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An Individual Person Data Meta-Analysis of Preoperative Magnetic Resonance Imaging and Breast Cancer Recurrence

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ABSTRACT

Purpose
There is little consensus regarding preoperative magnetic resonance imaging (MRI) in breast cancer (BC). We examined the association between preoperative MRI and local recurrence (LR) as primary outcome, as well as distant recurrence (DR), in patients with BC.

Methods
An individual person data (IPD) meta-analysis, based on preoperative MRI studies that met predefined eligibility criteria, was performed. Survival analysis (Cox proportional hazards modeling) was used to investigate time to recurrence and to estimate the hazard ratio (HR) for MRI. We modeled the univariable association between LR (or DR) and MRI, and covariates, and fitted multivariable models to estimate adjusted HRs. Sensitivity analysis was based on women who had breast conservation with radiotherapy.

Results
Four eligible studies contributed IPD on 3,180 affected breasts in 3,169 subjects (median age, 56.2 years). Eight-year LR-free survival did not differ between the MRI (97%) and no-MRI (95%) goups ($P = .87$), and the multivariable model showed no significant effect of MRI on LR-free survival: HR for MRI (versus no-MRI) was 0.88 (95% CI, 0.52 to 1.51; $P = .65$); age, margin status, and tumor grade were associated with LR-free survival (all $P < .05$). HR for MRI was 0.96 (95% CI, 0.52 to 1.77; $P = .90$) in sensitivity analysis. Eight-year DR-free survival did not differ between the MRI (89%) and no-MRI (93%) groups ($P = .37$), and the multivariable model showed no significant effect of MRI on DR-free survival: HR for MRI (*v* no-MRI) was 1.18 (95% CI, 0.76 to 2.27; $P = .48$) or 1.31 (95% CI, 0.76 to 2.27; $P = .34$) in sensitivity analysis.

Conclusion
Preoperative MRI for staging the cancerous breast does not reduce the risk of LR or DR.

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INTRODUCTION

There is little consensus regarding the role of magnetic resonance imaging (MRI) in staging the cancerous breast in women with newly diagnosed breast cancer (BC), and its value in the preoperative setting is a relentlessly debated issue in BC treatment.[1-8] MRI has superior sensitivity to conventional imaging for detecting clinically occult cancer foci in women with BC.[2,6-8] It was initially hoped that detection of additional disease in the affected breast by MRI would translate into improved surgical treatment and improved local control. In recent years, evidence has indicated that the inclusion of MRI in preoperative assessment does not improve surgical treatment and may be harmful[2,5,7-9] by conversion of candidates for breast conservation to more extensive resection or to mastectomy.[7,9] A meta-analysis has also shown that preoperative MRI does not reduce re-excisions, and that it significantly increases the odds of receiving mastectomy for BC treatment.[9]

An area of uncertainty underlying the preoperative MRI debate relates to its long-term effect, in particular, its effect on in-breast recurrence. This has been investigated in a few studies, all but one of which found a lack of association between MRI and recurrence.[10-13] However, primary studies, taken individually, may have limited power to examine long-term end points such as local (in-breast) recurrence. We report an individual patient data meta-analysis that investigates the association between

preoperative MRI and BC recurrence, specifically local recurrence (LR) as primary outcome, and distant recurrence (DR) as secondary outcome, in women treated for BC.

METHODS

We performed an individual person data (IPD) meta-analysis using data sourced from published studies that have compared cohorts of women with BC who received preoperative assessment with conventional imaging only with those who had also received preoperative MRI.

Study Identification and Eligibility Criteria

Appendix Figure A1 (online only) summarizes the literature search (at January 2013) and study identification process. Eligible studies had to have reported comparative data on the primary outcome (LR) in cohorts of patients with BC who had received preoperative conventional imaging only and those who had also received MRI. Authors of eligible studies were invited to participate in this collaborative work and were provided with the study plan and minimum data set required for IPD meta-analysis. All eligible studies,[10-12,14] but one,[13] agreed to provide de-identified data (details in Appendix Fig A1, including studies that did not meet eligibility criteria[15-17]). We did not restrict eligibility on the basis of surgical treatment, to minimize selection bias and thus allow investigation of any potential effect of MRI. Therefore, we considered studies that included breast-conserving surgery (BCS) candidates and/or those that included women who attempted BCS but received mastectomy as final surgical treatment, and we addressed this issue through sensitivity analysis (see Statistical Analysis).

Data Requested From Each Study

A minimum data set to conduct analyses of primary outcome (LR) was sought from each study, inclusive of whether or not a patient had MRI; age; date of surgery or start of treatment; final surgery; whether or not a patient received whole-breast radiation; systemic therapy (receipt of any, or none); final margins; follow-up time (time to event or to death or time to last follow-up if no event); type of event (at minimum, any LR occurring at any time). LR occurring simultaneously with regional recurrence was included in analysis of LR; however, regional-only recurrence was not included. DR was defined as distant metastases occurring at any time. Additional relevant variables (Table 1) were requested, but studies were not excluded if these variables were unavailable. We confirmed that each eligible study complied with institutional processes for use of de-identified data in research. A consistent classification was applied across all studies for categorical variables to allow joint modeling of the data. For surgical margins, we used a 2-mm threshold to classify negative margins.[10,18] MRI was performed before surgical treatment in all subjects, except for approximately 10% of the MRI group in the study by Solin et al[10] ($<$ 1% of subjects in our analysis) in whom MRI was performed postexcision but before radiation treatment.

