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

Brennan ME, Houssami N, Lord S, Macaskill P, Irwig L, Dixon JM, Warren RM, Ciatto S

CRD summary
This review found that magnetic resonance imaging detected contralateral lesions in a substantial proportion of women with a new diagnosis of invasive breast cancer, but did not reliably distinguish benign from malignant findings. These conclusions accurately reflected the data reported, but should be interpreted cautiously, given the limited scope of the searches and weaknesses in the selection process.

Authors' objectives
To assess the incremental detection yield and diagnostic accuracy of magnetic resonance imaging (MRI) to screen the contralateral breast of women with a new diagnosis of invasive breast cancer.

Searching
MEDLINE was searched for articles from inception to April 2008 and the search terms were reported in an online appendix. Additional studies were sought by screening the bibliographies of included studies, by contact with experts, and by review of the database of a related meta-analysis of MRI for staging of breast cancer. Studies that were not in English were excluded.

Study selection
Studies of preoperative MRI in women with suspected or proven invasive breast cancer were eligible for inclusion, provided they reported the numbers of true-positive and false-positive results for the contralateral breast. Studies were excluded if they did not verify most of the abnormal MRI results by histology. Because the review aimed to detect the incremental benefit of MRI, participants with known contralateral breast cancer, diagnosed by clinical examination or by other imaging techniques (38 participants, 10 studies), were excluded. Participants with benign index lesions (188 participants, five studies) were also excluded.

All studies performed contrast-enhanced MRI with a dedicated breast coil and all, except three, used morphologic and kinetic features to evaluate the lesions. The majority of studies did not verify the absence of cancer for negative MRI results; five studies used clinical and/or imaging follow-up at one year to confirm negative results. The mean or median age of participants, where reported, ranged from 48 to 62 years. Where specified, the baseline imaging consisted of mammography or mammography plus ultrasound.

Studies were screened for inclusion by one reviewer and, in cases of uncertainty, a second reviewer was consulted (reported in the online appendix).

Assessment of study quality
The authors stated that the included studies were assessed based on the standards for test accuracy, adapted for breast cancer staging, and these included methodological and clinical variables. The criteria were reported in the online appendix and included study characteristics (design and population spectrum), methodology (consecutive recruitment, adequacy of reference standard, application of reference standard to all participants), and clinical variables (baseline imaging and MRI interpretation).

Quality assessment was performed independently by two reviewers and disagreements were resolved by consensus.

Data extraction
Data were extracted on the numbers of true-positive, false-negative, false-positive, and true-negative results of MRI scans. The positive predictive value and incremental cancer detection rate, with 95% confidence intervals, were
calculated for each study. Estimates of sensitivity and specificity were not computed because most studies did not verify the absence of disease in women with a negative MRI result. Where reported, the data on tumour characteristics and surgical management were also extracted.

Data were extracted independently by two reviewers and disagreements were resolved by consensus.

**Methods of synthesis**
Random-effects logistic regression models were used to derive the summary estimates of positive predictive value and incremental cancer detection rate, with 95% confidence intervals, and to investigate whether variation in the positive predictive values, incremental cancer detection rates, or any MRI detection, was associated with the study design or quality criteria. The distribution of the random effects was checked for each model to ensure that normality assumptions were met. Pooled estimates were not reported for studies of patients with invasive lobular cancer as their index lesion, as this group consisted of only four studies with small numbers of patients.

**Results of the review**
Twenty-two studies (3,253 participants) were included. Eleven studies were prospective, 10 were retrospective, and one did not report the study design. Quality appraisal showed that few studies included a consecutive cohort of women with newly diagnosed breast cancer (an appropriate spectrum of patients), suggesting that the results from these studies might not be generalisable to routine practice.

Eighteen studies reported 123 MRI-detected contralateral breast cancers and six false-negative results, in 3,147 women with index lesions that included invasive ductal, invasive lobular, and other invasive tumours. The tumour types were reported for 114 cases; 40 were ductal carcinoma in situ and 74 were invasive cancers. The median tumour size was 5.5mm (range 1 to 25) for 18 ductal carcinoma in situ and 9mm (range 3 to 17) for 25 invasive tumours. The pooled estimate of positive predictive value was 47.9% (95% CI 31.8 to 64.6). The positive predictive value did not vary with study quality nor cancer prevalence, but it did decrease with an increasing number of positive tests in a study (p=0.024) and it was associated with the baseline imaging technique, being higher for studies using mammography with ultrasound than for those using mammography alone (p=0.042). The pooled estimate of the incremental cancer detection rate was 4.1% (95% CI 2.7 to 6.0) and this was not significantly associated with baseline imaging.

Four studies, of 106 women with only invasive lobular cancer as the index lesion, reported eight MRI-detected contralateral breast cancers and no false-negative results. The tumour type and size were not reported. Eleven studies described the management of contralateral breast cancer and indicated that mastectomy was frequently used, for various reasons.

**Authors’ conclusions**
MRI detected contralateral lesions in a substantial proportion of women, but did not reliably distinguish benign from malignant findings. The relatively high incremental cancer detection rates might be due to selection bias and/or over detection.

**CRD commentary**
This review addressed a clearly stated question, defined by appropriate inclusion criteria. The search strategy was limited to a single bibliographic database and no attempts to identify unpublished studies were described. It is therefore possible that relevant studies were omitted and there is a possibility of publication bias. Only English-language studies were included, creating the possibility of language bias. Measures to reduce error and/or bias were applied throughout the review process and reported in an online appendix. Relevant details of the individual studies were reported and the meta-analytic methods were appropriate.

The authors’ conclusions accurately reflected the data presented, but should be interpreted cautiously, given the potential for missing data and the limitations in the study selection process.

**Implications of the review for practice and research**
Practice: The authors stated that the ability of MRI to identify additional occult contralateral malignancies should be balanced against its limited performance in distinguishing benign from malignant lesions, and that women must be informed of the uncertain benefit and potential harm of MRI screening, including additional investigations and surgery. When lesions suggestive of abnormality are found from preoperative MRI screening of the contralateral breast, biopsy confirmation is needed before surgery.

Research: The authors suggested that a randomised controlled trial (RCT) would provide definitive answers on the relative benefits and harms of MRI screening for contralateral breast cancer. They further stated that, because of the requirement for long-term data on recurrence and contralateral events, the possibility of using data from RCTs primarily designed to investigate the impact of preoperative MRI on local staging of the ipsilateral breast, should be considered.

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