recurrence found similar results. Third, while the SEER program has developed an algorithm to determine cancer-specific cause of death, [24,25] the accuracy of cancer-specific mortality is unknown. Thus, the results regarding cancer specific mortality must be interpreted with caution. However, it is unlikely that breast cancer deaths reported in the SEER database would differ by MRI use. Hence, our results are unlikely to be biased because of this issue. Finally, our study was limited to older patients and the median follow-up duration was only 5.6 years. Our findings may not be generalizable to a younger population who may have different risks of recurrence. Longer follow-up information is necessary, particularly as this is a population who is typically on endocrine therapy, which would likely decrease subsequent breast cancer occurrence. Thus, the ipsilateral recurrence rate might increase after 5 years if the patients have stopped hormone therapy.

In conclusion, MRI use did not reduce the long-term mastectomy rate or breast cancer mortality among older women with breast cancer receiving BCS plus RT. For patients who elected BCS without RT, MRI use is potentially associated with a decrease in breast cancer mortality and long-term mastectomy. Future research is needed to explore whether MRI use could identify patients who would be willing to be treated alongside the C9343 paradigm.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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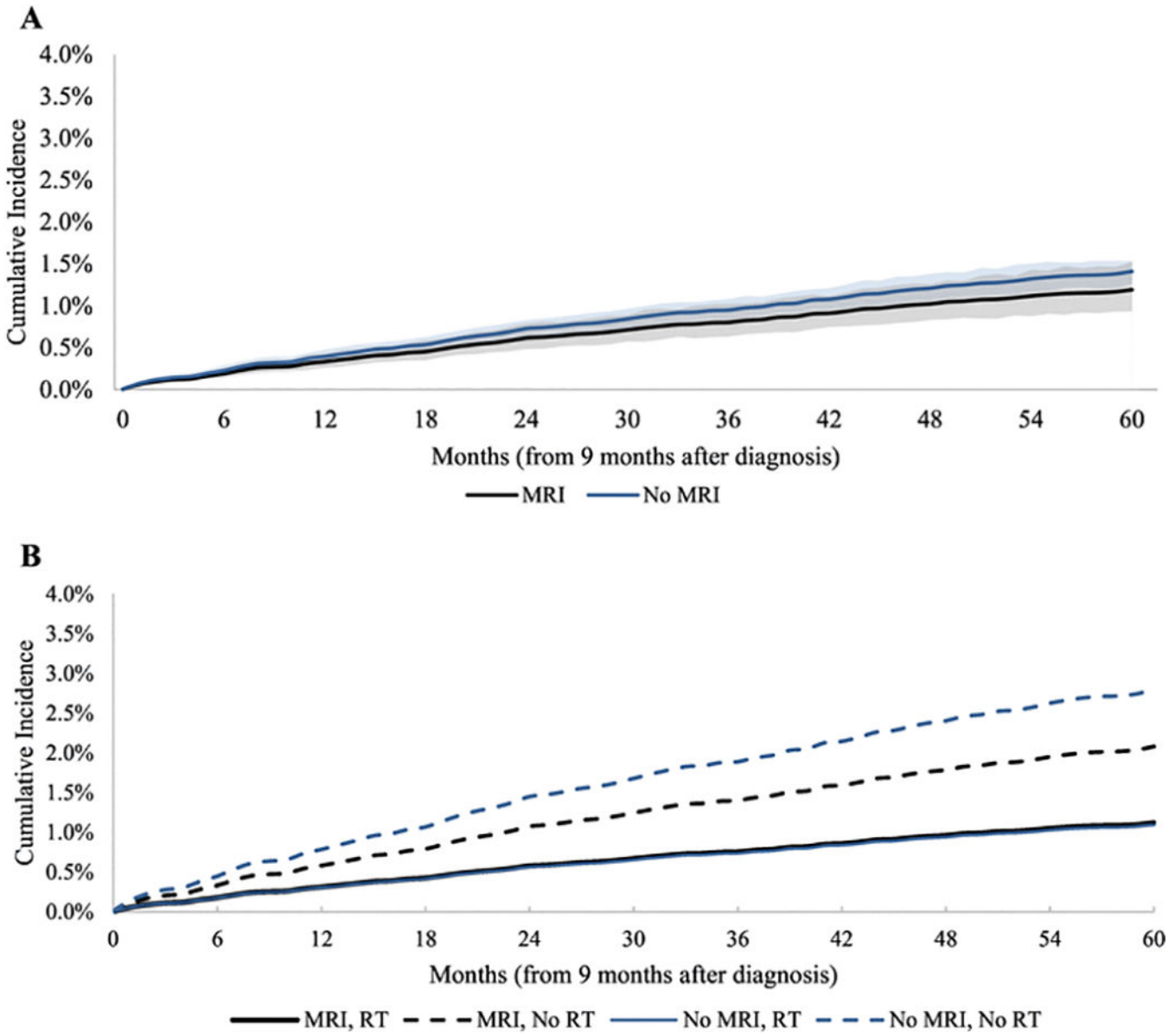