Follow-Up Time

We required a minimum follow-up time of 90 days from surgery date; therefore, the number of subjects from each study in this meta-analysis slightly differs from that in some of the original publications. Follow-up duration was calculated from the date of surgery (or date of commencing radiation therapy for one study[10]) to last date of known follow-up, or to occurrence of event or to death from any cause.

Statistical Analysis

Preliminary analyses were used to describe the distribution of each variable separately for each study and for the pooled data set. For continuous measures, the median and interquartile range (IQR) were calculated. For categorical outcomes, the percentage in each category was computed. A Kaplan-Meier survival curve was generated for time to LR for each study. Survival curves for MRI versus no MRI were computed using the pooled data set, and differences in the survival functions were initially tested using the log-rank test. For women who did not have LR, their censoring time was time of death from any cause if applicable, or time of last follow-up.

Survival analysis (Cox proportional hazards modeling) was used to investigate time to LR and to estimate the hazard ratio (HR) for MRI. We modeled 5- and 8-year LR-free survival and report models for 8-year rates because the findings were consistent for both time frames. We examined whether the hazard functions were proportional across time between the studies and whether the association between MRI and LR differed between studies. Informed by these preliminary analyses, all models allowed the baseline hazard to differ by study. A series of models were fitted to investigate the univariable association between LR and preoperative MRI, as well as potential confounding variables. We also tested for interaction between MRI and the covariates age, margins, and tumor histology. A competing risks model (that did assume proportional hazards between studies) was fitted to assess the effect of loss to follow-up as a result of death on estimates for MRI versus no MRI, adjusted for study (as a fixed effect), compared with the univariable model.

A multivariable model was fitted to estimate the HR for MRI, adjusted for potential confounding variables found to be associated with recurrence ($P \leq .01$) in univariable analyses. A stringent criterion for statistical significance was used because of the number of events relative to the number of covariates and corresponding model parameters. Because progesterone receptor (PR) status is correlated with estrogen receptor (ER) status, only the latter was included in the model. Age was fitted as a continuous variable in the multivariable model to limit the number of parameters. We used the same methods to perform equivalent univariable and multivariable analyses for DR, after excluding Hwang et al,[11] which did not report DR as an end point.

Sensitivity analysis excluded women who had mastectomy or did not receive radiotherapy, to estimate the HR for MRI for the majority of subjects who had breast-conserving therapy (BCS and whole-breast radiation therapy). All analyses were performed using SAS 9.3 and Stata 11. Statistical significance was set at $P < .05$.

RESULTS

Four eligible studies[10-12,14] contributed IPD on 3,180 affected breasts in 3,169 subjects (11 with bilateral cancer) who were eligible for inclusion in this meta-analysis: 1,833 (57.6%) had not received MRI, and 1,347 (42.4%) had received MRI. Additional details about eligible studies are in Appendix Table A1 (online only) and Appendix Figure A1. One study was a randomized controlled trial (RCT; COMICE, Turnbull et al),[12,19] and three were nonrandomized studies (Solin[10]; Hwang[11]; Miller[14]) that compared BC cohorts who had received MRI with those who had not received MRI. At a median follow-up of 2.9 years (IQR, 1.6-4.5 years), there were 64 LRs (counting any in-breast recurrence), a crude LR rate of 2.0%: crude LR rates were 1.8% in subjects who had MRI and 2.2% in those who did not have MRI. DR occurred in 93 of 2,708 subjects (3.4%), excluding the study that did not report DR as an end point.[11] Median age was 56.2 years (IQR, 49.0-64.3 years); median tumor size was 15.0 mm (IQR, 10.0-21.0 mm). Appendix Table A1 shows additional descriptive results by study, and by whether or not subjects received MRI. The overall distribution of variables is shown in Table 1.

LR

Appendix Figure A2 (online only) shows the Kaplan-Meier LR-free survival curves by study. Because follow-up time for the RCT was relatively less than for the other studies, the assumption that the survival functions are proportional over time between studies was tested using a 5-year follow-up model. This indicated that the assumption was not met, and pair-wise comparisons showed differences between the survival function of the RCT[12,19] and the other studies. Therefore, all models allowed the baseline hazard function to differ by

Table 1. Cox Proportional Hazards Models of the Univariable Association Between Preoperative MRI, All Variables, and 8-Year Local Recurrence Rates

