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REVIEW ARTICLE

Magnetic Resonance Imaging Screening of the Contralateral Breast in Women With Newly Diagnosed Breast Cancer: Systematic Review and Meta-Analysis of Incremental Cancer Detection and Impact on Surgical Management

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
Preoperative magnetic resonance imaging (MRI) is increasingly used for staging women with breast cancer, including screening for occult contralateral cancer. This article is a review and meta-analysis of studies reporting contralateral MRI in women with newly diagnosed invasive breast cancer.

Methods
We systematically reviewed the evidence on contralateral MRI, calculating pooled estimates for positive predictive value (PPV), true-positive:false-positive ratio (TP:FP), and incremental cancer detection rate (ICDR) over conventional imaging. Random effects logistic regression examined whether estimates were associated with study quality or clinical variables.

Results
Twenty-two studies reported contralateral malignancies detected only by MRI in 131 of 3,253 women. Summary estimates were as follows: MRI-detected suspicious findings (TP plus FP), 9.3% (95% CI, 5.8% to 14.7%); ICDR, 4.1% (95% CI, 2.7% to 6.0%), PPV, 47.9% (95% CI, 31.8% to 64.6%); TP:FP ratio, 0.92 (95% CI, 0.47 to 1.82). PPV was associated with the number of test positives and baseline imaging. Few studies included consecutive women, and few ascertained outcomes in all subjects. Where reported, 35.1% of MRI-detected cancers were ductal carcinoma in situ (mean size = 6.9 mm), 64.9% were invasive cancers (mean size = 9.3 mm), and the majority were stage pTis or pT1 and node negative. Effect on treatment was inconsistently reported, but many women underwent contralateral mastectomy.

Conclusion
MRI detects contralateral lesions in a substantial proportion of women, but does not reliably distinguish benign from malignant findings. Relatively high ICDR may be due to selection bias and/or overdetection. Women must be informed of the uncertain benefit and potential harm, including additional investigations and surgery.

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INTRODUCTION

In women with newly diagnosed breast cancer, synchronous contralateral breast cancer (CBC) is reported in 1% to 3%.[1-3] Bilateral breast cancer may have a worse prognosis than unilateral breast cancer.[1,2] Magnetic resonance imaging (MRI) of the breast is used in screening high-risk women and for local staging of the affected breast in women with breast cancer in some settings. Although many studies have shown that preoperative MRI identifies multifocal/multicentric ipsilateral disease unrecognized on conventional (clinical, mammography, and ultrasound) assessment, there is also evidence that it leads to more extensive surgery without clear evidence of benefit.[4-6] Because MRI is a sensitive test, its role has been further extended to screening for occult contralateral disease in women newly diagnosed with breast cancer.[7-9]

This article systematically reviews the evidence for MRI screening of the contralateral breast in women with a new diagnosis of invasive breast cancer to determine its incremental detection yield and accuracy. The characteristics of the cancers detected only with MRI and the impact of their detection on patient management are reported.

METHODS

A detailed description of the methodology is provided in the Appendix (online only) and flowchart (Appendix Figure A1, online only). Articles were identified by searching MEDLINE (Ovid 1950 through April 2008) and reference lists and through discussion with experts. Eighty abstracts were possibly relevant, with 22 eligible for inclusion in final analysis,[7,9-29] including four studies of only subjects with invasive lobular cancer (ILC) as the index lesion.[26-29]

Selection of Studies

Inclusion criteria were as follows: (1) studies of preoperative MRI in women with suspected or proven invasive breast cancer reporting contralateral findings relative to the index cancer, which (2) provided data for both true-positive (TP) and false-positive (FP) detection in the contralateral breast as a minimum measure of accuracy. Because this review aimed to determine the incremental benefit of MRI (its ability to detect cancer above what has been identified on clinical and imaging evaluation), subjects with CBC detected or suspected on clinical and/or conventional imaging assessment were excluded (38 subjects in 10 studies[12,13,16,17,20-25]). Studies not histologically verifying the majority of MRI-detected abnormalities were ineligible for inclusion. Subjects with a benign index lesion (188 subjects in five studies[11,20,21,24,25]) were excluded from analysis. Many studies also provided information about the index cancer and/or multifocality/multicentricity in the ipsilateral breast. This was the focus of an earlier meta-analysis.[4]

Data Extraction

All eligible studies were appraised using quality criteria adapted for breast cancer staging,[4] consisting of study characteristics and methodologic and clinical variables. Quantitative data were entered onto 2 × 2 tables to obtain the number of TPs, FPs, false negatives (FNs), and true negatives (TNs). Where reported, data were also extracted on tumor characteristics and surgical management.

Statistical Analysis

For each study, positive predictive value (PPV; TP/[TP + FP]), TP:FP ratio, incremental cancer detection rate (ICDR; TP/[TP + FP + TN + FN]), and overall proportion with positive MRI findings (POS; [TP + FP]/[TP + FP + TN + FN]) were computed. Study-specific estimates and 95% CIs for PPV and ICDR were displayed in forest plots with studies ordered by the number of test positives (suspicious contralateral lesions [TP + FP] detected on MRI.) Exact CIs were computed using SAS (SAS Institute, Cary, NC).[30] Estimates of sensitivity and specificity were not computed because most studies did not verify the absence of disease in women with negative MRI.