Figure 1. Long-term Treated Recurrence Cumulative Incidence According to (A) MRI Status and (B) MRI and RT Status

MRI: Magnetic resonance imaging; RT: Radiotherapy.

Number of patients being followed:

Time Period (years)	0	1	2	3	4	5
MRI	4517	4437	4324	4187	3345	2365
No MRI	19465	18585	17563	16543	13957	11060
All Patients	23982	23022	21887	20730	17302	13425

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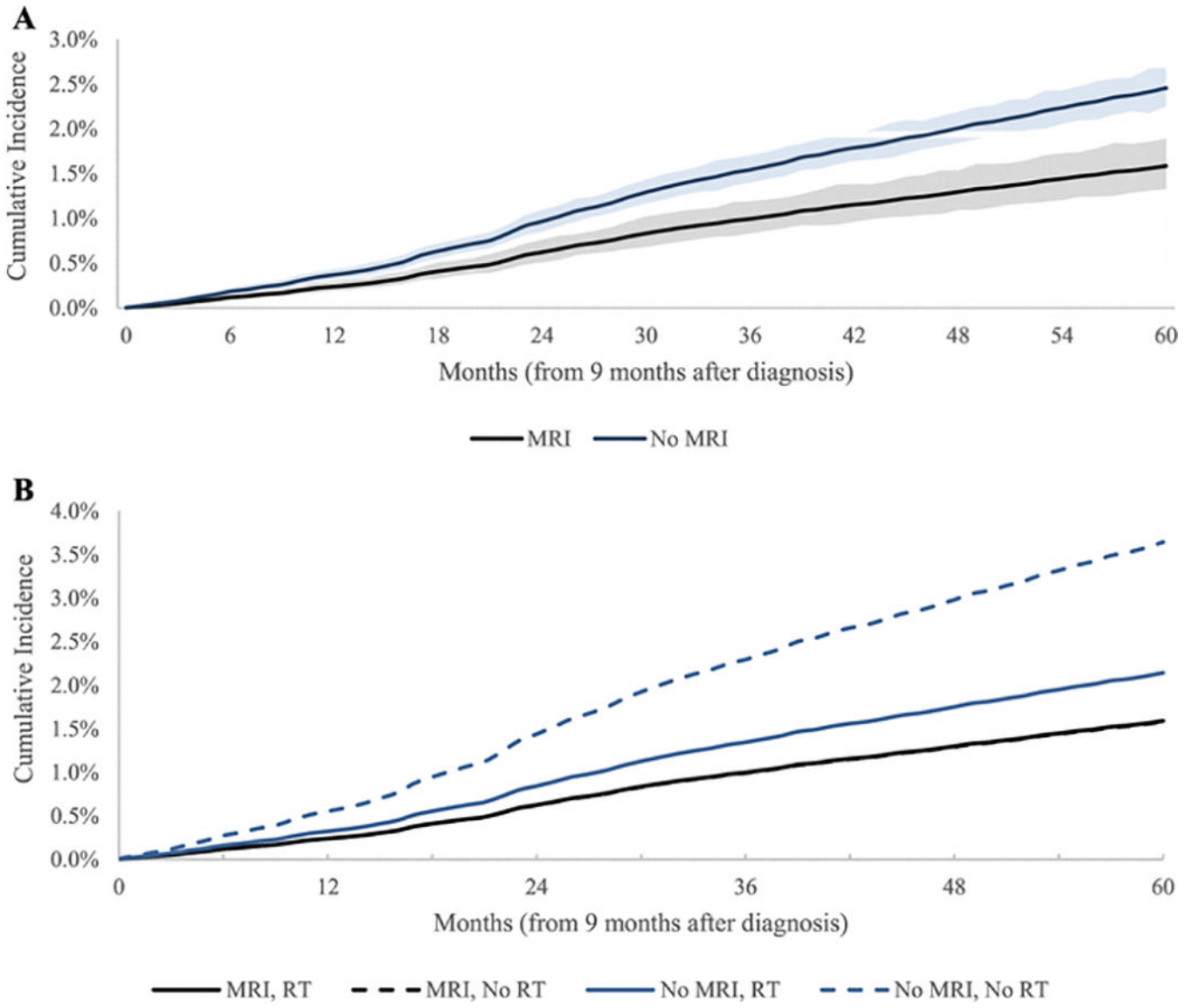