Variable	Total No. in Model	Did Not Have MRI		Had MRI		HR	95% CI	*P* for Variable
		No.	%	No.	%			
Receipt of preoperative MRI	3,180*							.69
No		1,833	57.6		NA	1.00 (Ref)		
Yes		NA		1,347	42.4	0.90 [1.01]†	0.52 to 1.54	
Age, continuous	3,179, (excludes 1 missing age data)					0.96	0.93 to 0.98	< .001
Age group, years	3,179							.0065
< 40		119	6.5	108	8.0	2.12	0.99 to 4.55	
40-49		352	19.2	308	22.9	1.23	0.63 to 2.41	
50-59		599	32.7	486	36.1	1.00 (Ref)		
60-69		503	27.5	346	25.7	0.76	0.37 to 1.54	
≥ 70		259	14.1	99	7.3	0.14	0.02 to 1.05	
Pathologic tumor size category, mm	2,997 (excludes NA or NR)							.088
≤ 10		488	28.3	345	27.1	1.00 (Ref)		
> 10 to ≤ 20		820	47.5	581	45.7	0.70	0.35 to 1.39	
≥ 20‡		417	24.2	346	27.2	1.43	0.72 to 2.83	
Tumor histology	3,180							.104
DCIS		186	10.1	106	7.9	1.00 (Ref)		
Invasive ductal carcinoma		1,358	74.1	981	72.8	0.55	0.27 to 1.13	
Invasive lobular carcinoma		121	6.6	108	8.0	0.36	0.10 to 1.33	
Other invasive types (includes special types or invasive not further defined)		168	9.2	152	11.3	0.20	0.04 to 0.94	
Tumor grade	3,180							< .001
I		341	18.6	271	20.1	1.00 (Ref)		
II		627	34.2	537	39.9	3.80	0.86 to 16.74	
III		590	32.2	378	28.1	10.73	2.55 to 45.24	
NR		275	15.0	161	12.0	11.47	2.54 to 51.79	
Final margin status	3,180							.0099
Negative		1,214	66.2	853	63.3	1.00 (Ref)		
Close		395	21.5	334	24.8	2.08	1.15 to 3.75	
Positive		145	7.9	98	7.3	3.01	1.34 to 6.73	
NR		79	4.3	62	4.6	3.26	1.11 to 9.58	
Node status (based on histology)	2,708 (excludes NA)							.026
Negative		927	62.3	809	66.3	1.00 (Ref)		
Positive		355	23.9	287	23.5	1.96	1.02 to 3.74	
NR		206	13.8	124	10.2	2.50	1.20 to 5.25	
ER status	3,180							< .001
Negative		333	18.2	224	16.6	1.00 (Ref)		
Positive		1,292	70.5	1,006	74.7	0.26	0.15 to 0.45	
NR		208	11.3	117	8.7	0.58	0.25 to 1.32	
PR status	3,180							.0045
Negative		553	30.2	351	26.1	1.00 (Ref)		
Positive		913	49.8	722	53.6	0.40	0.23 to 0.70	
NR		367	20.0	274	20.3	0.45	0.20 to 1.01	

(continued on following page)

Table 1. Cox Proportional Hazards Models of the Univariable Association Between Preoperative MRI, All Variables, and 8-Year Local Recurrence Rates (continued)

Variable	Total No. in Model	Did Not Have MRI		Had MRI		HR	95% CI	*P* for Variable
		No.	%	No.	%			
HER2 receptor status§	995							.16
Negative		456	81.4	354	81.4	1.00 (Ref)		
Positive		104	18.6	81	18.6	1.94	0.80 to 4.70	
Surgery	3,180							.62
Breast conservation		1,702	92.9	1,146	85.1	1.00 (Ref)		
Mastectomy‖		131	7.1	201	14.9	0.80	0.32 to 1.99	
Receipt of breast radiation	3,180							.75
No¶		152	8.3	171	12.7	1.00 (Ref)		
Yes		1,629	88.9	1,111	82.5	0.73	0.32 to 1.64	
NR		52	2.8	65	4.8	0.90	0.11 to 7.17	
Receipt of systemic therapy (endocrine or chemotherapy)	3,180							.31
No systemic therapy		405	22.1	212	15.7	1.00 (Ref)		
Any systemic therapy		1,380	75.3	1,074	79.7	0.64	0.35 to 1.15	
NR		48	2.6	61	4.5	1.14	0.14 to 9.05	
Year treatment received#	3,180							.33
1992-1999		504	27.5	155	11.5	1.00 (Ref)		
2000-2004		738	40.3	485	36.0	1.31	0.40 to 4.36	
2005 or later		591	32.2	707	52.5	0.75	0.18 to 3.09	

Abbreviations: DCIS, ductal carcinoma in situ; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; MRI, magnetic resonance imaging; NA, not applicable; NR, not reported; PR, progesterone receptor; Ref, referent.

*Total based on 3,180 affected breasts in 3,169 subjects (11 subjects with bilateral breast cancer), hence we report 3,180 as denominator in analysis.

†Sensitivity analysis, based on subjects that received breast-conserving therapy (n = 2,606) gave an HR for MRI of 1.01 (95% CI, 0.55 to 1.85; $P = .98$).

‡This group included 30 subjects with pT3 (> 50 mm) cancers; reanalysis of pathologic tumor size with the additional category for T3 cancers did not substantially alter findings ($P = .18$).

§Because of the limited data available for HER2 status, this analysis was based on the subset with known HER2 status.

‖Reports the proportion of subjects who received mastectomy from the pooled data set; however, only two[12,14] of the eligible studies included subjects who received mastectomy as final surgical treatment; the proportion receiving mastectomy based on those studies (from 1,977 subjects) was 13.5% in the no-MRI group and 20.0% in the MRI group ($P < .001$).

¶Supplementary analysis in the subgroup of subjects who did not receive radiation therapy is shown in Table A4.

#Based on date of surgical treatment, except for the study from Solin,[10] which was based on date commenced radiotherapy.

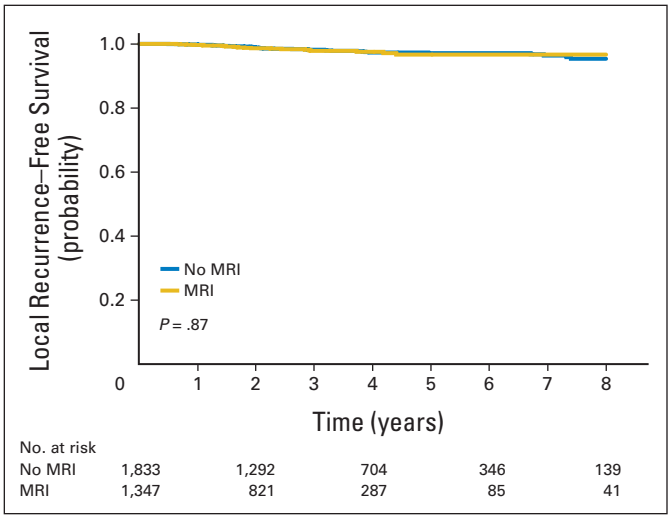

Fig 1. Kaplan-Meier local recurrence–free survival curves for magnetic resonance imaging (MRI) versus no MRI. *P* value is based on the log-rank test for equality of survival function curves.