Random effects logistic regression was used to investigate whether variation in the PPV, ICDR, or any MRI detection was associated with study design or quality criteria. Summary estimates and their 95% CIs were derived using these models. The random effects model takes into account the within-study variability (sampling error) as well as between study variability. Hence smaller studies will have less weight in our overall estimate than larger studies. Corresponding summary estimates of the TP:FP ratio were obtained from the models for PPV (because PPV/[1 − PPV] = TP/FP). Random effects logistic regression models were fitted using PROC NLMIXED in SAS.[30] The distribution of the random effects was checked for each model to ensure that normality assumptions were met.

Pooled estimates are not reported for the studies that included only subjects with ILC as their index lesion, as this group consisted of only four studies with small numbers of subjects.[26-29] We also examined whether there was an association between study design and sample size using the Wilcoxon two-sample test, specifically testing for association between design and (1) number of MRI positives (TP + FP) and (2) sample size (TP + FP + TN + FN).

RESULTS

Twenty-two studies were eligible for inclusion, reporting CBCs in 137 of 3,253 women. These consisted of 18 studies reporting 123 MRI-detected CBCs (and six malignancies occult to MRI) in 3,147 women with index lesions that included invasive ductal, invasive lobular, and other invasive tumors (group 1),[7,9-25] and four studies reporting eight MRI-detected CBCs (and no FN MRI scans) in 106 women with only ILC as the index lesion (group 2).[26-29] Quality appraisal of the 22 studies is presented in Table 1. There were 11 prospective studies,[7,9,11-13,17,18,20,23-25] 10 retrospective studies,[10,14-16,19,22,26-29] and one study that did not report design.[21] There were no randomized trials of MRI in this setting. Baseline imaging consisted of mammography alone[7,9,12-14] or mammography with ultrasound,[10,11,15,17,20,21,24,25,27] but eight studies did not specify baseline imaging[16,18,19,22,23,26,28,29] (Table 1).

All studies performed contrast-enhanced MRI with a dedicated breast coil. All used morphologic and kinetic features to evaluate lesions, with the exception of three studies[14,16,25] that used morphologic features alone. All studies verified all or nearly all MRI-detected lesions with histology (percutaneous or excision biopsy, Table 1). The majority of studies did not ascertain absence of cancer in those negative on MRI, with only five studies[7,11,13,20,23] using clinical and/or imaging follow-up at 12 months to confirm a negative study. Data therefore have not been reported on the sensitivity and specificity of MRI in this setting.

INCREMENTAL ACCURACY (PPV, TP:FP RATIO) AND INCREMENTAL DETECTION

On the basis of the 18 studies in group 1, the pooled estimate for detecting a suspicious- appearing MRI abnormality occult to conventional imaging (MRI positives: TP and FP) was 9.3% (95% CI, 5.8% to 14.7%), with an interquartile range (IQR) of 3.8% to 13.9%. Study-specific PPV (Fig 1) ranged from 17% to 100% (IQR, 29% to 100%). The summary estimate of PPV was 47.9% (95% CI, 31.8% to 64.6%). The corresponding summary TP:FP ratio was 0.92 (95% CI, 0.47 to 1.82). The PPV and TP:FP ratio did not vary by study quality (including whether the study design was prospective or retrospective) or cancer prevalence. However, there was evidence that PPV (and hence TP:FP ratio) decreased with increasing number of test positives (TP + FP) in a study ($P = .024$). Study-specific estimates are thus displayed in the forest plot by decreasing number of test positives (Fig 1) and similarly ordered in data tables. On the basis of the 13 group 1 studies in which baseline imaging was specified, there was also evidence that PPV was associated with baseline imaging ($P = .042$): the estimated PPV was 31.0% (95% CI, 16.0% to 52.0%) for the five studies specifying mammography as baseline imaging and 57.0% (95% CI, 39.0% to 74.0%) for the eight studies specifying mammography with ultrasound.

Study-specific ICDRs are shown in Figure 2. The summary estimate for ICDR was 4.1% (95% CI, 2.7% to 6.0%), with an IQR of 2.6% to 4.8%. ICDR was not significantly associated with baseline imaging: median ICDR was 3.9% for studies specifying mammography only and 3.1% for studies specifying mammography with ultrasound (and 3.7% where this information was not provided).

Excluding the one study for which design was not reported, there was no evidence of an association between study design and sample size for either MRI positives (TP and FP; $P = .96$) or all subjects (TP + FP + TN + FN; $P = .73$).