Figure 2. Breast Cancer Mortality Cumulative Incidence According to (A) MRI Status and (B) MRI and RT Status

MRI: Magnetic resonance imaging; RT: Radiotherapy

Number of patients being followed:

Time Period (years)	0	1	2	3	4	5
MRI	4691	4631	4549	4427	3554	2542
No MRI	19688	18996	18092	17154	14606	11640
All Patients	24379	23627	22641	21581	18160	14182

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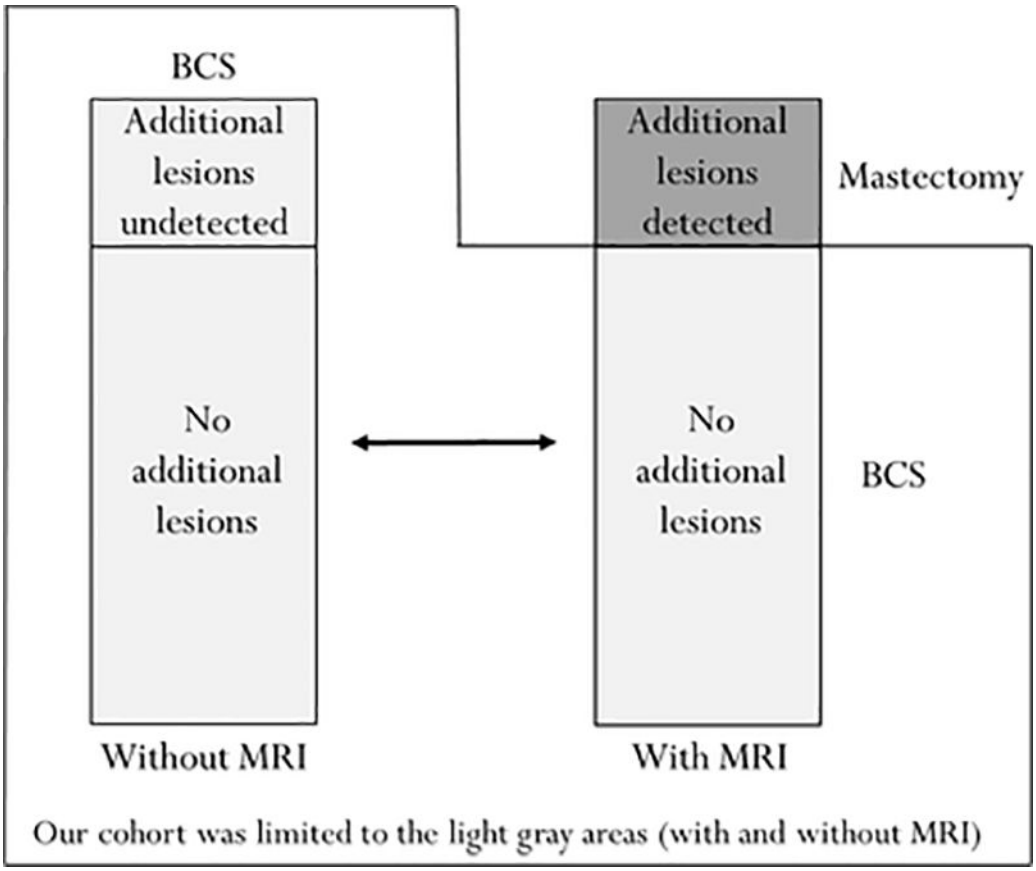

Figure 3.
A schematic depiction of our sample

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Table 1.