study, although supplementary analyses assuming proportional hazards across time between studies did not alter the results. There were no significant differences in the HRs for MRI versus no MRI between studies ($P = .61$), and the ratio of hazards was constant across time for the effect of MRI (test for proportional hazards, $P = .22$). Figure 1 shows Kaplan-Meier survival curves for MRI versus no MRI, based on the pooled data set: 8-year LR-free survival for MRI (97%; 95% CI, 95% to 98%) versus no MRI (95%; 95% CI, 93% to 97%) did not differ ($P = .87$). Appendix Table A2 (online only) reports these data at 5 and at 8 years.

Table 1 also summarizes the models of the univariable analysis of variables and 8-year LR rates: 59 LRs had occurred at 8 years. Significant associations were found for age (when analyzed both as a categorical and as a continuous [linear]variable), margin status, node status, ER and PR status, and tumor grade. There was no evidence of association between preoperative MRI and LR-free survival in univariable analysis: the HR for MRI was 0.90 (95% CI, 0.52 to 1.54; $P = .69$); sensitivity analysis showed that the HR for MRI was 1.01 (95% CI, 0.55 to 1.85; $P = .98$). There were no significant interactions between MRI and the covariates age ($P = .30$), margin status ($P = .09$), or tumor histology ($P = .36$). When competing risks due to death from any cause were allowed for in univariable analysis, there was no substantial change to the association between MRI and LR (HR = 0.96; 95% CI, 0.54 to 1.71; $P = .88$).

Table 2 reports the multivariable model for 8-year LR-free survival: adjusted HR for MRI (versus no MRI) was 0.88 (95% CI, 0.52 to 1.51; $P = .65$); and age, margin status, and tumor grade were significantly associated with LR-free survival (all $P < .05$). Sensitivity analysis showed that the HR for MRI was 0.96 (95% CI, 0.52 to 1.77; $P = .90$).

DR

Figure 2 shows Kaplan-Meier DR-free survival curves, based on three studies reporting DR data (2,707 subjects): 8-year DR-free survival for MRI (89%; 95% CI, 83% to 93%) versus no MRI (93%; 95% CI, 90% to 95%) did not significantly differ ($P = .37$). Appendix Table A2 reports these data at 5 and at 8 years. Table 3 reports the univariable and multivariable models for 8-year DR-free survival. MRI was not significantly associated with risk of DR in univariable analysis: HR for

Table 2. Multivariable Model of the Association Between MRI, Variables Associated With Local Recurrence (in univariable analysis), and 8-Year Local Recurrence Rates

	Model (n = 3,179)*			Sensitivity Analysis (n = 2,606)†		
Variable	HR	95% CI	*P*	HR	95% CI	*P*
Receipt of preoperative MRI			.65			.901
No	1.00 (Ref)			1.00 (Ref)		
Yes	0.88	0.52 to 1.51		0.96	0.52 to 1.77	
Age, years‡	0.97	0.95 to 0.99	.0086	0.96	0.94 to 0.99	.0058
Tumor grade			.0097			.0078
I	1.00 (Ref)			1.00 (Ref)		
II	3.38	0.77 to 14.89		2.63	0.57 to 12.04	
III	5.54	1.26 to 24.30		4.67	1.05 to 20.80	
NR	8.29	1.75 to 39.23		10.20	2.05 to 50.74	
Final margin status			.0395			.107
Negative	1.00 (Ref)			1.00 (Ref)		
Close	1.89	1.03 to 3.46		1.94	1.01 to 3.73	
Positive	2.70	1.20 to 6.09		2.68	1.00 to 7.19	
NR	2.57	0.86 to 7.67		2.18	0.49 to 9.71	
ER status						.112
Negative	1.00 (Ref)		.028	1.00 (Ref)		
Positive	0.43	0.23 to 0.80		0.53	0.27 to 1.04	
NR	0.55	0.21 to 1.42		0.39	0.12 to 1.23	

Abbreviations: ER, estrogen receptor; HR, hazard ratio; MRI, magnetic resonance imaging; NR, not reported; Ref, referent.
*Multivariable model excludes one subject missing age data.
†Sensitivity analysis is based on subjects that received breast-conserving therapy.
‡Age, analyzed as increasing (continuous) variable, was associated with reduced risk of local recurrence (HR shown for each year of increasing age); results did not differ whether age was analyzed as a continuous or as a categorical variable in the model.

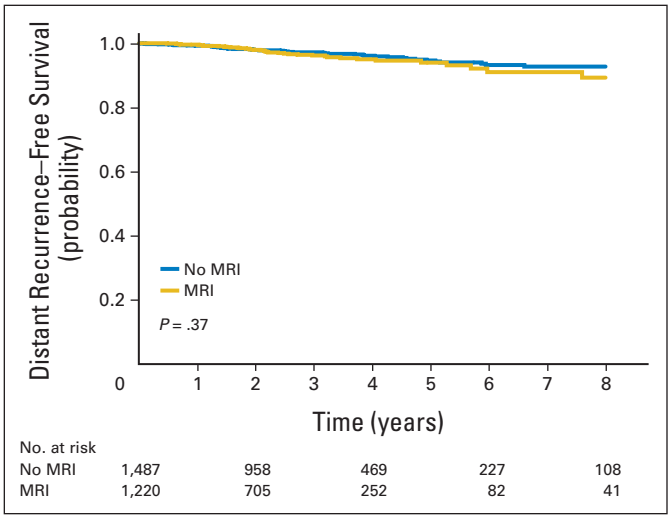

Fig 2. Kaplan-Meier distant recurrence–free survival curves for magnetic resonance imaging (MRI) versus no MRI. *P* value is based on the log-rank test for equality of survival function curves.