Table 1. Systematic Quality Appraisal of Studies of MRI Evaluation of the Contralateral Breast in Women With Breast Cancer

First Author and Year	Study Design	Description of Subjects	Baseline (pre-MRI) Imaging	No. of Subjects	No. Included in This Analysis	Age (years)		Consecutive Patients Included?	Reasons for Exclusion of Some Subjects From Analysis*	Positive MRI Cases, Reference Standard†: Histology (mastectomy, percutaneous biopsy, or surgical biopsy)	Negative MRI Cases, Reference Standard*: Follow-Up (clinical and/or imaging) in 12 Months
						Mean or Median	Range				
Group 1: index tumor-invasive cancer, any type											
Lehman 2007[7]	P	Recent diagnosis ipsilateral breast cancer with normal imaging of contralateral breast; reporting contralateral MRI findings only	M	969	969	53	42-65	NR	None	Yes	Yes
Liberman 2003[14]	R	Recent diagnosis ipsilateral breast cancer with normal imaging of contralateral breast; reporting contralateral MRI findings only	M	223	212	48	28-79	No	11 positive MRI cases had no biopsy (inadequate reference standard)	Yes	No/NR
Hollingsworth 2006[16]	R	Recent diagnosis ipsilateral breast cancer with normal imaging of contralateral breast; reporting bilateral MRI findings	NR	334	330	NR		No	4 cancers suspected on conventional assessment	Yes	No/NR
Fischer 1999[21]	NR	Probably- benign or suspicious lesions on conventional assessment; reporting bilateral MRI findings	M+U	463	332	54		No	127 benign index lesions; 4 cancers suspected on conventional assessment	Yes	No/NR
Pediconi 2007[11]	P	Recent diagnosis ipsilateral breast cancer or high-risk lesion; reporting contralateral MRI findings only	M+U	118	91	52	35-78	Yes	23 benign index lesions; 4 lymphomas	Yes	Yes
Deurloo 2005[23]	P	Recent diagnosis ipsilateral breast cancer suitable for breast conservation; reporting bilateral MRI findings	NR	116	114	54		Yes	2 cancers suspected on conventional assessment	Yes	No/NR
Lee 2003[9]	P	Recent diagnosis ipsilateral breast cancer by core biopsy or excision with close margins; reporting contralateral MRI findings only	M	182	182	50	22-78	No	None	Yes	No/NR
Lehman 2005[12]	P	Recent diagnosis ipsilateral breast cancer with normal imaging of contralateral breast; reporting contralateral MRI findings only	M	103	100	52	NR	NR	3 cancers suspected on conventional assessment	Yes	No/NR
Bilimoria 2007[15]	R	Suspected ipsilateral breast cancer on conventional assessment; reporting bilateral MRI findings	M+U	155	155	53	34-75	No	None	Yes	No/NR
Hlawatsch 2002[24]	P	Suspected ipsilateral breast cancer on conventional assessment; reporting bilateral MRI findings	M+U	104	94	60		Yes	3 benign index lesions; 7 cancers suspected on conventional assessment	Yes	No/NR
Schelfout 2004[25]	P	Suspected ipsilateral breast cancer on conventional assessment; reporting bilateral MRI findings	M+U	204	165	57		Yes	34 benign index lesions; 5 cancers suspected on conventional assessment	Yes	No/NR

(continued on following page)

Table 1. Systematic Quality Appraisal of Studies of MRI Evaluation of the Contralateral Breast in Women With Breast Cancer (continued)

First Author and Year	Study Design	Description of Subjects	Baseline (pre-MRI) Imaging	No. of Subjects	No. Included in This Analysis	Age (years) Mean or Median	Age (years) Range	Consecutive Patients Included?	Reasons for Exclusion of Some Subjects From Analysis*	Positive MRI Cases, Reference Standard†: Histology (mastectomy, percutaneous biopsy, or surgical biopsy)	Negative MRI Cases, Reference Standard*: Follow-Up (clinical and/or imaging) in 12 Months
Slanetz 2002[18]	P	Recent diagnosis ipsilateral breast cancer by core biopsy or excision with close margins; reporting contralateral MRI findings only	NR	17	17	v49	34-78	NR	None	Yes	No/NR
Buxant 2007[10]	R	Suspected ipsilateral breast cancer on conventional assessment; reporting bilateral MRI findings	M+U	105	105	55	27-77	NR	None	Yes	No/NR
Lee 2004[13]	P	Breast conservation with recent ipsilateral cancer diagnosis by excision biopsy with close or positive margins; reporting bilateral MRI findings	M	80	78	52	28-80	NR	2 cancers suspected on conventional assessment	Yes	Yes
Rieber 1997[22]	R	Recent diagnosis ipsilateral breast cancer; reporting bilateral MRI findings	NR	34	32	56		No	2 cancers suspected on conventional assessment	Yes	No/NR
Rieber 2002[17]	P	Suspected ipsilateral breast cancer on conventional assessment undergoing MRI and/or PET scan; reporting bilateral MRI findings	M+U	43	42	53	27-84	No	1 cancer suspected on conventional assessment	Yes	No/NR
Bagley 2004[19]	R	Suspected or recently diagnosed ipsilateral breast cancer; reporting bilateral MRI findings	NR	27	27	NR		No		Yes	No/NR
Berg 2004[20]	P	Suspected or recently diagnosed ipsilateral breast cancer; reporting bilateral MRI findings	M+U	111	102	48	26-81	Yes	1 benign index lesion; 8 cancers suspected on conventional assessment	Yes	Yes
Total group, 1				3,338	3,147						
Group 2: index tumor-invasive lobular carcinoma only											
Quan 2003[28]	R	Recent diagnosis ipsilateral invasive lobular carcinoma; reporting bilateral MRI findings	NR	57	53	53		No	4 lesions: correlation between MRI and histology not possible	Yes	No/NR
Munot 2002[27]	R	Recent diagnosis ipsilateral invasive lobular carcinoma; reporting bilateral MRI findings	M+U	20	20	61		No	None	Yes	No/NR
Yeh 2003[29]	R	Recent diagnosis ipsilateral invasive lobular carcinoma; reporting bilateral MRI findings	NR	19	19	59		No	None	No	No/NR
Kepple 2005[26]	R	Recent diagnosis ipsilateral invasive lobular carcinoma; reporting bilateral MRI findings	NR	14	14	62		No	None	Yes	No/NR
Total, group 2				110	106						
Total, groups 1 + 2				3,608	3,253						