Selected characteristics of early breast cancer patients, according to MRI status

	MRI N= 4,691 (19.2%)		No MRI N= 19,688 (80.8%)		P-value
	N	Col %	N	Col %	
Age					
67–69	1199	25.6%	3061	15.5%	<.001
70–74	1602	34.2%	5016	25.5%	
75–79	1061	22.6%	4941	25.1%	
80–84	600	12.8%	3983	20.2%	
85+	229	4.9%	2687	13.6%	
Race					
White	4382	93.4%	17935	91.1%	<.001
Black	159	3.4%	1036	5.3%	
Other	150	3.2%	717	3.6%	
Education of zip code (≤HS)					
<30 %	1936	41.3%	5043	25.6%	<.001
30 to 40%	921	19.6%	3437	17.5%	
40 to 50 %	781	16.6%	3786	19.2%	
50 to 60%	536	11.4%	3521	17.9%	
≥ 60%	517	11.0%	3901	19.8%	
Elixhauser Comorbidity					
None	2460	52.4%	8587	43.6%	<.001
1 to 2	1767	37.7%	7820	39.7%	
3 or more	464	9.9%	3281	16.7%	
Disability Index					
Q1 (least disabled)	1397	29.8%	4722	24.0%	<.001
Q2	1284	27.4%	4871	24.7%	
Q3	1046	22.3%	4580	23.3%	
Q4 (most disabled)	964	20.5%	5515	28.0%	
Grade					
Well differentiated	1437	30.6%	5820	29.6%	<.001
Moderately differentiated	2194	46.8%	8760	44.5%	
Poorly differentiated	876	18.7%	4106	20.9%	
Undifferentiated	16	0.3%	110	0.6%	
Unknown	168	3.6%	892	4.5%	
Stage					
I	3384	72.1%	14299	72.6%	.50
II	1307	27.9%	5389	27.4%	
Tumor size					

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	MRI N= 4,691 (19.2%)		No MRI N= 19,688 (80.8%)		P-value
	N	Col %	N	Col %	
<2.0 cm	>3626	>77.3%	14861	75.5%	.07
2.0-<=5.0 cm	1022	21.8%	4636	23.5%	
>5.0 cm	34	0.7%	158	0.8%	
Missing	<11	<0.2%	33	0.2%	
Number of positive lymph nodes					
No positive nodes/unknown	640	13.6%	2353	12.0%	<.001
1+ positive nodes	246	5.2%	3109	15.8%	
No nodes examined	3805	81.1%	14226	72.3%	
Hormone receptors					
ER+ or PR+	4098	87.4%	16624	84.4%	<.001
ER− and PR−	466	9.9%	2109	10.7%	
Missing	127	2.7%	955	4.9%	
Chemotherapy					
Yes	830	17.7%	2463	12.5%	<.001
No	3861	82.3%	17225	87.5%	
Trastuzumab					
Yes	201	4.3%	480	2.4%	<.001
No	4490	95.7%	19208	97.6%	
Radiation Therapy					
Yes	3876	82.6%	14663	74.5%	<.001
No	815	17.4%	5025	25.5%	
Breast Surgeon Volume					
Surgeon not identified	657	14.0%	3078	15.6%	<.001
1 patient	101	2.2%	906	4.6%	
2–6 patients	204	4.3%	1601	8.1%	
7–19 patients	332	7.1%	2143	10.9%	
≥20 patients	3397	72.4%	11960	60.7%	

MRI: Magnetic resonance imaging

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Table 2.

Long-term treated recurrence rates and breast cancer mortality, according to MRI status and stratified by receipt of RT

	All			Radiation Therapy			No Radiation Therapy		
Treated Recurrence									
	MRI N=4,517	No MRI N=19,465	P-value	MRI N=3,727	No MRI N=14,508	P-value	MRI N=790	No MRI N=4,957	P-value
Incidence Rate (/1K PY)	3.2	4.1	.03	2.8	2.8	1.00	5.6	9.2	.02
Crude Hazard Ratio	0.80 (0.63–1.02)	Ref	.08	1.03 (0.77–1.38)	Ref	.84	0.65 (0.42–1.02)	Ref	.06
Adjusted Hazard Ratio	0.92 (0.70–1.19)	Ref	.51	1.17 (0.84–1.61)	Ref	.35	0.60 (0.37–0.98)	Ref	.04
Breast Cancer Mortality									
	MRI N=4,691	No MRI N=19,688	P-value	MRI N=3,876	No MRI N=14,663	P-value	MRI N=815	No MRI N=5,025	P-value
Incidence Rate (/1K PY)	5.3	8.7	<.001	5.2	7.1	.002	5.5	14.9	<.001
Crude Hazard Ratio	0.62 (0.52–0.75)	Ref	<.001	0.74 (0.61–0.91)	Ref	.004	0.41 (0.27–0.64)	Ref	<.001
Adjusted Hazard Ratio	0.89 (0.73–1.08)	Ref	.23	1.00 (0.80–1.24)	Ref	.99	0.57 (0.36–0.92)	Ref	.020

MRI: Magnetic resonance imaging; RT: Radiotherapy