MRI was 1.28 (95% CI, 0.83 to 1.97; $P = .27$). When competing risks due to death were allowed for in the univariable model, there was no change in the association between MRI and DR (HR = 1.28; 95% CI, 0.83 to 1.97; $P = .27$).

To fit the multivariable model, subjects missing data for node status, pathologic tumor size, or systemic therapy were excluded; therefore, the model included 2,230 subjects (83 DRs). In the multivariable model, the adjusted HR for MRI was 1.18 (95% CI, 0.76 to 2.27; $P = .48$), or 1.31 (95% CI, 0.76 to 2.27; $P = .34$) in sensitivity analysis. In the multivariable model, pathologic tumor size, tumor grade, node status, ER status, receipt of mastectomy, and nonreceipt of systemic therapy were significantly associated with DR.

DISCUSSION

MRI for staging the breast in newly diagnosed BC has been integrated into practice because it detects additional disease that is occult on conventional imaging, with the assumption that this leads to improved treatment and hence improved outcomes.[1,2,4-6,8,20,21] This has occurred despite little to no evidence that preoperative MRI confers benefit.[1-5,8-10,12,16,21-24] The lack of consensus and uncertainty about the effect of preoperative MRI, in particular the limited evidence on long-term outcomes, is highlighted in divergent opinions and recommendations.[1,3,20,24-27] Our IPD meta-analysis addresses a major gap in the evidence on this issue, and shows that preoperative MRI is not associated with reduced risk of LR or DR, evidenced by the adjusted HRs for MRI for 8-year recurrence-free survival, as well as in sensitivity analysis.

In an era of evidence-based practice, the absence of consensus on preoperative breast MRI[1,2,4-8,20,21] should be placed in context. There is consistent evidence that MRI does not improve surgical outcomes in BC,[1,4,9,12,15,16] and MRI increases the odds of receiving mastectomy for BC treatment.[1,9] Other disadvantages of preoperative MRI include false-positive detection, increased time to treatment, increase in contralateral mastectomy, and increased costs.[1,2,4,8,28,29] However, the possibility that MRI, by identifying additional disease and guiding more extensive surgery, could be beneficial in reducing in-breast recurrence is one reason for its use, as reflected in reports that MRI contributes to local control[13,17] and in recommendations for preoperative MRI to assess disease extent.[24-26] Therefore, this IPD meta-analysis represents the best available evidence to inform clinicians and to underpin evidence-based recommendations, and should facilitate consensus that routine preoperative MRI in BC does not significantly reduce the risk of recurrence. Our findings also suggest that additional disease detected only by MRI is either biologically inconsequential or, a more likely explanation, that it is adequately treated through contemporary breast surgery and pathology evaluation and through adjuvant systemic therapies, including radiotherapy. Although we explored the latter possibility using subgroup analysis (Appendix), this was limited by few data in subjects who did not receive radiation.

This study is the only meta-analysis to our knowledge to investigate the potential association between preoperative MRI and BC recurrence; however, both the strengths and limitations of our work should be considered. First, this is the largest analysis to date of breast MRI and LR. Second, it uses IPD for meta-analysis and includes a relatively large number of events. Third, by using IPD, we adjusted for covariates found to be associated with outcomes, therefore our findings have allowed for potential confounding, which is particularly relevant given that three of the included studies were nonrandomized.Thus our statistical adjustments reduce the effect of possible selection of higher risk patients to MRI in the nonrandomized studies. Fourth, because a main effect of MRI is conversion from BCS to mastectomy[2,5,7-9] (also evident in our data, Table 1), we conducted our analyses with and without mastectomy patients to ensure that any potential effect from MRI is elucidated. Although surgical treatment and radiation therapy were not statistically associated with LR in our data, this is because the vast majority of subjects had BCS and radiation (Table 1).

Research using SEER-Medicare data has shown increasing use of preoperative MRI in BC, and that MRI was more frequently used in younger patients. Preoperative MRI has been broadly recommended for staging the breast in some guidelines,[25,26] and others[20,25,30,31] describe various criteria for its use, with the common theme of young age, invasive lobular histology, or dense breasts. Notwithstanding that these MRI criteria are largely based on expert opinion,[32] and that our meta-analysis was not designed to investigate specific selection criteria, we found no evidence of an interaction between MRI and histology or age, indicating that the effect of MRI on LR did not differ by histology type or age in our analysis.

Potential limitations of this analysis are that it included only four studies, with relatively modest follow-up duration, and that one study could not be included (Appendix Fig A1). The latter is the study from Fischer, the smallest of the preoperative MRI studies that reported on LR, which showed that MRI reduced LR rates.[13] As outlined by other authors[1,22] the results from that study are difficult to interpret because of differences between the MRI and no-MRI groups and because results were not adjusted for covariates. Furthermore, supplementary pooled analysis incorporating study-level data from Fischer[13] (Appendix) suggests that inclusion of that study would be unlikely to substantially alter our findings. Regarding follow-up, although we found no effect from MRI based on 8-year proportional hazards, we cannot exclude the possibility that longer follow-up could show an MRI-related benefit. Some might argue that our meta-analysis included studies using older MRI technology; this does not limit our work

Table 3. Cox Proportional Hazards Models of the Association Between Preoperative MRI, All Other Variables, and 8-Year Distant Recurrence Rates