NOTE. Studies are ordered according to the number of test positives (suspicious contralateral lesions [true positives plus false positives]) detected on MRI.

Abbreviations: MRI, magnetic resonance imaging; P, prospective; M, mammography; NR, not reported; R, retrospective; M+U, mammography plus ultrasound; PET, positron emission tomography.

*Exclusions: Represent subjects not eligible for inclusion in our analysis for reasons outlined in the column, accounting for differences between reported No. of subjects in each study and total in the pooled analysis.

†Applied to all or nearly all cases.

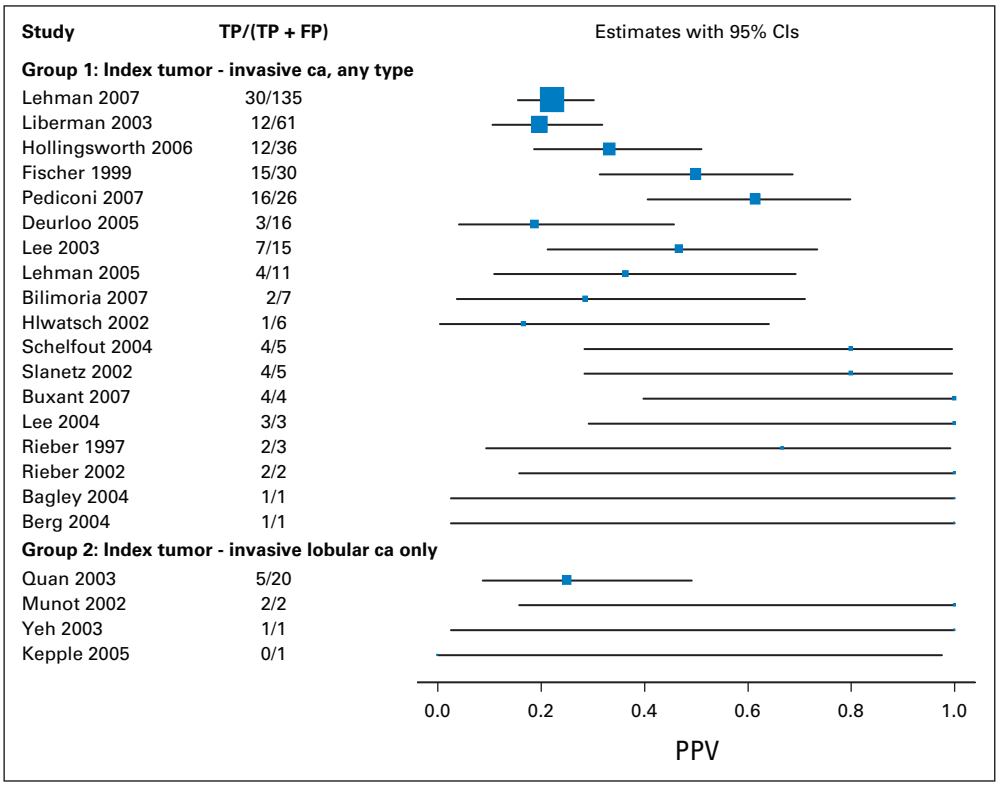

Fig 1. Magnetic resonance imaging (MRI) of the contralateral breast in women with newly diagnosed breast cancer (ca): study-specific positive predictive value (PPV). Studies are ordered according to the number of test positives (suspicious contralateral lesions [true positives {TPs} plus false positives {FPs}]) detected on MRI.

CHARACTERISTICS OF MRI-DETECTED TUMORS

Table 2 summarizes tumor characteristics for the 14 studies that reported tumor type[7,9,11-14,16-19,21,22,24,28] and the eight studies that reported tumor size[7,9,11,12,21,24,29,31] for all or most CBCs detected on MRI.

Tumor type was reported for 114 of 123 MRI-detected CBCs reported in group 1 (index lesion any histologic type), showing that 35.1% (40 of 114) were pure ductal carcinoma in situ (DCIS), and 64.9% (74 of 114) were invasive cancers. Individual tumor size was reported for 43 of the 123 MRI-detected CBCs in group 1. For DCIS (18 tumors), mean tumor size was 6.9 mm (median, 5.5 mm; IQR, 4 to 8 mm; range, 1 to 25 mm), and invasive cancers (25 tumors in four studies) had a mean tumor size of 9.3 mm (median, 9 mm; IQR, 7 to 10 mm; range, 3 to 17 mm). Both tumor type and size of individual lesions was not reported in any of the studies in group 2 (index lesion of ILC only).

In studies in which pathologic tumor stage was reported, all but two tumors were stage pTis or pT1, and one of the two remaining was a 42-mm node-negative ILC.[7] This latter study did not report type and size for all MRI-detected tumors, so this case was not included in the analysis of size reported above. An additional study reported a 35-mm CBC (type not reported) in a woman with a 30-mm ILC index cancer. Lymph node status was reported for 21 invasive cancers (pNx, n = 3; pN0, n = 17; pNmi, n = 1).

IMPACT ON PATIENT MANAGEMENT

Management of the contralateral breast is summarized in Table 3. Few studies reported management for all cancers; therefore, we have not provided pooled estimates. Eleven studies described management of CBCs in some cases,[7,9,10,12-16,21,22,26] indicating frequent use of mastectomy as surgical treatment for varying reasons (Table 3). Only one study reported breast conservation treatment in the majority of MRI-detected contralateral cancers.[21] Mastectomy as a diagnostic procedure (in women who didn't have preoperative percutaneous biopsy) was performed in 10 subjects with a positive contralateral MRI, including two with borderline (B3) lesions[32] on preoperative core biopsy. Three of these 10 (including one B3 lesion) showed malignancy in the mastectomy specimen; the remaining seven were benign. There were 42 reported prophylactic mastectomies in women with a negative contralateral MRI: five unexpected malignancies were identified on histology (MRI FN rate of 11.9% [five of 42] in this group of subjects).

DISCUSSION

Pooled analysis of studies of women with newly diagnosed breast cancer showed that MRI, when used to screen the contralateral breast, detects contralateral lesions suggestive of abnormality not seen on conventional imaging in 9.3% of women. Because more than one half of these represent FP MRI-only detected lesions, the ICDR for MRI is 4.1%. The summary PPV of 47.9%, and associated TP:FP ratio of 0.92, indicate that MRI does not differentiate well between benign and malignant findings in the context of screening for occult CBC. Although studies of ILC were too few with few subjects to consider pooled estimates, they showed similar data for detection rate and TP to FP trade-off.

Given that MRI is intended as an add-on test, its use is driven by its incremental TP and FP detection rate. Included studies used

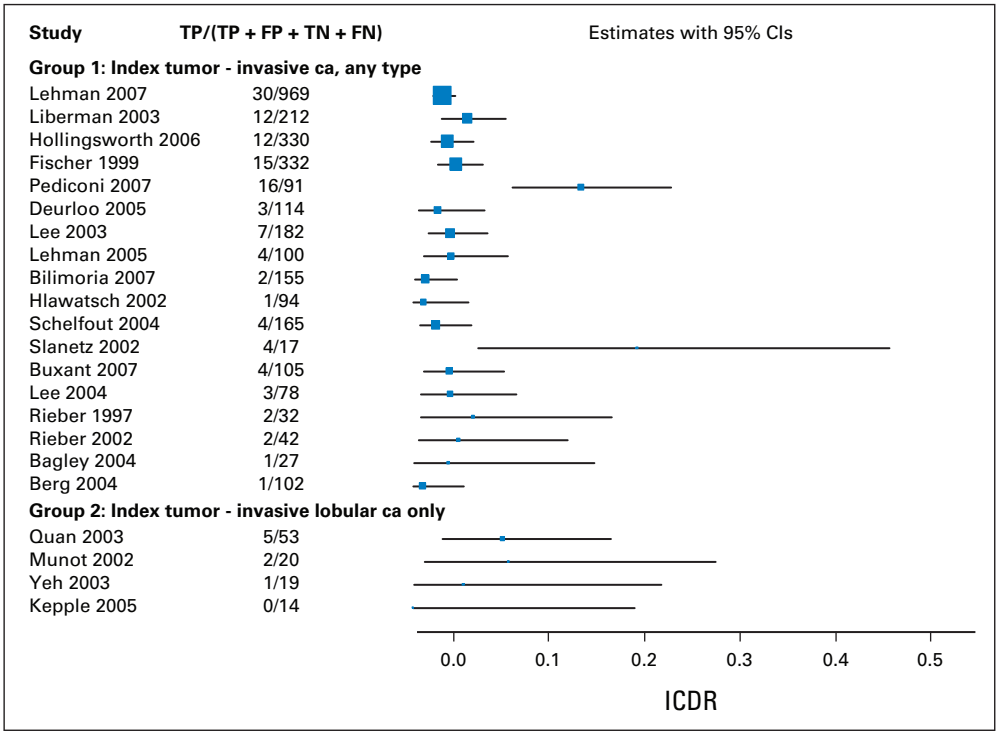

Fig 2. Magnetic resonance imaging (MRI) of the contralateral breast in women with newly diagnosed breast cancer (ca): estimates of incremental cancer detection rate (ICDR). Studies are ordered according to the number of test positives (suspicious contralateral lesions [true positives {TPs} plus false positives {FPs}]).

histology to verify all or nearly all MRI-positive lesions; therefore, estimates of detection rates and PPV can be validly quantified (as shown in our summary estimates). However, few studies ascertained outcomes in subjects with negative contralateral MRI,[7,11,13,20,23] so we were unable to estimate sensitivity and specificity. The finding of cancer in 11.9% of selected subjects testing negative on MRI who underwent mastectomy indicates MRI sensitivity is not perfect. It could be argued that verification of negative MRI scans is less critical, as these patients receive no change in management. Even so, optimal study design would include an adequate reference standard in all patients. In this setting, clinical follow-up may be a more appropriate reference standard for the identification of clinically relevant disease after a negative MRI than mastectomy.