Variable		Univariable Models			Multivariable Model*		
		HR	95% CI	*P*	HR	95% CI	*P*
Receipt of preoperative MRI	2,707			.27			.48
No		1.00 (Ref)			1.00 (Ref)		
Yes		1.28	0.83 to 1.97		1.18 [1.31]†	0.76 to 2.27	
Age, continuous‡	2,706 (excludes 1 missing age data)	0.98	0.96 to 0.99	.011	1.00	0.99 to 1.03	.59
Age group, years‡	2706			.017			
< 40		2.94	1.56 to 5.54				
40-49		1.39	0.77 to 2.53				
50-59		1.00 (Ref)					
60-69		0.94	0.50 to 1.79				
≥ 70		1.31	0.64 to 2.71				
Pathologic tumor size, mm	2,524 (excludes NA or NR)			< .001			.0094
≤ 10		1.00 (Ref)			1.00 (Ref)		
> 10 to ≤ 20		2.62	1.29 to 5.29		2.00	0.94 to 4.24	
> 20		5.73	2.82 to 11.65		3.14	1.42 to 6.93	
Tumor histology	2,415 (excludes DCIS for model fit)			.72	—	—	—
Invasive ductal carcinoma		1.00 (Ref)					
Invasive lobular carcinoma		0.94	0.40 to 2.18				
Other invasive types (includes special types or invasive not further defined)		1.32	0.67 to 2.58				
Tumor grade	2,707			< .001			< .001
I		1.00 (Ref)			1.00 (Ref)		
II		2.96	0.86 to 10.17		2.14	0.62 to 7.41	
III		11.51	3.58 to 37.01		5.82	1.77 to 19.18	
NR		2.68	0.72 to 10.01		4.63	1.17 to 18.42	
Final margin status	2,707			.70	—	—	—
Negative		1.00 (Ref)					
Close		0.97	0.55 to 1.69				
Positive		1.45	0.65 to 3.23				
NR		1.57	0.56 to 4.40				
Node status	2,377 (excludes NR for model fit)			< .001			< .001
Negative		1.00 (Ref)			1.00 (Ref)		
Positive		3.49	2.29 to 5.33		3.10	1.86 to 5.16	
ER status§	2,707			< .001			< .001
Negative		1.00 (Ref)			1.00 (Ref)		
Positive		0.32	0.21 to 0.50		0.37	0.22 to 0.60	
NR		0.12	0.04 to 0.33		0.40	0.14 to 1.16	
HER2 receptor status‖	706			.71	—	—	—
Negative		1.00 (Ref)					
Positive		0.87	0.40 to 1.88				
Surgery	2,707			< .001			
Breast conservation		1.00 (Ref)			1.00 (Ref)		< .001
Mastectomy		5.22	2.84 to 9.60		4.95	2.56 to 9.56	

(continued on following page)

Table 3. Cox Proportional Hazards Models of the Association Between Preoperative MRI, All Other Variables, and 8-Year Distant Recurrence Rates (continued)

Variable		Univariable Models			Multivariable Model*		
		HR	95% CI	*P*	HR	95% CI	*P*
Receipt of breast radiation	2,707			.88	—	—	—
No		1.00 (Ref)					
Yes		0.94	0.45 to 1.96				
NR		1.36	0.29 to 6.32				
Receipt of systemic therapy (endocrine or chemotherapy)	2,600			.015			.019
No systemic therapy		1.00 (Ref)			1.00 (Ref)		
Any systemic therapy		1.98	1.10 to 3.57		0.41	0.20 to 0.84	
Year treatment received				.96	—	—	—
1992-1999		1.00 (Ref)					
2000-2004		0.94	0.36 to 2.45				
2005 or later		0.86	0.27 to 2.76				

Abbreviations: DCIS, ductal carcinoma in situ; HR, hazard ratio; MRI, magnetic resonance imaging; NA, not applicable (not done or not reported in a study); NR, not reported; Ref, referent.
*Multivariable analysis included 2,230 subjects; subjects with missing data for node status, pathologic tumor size category, and systemic therapy were excluded (see Methods).
†Sensitivity analysis, based on breast-conserving therapy subjects (n = 1,864) gave an adjusted HR for MRI of 1.31 (95% CI, 0.76 to 2.27; *P* = .34).
‡Age was examined as a continuous and also as a categorical variable in both univariable and multivariable models (continuous shown for multivariable model); results did not differ whether age was analyzed as a continuous or as a categorical variable.
§Analysis using PR status showed very similar results to the estimates shown for ER status.
‖Because of the limited data available for HER2 status, this analysis was based on the subset with known HER2 status.

because any study examining long-term end points must include cohorts evaluated with MRI years earlier than the most current technology. Importantly, there was no significant effect of time frame in our results.

This meta-analysis has focused on preoperative MRI in routine staging of patients with BC; its findings do not apply to specific clinical situations in which MRI may be used, such as for investigating women with axillary node metastases and unknown primary cancer,[1] or in monitoring response to neoadjuvant therapy.[1,33,34] Screening the contralateral breast has also been suggested as an MRI indication[8,25,35,36]; however, we were unable to investigate this because most of the studies in our analysis did not report on contralateral events. Although MRI detects clinically occult contralateral BC,[8] only two retrospective studies have reported that this reduces contralateral cancer rates at follow-up,[13,36] but neither study used methods to determine the prognostic effect of contralateral screening for patients with BC. One of these studies was that by Fischer et al[13] (its limitations have been discussed earlier), whereas the other, from Kim et al,[36] compared nonconcurrent cohorts and reported that MRI reduced contralateral BC incidence. In contrast, Solin et al[10] did not find a reduction in contralateral BC rates from MRI. We cannot make definitive conclusions about MRI screening of the contralateral breast in patients with BC on the basis of our analysis or the conflicting information in the literature.