Quality appraisal showed that few studies included a truly consecutive cohort of women with newly diagnosed breast cancer, suggesting that the results from these primary studies may only apply to selected women. Even in studies that have reported consecutive series, women were included on the basis of prerequisite study criteria, so there is some concern about generalizability to women with newly diagnosed breast cancer. For example, the study by Pediconi et al[11] reported CBC in 18% of a group of so-called consecutive women. The prevalence of CBC in this study is questionable and may not truly represent an accurate estimate of CBCs in a consecutive series of patients presenting with a unilateral breast cancer. Clinicians are therefore recommended to interpret ICDR with caution, because our estimates of ICDR may be affected by selection bias and are likely to have overestimated MRI cancer detection yield. The PPV and ratio of TP to FP detection, however, are less prone to such bias.

Our regression modeling did not identify significant associations between pooled estimates and study design or other predefined variables, with the exception of a significant association between PPV and number of test positives (total TP and FP) in each study. This suggests that the larger studies, in terms of MRI-positive results (these were generally but not consistently the studies with the largest number of subjects), yielded a lower PPV. We also found that the ICDR for MRI was not significantly associated with type of baseline imaging: studies specifying mammography only had a median ICDR of 3.9%, and those specifying mammography with ultrasound had a median ICDR of 3.1%. It is possible that studies using ultrasound in some but not all cases may have stated mammography as the primary baseline test, which would underestimate detection with ultrasound (and thus overestimate the ICDR of MRI). The PPV, however, was associated with type of baseline imaging, being higher for studies specifying mammography with ultrasound (PPV of 57.0%) than those using mammography only as baseline imaging (31.0%). From a clinical perspective, these data raise the possibility that the inclusion of ultrasound with mammography in imaging the contralateral breast, although not significantly increasing ICDR, assists the radiologist in the interpretation of MRI-detected lesions, leading to fewer FP MRI results (increased PPV).

The clinical value of MRI detection of (otherwise occult) cancer in the contralateral breast is difficult to judge. Few studies have reported complete data on tumor characteristics, and fewer have reported the impact of MRI findings on patient management in all cases. There is lack of clarity about why mastectomy was performed in some patients in whom no diagnosis was established before surgery. Faced with the news that there is an abnormality in the opposite breast, a patient may request mastectomy in fear (or haste) rather than undergo further investigation to establish a preoperative diagnosis. When provided, the data on tumor features are consistent with detection of early-stage disease (carcinoma in situ or stage pT1) in the vast majority of cases. However, the high percentage of DCIS (35%) raises the possibility that some of the additional MRI-only detected lesions are of low malignant potential, and treatment of these lesions at this early

Table 2. Characteristics of Contralateral Breast Cancers Detected on MRI Only: Tumor Histology, Size, and Stage

First Author and Year	No. of Patients	Cancers Detected on MRI Only*	Total Cancers in Study	Tumor Histology Type				Tumor Size (mm)		Tumor Stage	No. of Cases	Characteristics of MRI-Occult (FN) Cancers
				Pure DCIS	IDC ± DCIS	ILC	Other Invasive	Median or Mean	Range			
Group 1: index tumor-invasive cancer, any type												
Lehman 2007[7]	969	30	33	12	12	4	2 (tubular)	All tumors combined, 11	1-42	Tis	12	3 cases DCIS, size 1 mm, 3 mm, 4 mm; BIRADS 1 or BIRADS 3 MRI
										T1	17	
										T2	1	
										N (invasive only)		
										Nx	3	
										nN0	15	
Liberman 2003[14]	212	12	12	6	4	1	1 (mixed IDC/ILC)	Tumor type NR				N/A
								5†	1-10			
Hollingsworth 2006[16]	330	12	14	1	9	2	2 invasive cancers, type nr	NR		NR		2 cases ILC, size not reported
Fischer 1999[21]	332	15	15	3	9	2	1 (mucinous)	DCIS 12	8-12	Tis	3	N/A
								IDC 10	4-16	T1	14	
								ILC 8	8			
								Mucinous 8 mm	1 case			
Pediconi 2007[11]	91	16	16	10	4	2	0	DCIS 5	4-8	Tis	10	N/A
								IDC 10	8-14	T1	6	
								ILC 11	7-15			
Lee 2003[9]	182	7	7	4	3	0	0	DCIS 2	1-25	Tis	4	N/A
								IDC 6	1 case	T1	3	
								DCIS/IDC mixed 7	3-10			
Lehman 2005[12]†	100	4	4	0	2	0	2 (mixed IDC/ILC)	IDC 16	14-17	T1	4	N/A
								Mixed IDC/ILC 11	8-14			
Hlawatsch 2002[24]	94	1	1	1	0	0	0	DCIS 10 mm	1 case	Tis	1	N/A
Slanetz 2002[18]	17	4	4	0	2	6	1	NR‡	6-50			N/A
Lee 2004[13]	78	3	3	2	1	0	0	NR		NR		N/A
Rieber 1997[22]	32	2	2	1	1	0	0	NR		NR		N/A
Rieber 2002[17]†	42	2	2	0	2	0	0	NR				N/A
Bagley 2004[19]	27	1	1	0	1§	0	0	NR		NR		N/A
Group 2: index tumor-invasive lobular carcinoma only												
Quan 2003[28]	53	5	5	2	2	1	0	NR		1/3 invasive cancer node positive		N/A
										pN1mi	1	
										pN0	2	
Yeh 2003[29]	19	1	1	NR	NR	NR	NR	Type NR		T2	1	N/A
								35	1 case			

NOTE. Studies are ordered according to the number of test positives (suspicious contralateral lesions [true positives plus false positives] detected on MRI).
Abbreviations: MRI, magnetic resonance imaging; FN, false negative; DCIS, ductal carcinoma-in-situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; BIRADS, Breast Imaging Reporting and Data System; N/A, not applicable; NR, not reported.
*Total cancers in study; includes MRI-detected cancers (true positives) and false negatives (FNs).
†Size reported for five of 12 cases only.
‡Includes five contralateral cancers suspected on conventional assessment.
§Patient with two separate contralateral cancers (IDC and DCIS); considered as IDC in calculations.

stage may add little to long-term patient outcomes. Further information on the histologic grade of the MRI-detected DCIS would be valuable, because DCIS has a variable natural history partly dependant on grade.[33] Although the detection of DCIS is an inherent part of population breast screening, it is argued that (1) when it represents a large proportion of the extra detected cancers on MRI, it is unclear whether this will have the same benefit as shown for population mammographic screening, and (2) any potential benefit from this early detection is more uncertain in the scenario of women whose prognosis is largely and primarily determined by an existing ipsilateral invasive cancer.

In addition, contemporary use of effective systemic therapies (chemotherapy and endocrine therapy, including aromatase inhibitors) in the treatment of ipsilateral invasive cancer may prevent progression of undetected early (in situ or invasive) cancer in the contralateral breast so that it never becomes clinically evident.[34] In fact, the true rates of CBC in patients who do not have an MRI are concordant with this perspective.[34,35] We report a pooled estimate for

Table 3. Management of the Contralateral Breast in Women With Newly Diagnosed Breast Cancer (including cancers detected on MRI only*)

First Author and Year	No. of Patients	MRI Positive	FP	TP	Cancers Detected (TP + FN)	Management of MRI-Detected Contralateral Cancers	Contralateral Mastectomy: Reason for Surgery and Histology Results†			
							No. of Mastectomies Reported	Cancer Treatment (proven preoperative cancer)	Diagnosis (positive MRI but no preoperative diagnosis)	Prophylactic (negative MRI)
Lehman 2007[7]	969	135	105	30	33	NR	At least 3 (not reported for all cases)	NR	0	At least 3 (3 malignant histology; 1 × BIRADS-3, 2 × BIRADS-1)
Liberman 2003[14]	212	61	49	12	12	NR	12 (12 of 223 had mastectomy (may include some of the 11 excluded from analysis)	NR	NR	NR
Hollingsworth 2006[16]	330	36	24	12	14	NR	40	11 (preoperative diagnosis cancer)	1 (benign)	28 (2 with malignant histology had FN MRI)
Fischer 1999[21]	332	30	15	15	15	14 breast conservation, 1 mastectomy	NR	1	NR	NR
Lee 2003[9]	182	15	8	7	7	NR	8	2	0	6 (all benign histology)
Lehman 2005[12]	100	11	7	4	4	NR	At least 1 (not reported for all cases)	NR	1 (benign)	NR
Bilimoria 2007[15]	155	7	5	2	2	NR	At least 3 (not reported for all cases)	NR	3 (all benign)	NR
Buxant 2007[10]	105	4	0	4	4	2 breast conservation 2 mastectomy	2	2	0	0
Lee 2004[13]	78	3	0	3	3	3 mastectomy (all 3 cases with contralateral cancer had bilateral mastectomy)	3	2 (preoperative diagnosis of cancer)	1 (B3 lesion: ADH on preoperative biopsy; DCIS on excision histology)	0
Rieber 1997[22]	32	3	1	2	2	2 mastectomy for cancer (plus 1 mastectomy for FP MRI detection)	3	0	3 (2 malignant, 1 benign)	0
Kepple 2005[26]	14	1	1	0	0	N/A	6	0	1 (B3 lesion: ADH on preoperative biopsy; LCIS on excision histology)	5 (all benign histology)
Total	2,509	306	215	91	96		81*	18*	10*	42*

NOTE. Studies are ordered according to the number of test positives (suspicious contralateral lesions [true positives plus false positives] detected on MRI).
Abbreviations: MRI, magnetic resonance imaging; FP, false positive; TP, true positive; FN, false negative; NR, not reported; BIRADS, Breast Imaging Reporting and Data System; B3, borderline lesion of uncertain malignant potential[32]; ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ; N/A, not applicable; LCIS, lobular carcinoma in situ.
*Numbers reported in the series; individual columns may not add up to total as a result of missing data in reports of studies and incomplete reporting on surgical management.
†Table includes data for group 1 studies only (index tumor: invasive cancer, any type); group 2 studies (index tumor: invasive lobular carcinoma only) did not report management data.