Our work addresses a gap in the evidence on preoperative MRI by reporting the largest analysis to date of preoperative MRI and LR. In the absence of RCTs investigating the effect of MRI on LR as primary end point, and given that LR rates after BCT have decreased over time[18,37,38] and are particularly low in contemporary BC cohorts who receive adjuvant therapy,[39] IPD meta-analysis provides a reliable approach to examine this issue. Our adjusted estimates for MRI represent the best available evidence on the association of MRI and LR (or DR) and should be used to guide or change clinical practice. Clinicians using or recommending preoperative breast MRI should take into account that MRI does not reduce the risk of LR or DR during clinical decision making and discussions with patients newly diagnosed with BC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Provision of study materials or patients: Lindsay W. Turnbull, David R. McCready, Todd Tuttle, Neha Vapiwala, Lawrence J. Solin
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Manuscript writing: All authors
Final approval of manuscript: All authors

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Appendix

Exploratory Analysis

Our individual person data (IPD) meta-analysis was based on four studies that provided data.[10-12,14] We performed a simple exploratory analysis to assess whether including data from Fischer et al[13] (the study that did not contribute to our meta-analysis) might be expected to substantially alter the findings of the IPD meta-analysis. We pooled data from the four included studies and added study-level data from Fischer et al to calculate crude (unadjusted) local recurrence (LR) proportions (LR%). The difference in the crude LR% between cohorts of patients with breast cancer who received preoperative conventional imaging only (no MRI) and those who had also received MRI was compared by using a χ^2 test.

Because the Fischer et al[13] study reported crude LR data for women who had breast-conserving therapy, with a mean follow-up of 40 months, we calculated the proportions for the IPD studies at 3 years to approximate the follow-up from that study, and based the analysis on women who had breast-conserving therapy. The results, shown in Appendix Table A3, suggest that the inclusion of the data from Fischer et al[13] would be unlikely to alter the findings of the IPD meta-analysis.

Subgroup Analysis in Subjects Who Did Not Receive Radiation Therapy

A post hoc analysis was performed based on the subgroup of women who did not receive radiation therapy, in an attempt to gain insights into the potential effect of preoperative MRI in this subgroup. It should be emphasized that this post hoc analysis was based on a limited amount of data, and the data are shown in Appendix Table A4.

Table A1. Supplementary Descriptive Results by Study and by Whether Subjects Received MRI

Variable	Study-Specific Data*								By Preoperative MRI				Pooled Data Set†	
	Turnbull[12]		Solin[10]		Hwang[11]		Miller[14]		No MRI		MRI			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Study variable (MRI)														
Did not have preoperative MRI	778	49.6	521	71.3	345	73.1	189	46.2	1,833	57.6		NA		Total†
Had preoperative MRI‡	790	50.4	210	28.7	127	26.9	220	53.8	NA		1,347	42.4	3,180	
Continuous variables														
Follow-up time, years														
Median	2.03		4.6		4.5		2.9		3.1		2.3		2.9	
IQR	1.1, 3.0		2.6, 7.4		3.0, 6.0		1.5, 4.6		1.8, 5.2		1.2, 3.7		1.6, 4.5	
Age, years														
Median	57.6		55.0		56.8		53.0		57.2		55.0		56.2	
IQR	50.6, 64.2		47.0, 65.0		49.0, 65.9		45.0, 61.0		49.7, 65.5		48.0, 62.9		49.0, 64.3	
Pathologic tumor size, mm														
Median	15		13		15		15		15		15		15	
IQR	11, 21		9, 19		10, 22		10, 22		10, 20		10, 21		10, 21	
Outcome variables														
Local recurrence (occurring at any time)	23	1.5	19	2.6	11	2.3	11	2.7	40	2.2	24	1.8	64	2.0
Distant recurrence (occurring at any time)	29	1.8	46	6.3	NA		18	4.4	52	3.5	41	3.4	93	3.4

Abbreviations: IQR, interquartile range; MRI, magnetic resonance imaging; NA, not applicable.
*Number of subjects from each study may slightly differ from that in the original publication because our meta-analysis required a minimum follow-up time of 90 days (see also Methods).
†Total data set = 3,180 except where otherwise specified.
‡Preoperative MRI was performed before surgical treatment in all subjects classified as having had preoperative MRI in all of the included studies, with the exception of approximately 10% of the MRI group in Solin et al[10] who received MRI after surgical excision but before radiation treatment (see also Methods).

Table A2. Estimated Recurrence-Free Survival at 5 and 8 Years

Measure	Did Not Have MRI		Had MRI		*P**	*P* for Stratified Model
	%	95% CI	%	95% CI		
Local recurrence-free survival, years						
5	97	96 to 98	97	95 to 98	.68	.94
8	95	93 to 97	97	95 to 98	.87	.69
Distant recurrence-free survival, years						
5	95	93 to 96	94	91 to 96	.56	.43
8	93	90 to 95	89	83 to 93	.37	.27

**P* value based on the log-rank test for equality of survival function curves [*P* for stratified model is based on the same test allowing for stratification by study].

Table A3. Supplementary Analyses

Cohorts With Breast-Conserving Therapy	No. of Subjects, IPD Studies	LR, IPD Studies		No. of Subjects, Fischer	LR, Fischer		Total Proportion With LR (%)	*P**
		No.	%		No.	%		
No MRI	1,702	21	1.2	138	9	6.5	1.6	.71
MRI	1,146	17	1.5	86	1	1.2	1.5	

Abbreviations: IPD, individual person data; MRI, magnetic resonance imaging.
**P* for difference in proportions in total data.

Table A4. Univariable Models of the Association of Preoperative MRI and 8-Year LR Rates

Variable	No. of Subjects	No. of LR	HR	95% CI	*P*
Subgroup who did not receive radiation, including those who had mastectomy					.40
No MRI	152	5	1.00 (Ref)		
MRI	171	3	0.55	0.13 to 2.30	
Subgroup who did not receive radiation and had breast-conserving surgery					.50
No MRI	78	3	1.00 (Ref)		
MRI	60	3	1.82	0.31 to 10.55	

Abbreviations: HR, hazard ratio; LR, local recurrence; MRI, magnetic resonance imaging; Ref, referent.

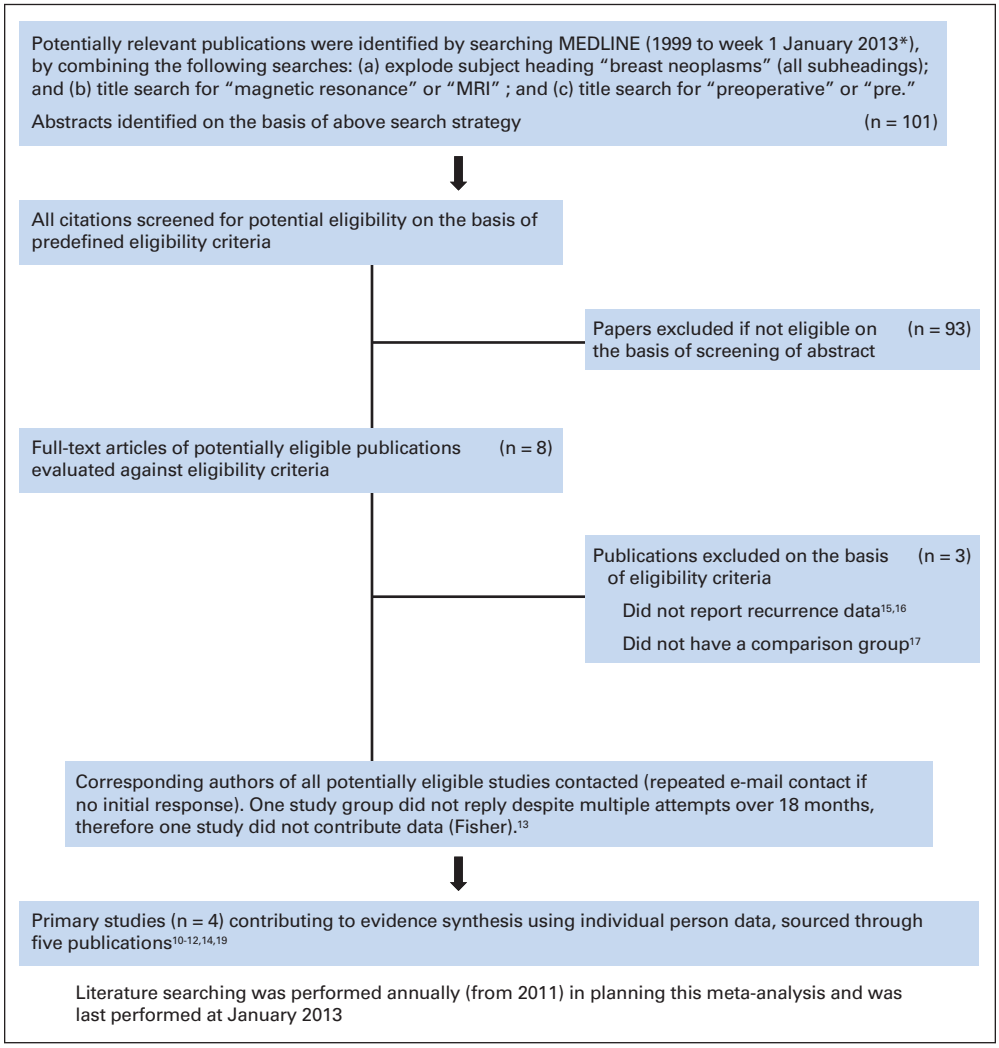

Fig A1. Flow diagram summarizing the literature search and study identification strategy. (*) Literature searching was performed annually (from 2011) in planning this meta-analysis, and was last performed at January 2013.

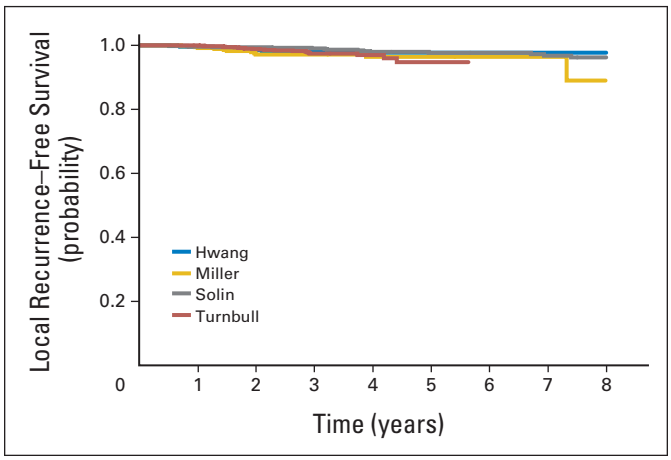

Fig A2. Study-specific Kaplan-Meier local recurrence-free survival curves for magnetic resonance imaging (MRI) versus no MRI.