ICDR of 4.1%. MRI used to screen for CBC at initial diagnosis therefore does lead to earlier detection of some or many of the cancers that would otherwise be detected by standard mammographic and clinical surveillance of breast cancer survivors or remain clinically silent.[36] Cumulative incidence rates for metachronous CBC after 10 years of follow-up are reported in contemporary series to be less than 5%,[34,35] approximating an absolute incidence of 0.4% per annum. Furthermore, the only study to report on long-term outcomes in women having preoperative MRI found no significant difference in the 8-year rates of CBC relative to women who did not have preoperative MRI.[5]

Surgical management of MRI-detected CBC was incompletely described in the majority of studies. In some studies, contralateral mastectomy was performed as often as or even more often than breast conservation, despite the dominance of small or early-stage tumors. Of particular concern is the suggestion of a trend in some series for patients to undergo bilateral mastectomy without biopsy when a suspicious contralateral lesion is identified on MRI. It is acknowledged that some of these women may be at high genetic risk of contralateral cancer, and this may have influenced their decision. It is also possible that these women, having already undergone the distress of investigation to diagnose the ipsilateral cancer, may have chosen to undergo bilateral mastectomy rather than go through the anxiety of further investigation of the contralateral breast, which may also possibly delay definitive surgery. It is also possible that women (and their treating clinicians) are placing excessive confidence in the ability of MRI to accurately distinguish benign from malignant lesions. The majority of

women with suspicious lesions on MRI had FP tests; it is therefore essential that these lesions are investigated, as it is impossible to have an informed discussion of the value of contralateral mastectomy without histologic confirmation of the nature of the lesion. It is essential that units performing MRI have well-defined protocols to deal with contralateral lesions, including immediate access to second-look ultrasound and image-guided biopsy. If this is unavailable and there is concern that an unacceptable delay in treatment of the ipsilateral breast will result, both lesions may be surgically excised, and further management options, including contralateral mastectomy, can be discussed with the benefit of detailed histologic information in a less rushed postoperative consultation.

We neither advocate nor reject the application of MRI in this setting; however, clinicians using MRI in their assessment should inform women of the risks, benefits, and the limited ability of MRI to accurately differentiate lesions. When lesions suggestive of abnormality are found on preoperative MRI screening of the contralateral breast, they must undergo biopsy before definitive surgery. We point out that none of the studies of MRI screening for CBC considered quality-of-life aspects, and this warrants further evaluation.

In conclusion, although there may be benefit in detecting clinically significant synchronous CBC to allow both tumors to be treated at the same time, evidence reported in this review calls for debate on the value of MRI screening of the contralateral breast. MRI's ability to identify a substantial proportion of additional occult contralateral malignancies should be balanced against its limited performance in distinguishing benign from malignant lesions. The large proportion of in situ cancers among MRI-detected malignant lesions raises the issue of whether detection of such lesions improves long-term outcomes and whether many of these lesions are clinically significant. This is a particularly relevant issue because the current management of ipsilateral invasive breast cancer is likely to include systemic therapies that may inhibit the progression of some CBCs. The potential harms of added anxiety, investigation, and possible delay in surgery that MRI screening of the contralateral breast and subsequent work-up may cause must be considered and acknowledged. These require further evaluation.

A randomized controlled trial (RCT) would provide answers to the questions raised in this review. Such a trial, however, would need to include a large number of consecutively treated patients and would require long-term data on recurrence and contralateral events. Given the substantial practical barriers to conducting this type of study, it may be more feasible to integrate this evaluation into RCTs primarily designed to investigate the impact of preoperative MRI on local staging of the ipsilateral breast, because the need for high-level evidence for the latter is now well-recognized.[4] The initial results from the United Kingdom–based RCT of preoperative MRI demonstrate both the importance and feasibility of conducting RCTs in this setting.[37] This RCT of MRI in women with newly diagnosed cancer was designed to evaluate the effect on initial surgical outcomes and has shown that MRI does not reduce re-excision rates as had been hypothesized.[37] The possibility of collecting data from RCTs powered to provide evidence for the ipsilateral breast to determine the impact of MRI on the incidence of CBC over the initial 5 years (or longer) of routine follow-up from diagnosis therefore deserves further consideration. MRI screening for CBC is already introduced into practice in some settings, so for the present clinicians might consider the information and estimates presented here to guide recommendations and discussions with patients about the value of pretreatment MRI in women with breast cancer.

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

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