A systematic review of the effectiveness of magnetic resonance imaging (MRI) as an addition to mammography and ultrasound in screening young women at high risk of breast cancer


CRD summary
This review found that adding breast magnetic resonance imaging (MRI) to conventional screening results in a very sensitive strategy for the early detection of breast cancer in young high-risk women. It is unclear to what extent high-risk young women receive the same benefits from early detection and treatment of MRI-detected cancers. These finding are likely to be reliable but there is a possibility of publication bias.

Authors' objectives
To determine the value of adding magnetic resonance imaging (MRI) to mammography with or without ultrasound and clinical breast examination (CBE) for screening young women at high risk of breast cancer.

Searching
MEDLINE, PREMEDLINE, EMBASE, the Cochrane Library and websites of health technology assessment agencies were searched from inception to March 2007; the search terms were reported. Only English language publications were sought.

Study selection
Study designs of evaluations included in the review
Diagnostic accuracy and comparative studies were eligible for inclusion. All of the included studies were prospective.

Specific interventions included in the review
Studies that evaluated the addition of MRI to mammography with and without ultrasound and/or CBE were eligible for inclusion. Studies that compared the addition of MRI to conventional imaging were also eligible for inclusion. MRI was performed at 1 to 1.5 Tesla in the included studies.

Reference standard test against which the new test was compared
Studies in which the reference standard was histology for a positive result and, as the minimum, a consensus of all tests for a negative result were eligible. In the included studies, the reference standards for negative test results included 6- to 12-month follow-up with CBE and or ultrasonography, or a combination of tests. Follow-up time ranged from 1 to 7 years.

Participants included in the review
Studies that assessed asymptomatic high-risk women were eligible for inclusion. The participants in the included studies were almost all women, with the exception of one study that included one man. Participants had a prior history of breast cancer, were carriers or had first-degree relatives with the BRCA1/BRCA2 genes, or had a strong family history of breast and/or ovarian cancer.

Outcomes assessed in the review
Studies that provided data on sensitivity and specificity were eligible for inclusion. Studies that provided data on prognostic tumour characteristics of invasive cancers detected, interval cancer rates, or relevant patient outcomes were also eligible for inclusion.

Assessment of study quality
Two reviewers independently assessed study quality using the Quality Assessment of Diagnostic Accuracy Studies
(QUADAS) criteria. Studies that fulfilled all QUADAS criteria were classified as high quality, while those that were not conducted prospectively or that did not meet the criteria relating to reference standard or test interval were classified as low quality; all other studies were classed as fair quality.

**Data extraction**

Data were extracted on cancer detection rates at the first and subsequent screening rounds, number of additional cancers detected, false-positive patient recall, benign biopsy rates and 2x2 tables of test performance on a per patient basis. One reviewer extracted the data and a second reviewer checked the extraction. The sensitivity, specificity and incremental sensitivity were calculated for test strategies with and without MRI. Relative risks and absolute risk differences of false-positive recall and benign biopsy rates, together with 95% confidence intervals (CIs), were calculated for the addition of MRI versus conventional testing alone.

**Methods of synthesis**

How were the studies combined?

The pooled sensitivity, specificity and incremental sensitivity were calculated, together with 95% CIs, using DerSimonian and Laird random-effects models.

How were differences between studies investigated?

Heterogeneity was assessed statistically using the chi-squared test.

**Results of the review**

Five studies provided data on accuracy (n=2,059), of which four (n=1,553) also reported on false-positive recall and benign biopsy rates.

Accuracy (5 studies).

The sensitivity of MRI combined with conventional tests ranged from 86 to 100%, and the specificity ranged from 77 to 96%. The sensitivity of mammography alone ranged from 25 to 59%, and from 49 to 67% for mammography combined with ultrasound with or without CBE.

Three studies assessed MRI added to mammography alone: the pooled sensitivity was 94% (95% CI: 86, 98) and the pooled incremental sensitivity was 58% (95% CI: 47, 70). There was no evidence of heterogeneity (p=0.84).

Three studies assessed MRI added to mammography plus ultrasound: the pooled incremental sensitivity was 44% (95% CI: 27, 61).

Two studies assessed MRI added to mammography plus ultrasound plus CBE: the respective incremental sensitivities were 31 and 33%.

Additional cancer yield (4 studies).

The additional cancer yield in women with negative findings based on conventional tests ranged from 10 to 24 additional cancers detected per 1,000 screening rounds. Four studies reported that mammography detected cancers not detected by MRI, and one also reported that ultrasound detected cancers not detected by MRI or mammography. CBE detected cancers that were not found by mammography or ultrasound, but all cancers found by CBE were also detected by MRI.

Test recall rates (3 studies).

The risk of being recalled for further investigation where cancer was subsequently excluded was 3 to 5 times greater with MRI combined with mammography than with mammography alone; this is equivalent to 71 to 74 additional false-positive recalls per 1,000 screening rounds. The relative risk of undergoing a benign percutaneous biopsy as a result of the addition of MRI ranged from 1.22 to 9.50; this is equivalent to 7 to 46 additional benign biopsies per 1,000 screening rounds.
Stage shift in cancer detection.

The size of the tumours detected with the addition of MRI was similar to those detected without MRI.

**Authors' conclusions**
The addition of breast MRI to conventional screening results in a very sensitive strategy for the early detection of breast cancer in young high-risk women. MRI may increase false-positive findings and hence patient recall rates; the size of this trade-off is less certain. It is unclear to what extent high-risk young women receive the same benefits from early detection and treatment of MRI-detected cancers.

**CRD commentary**
This review addressed a focused question that was supported by clearly defined inclusion criteria. The search was adequate but only published English language studies were eligible, so the review may be subject to language and publication bias. A detailed quality assessment was conducted using appropriate criteria. Appropriate steps were taken to minimise error and bias in the review process. The methods used to pool the studies were acceptable, although the use of more statistically robust models to pool accuracy data would have been preferable.

The accuracy section of the review focused on sensitivity, with little information reported on specificity; it appears that this was as a result of greater heterogeneity in specificity and how false-negative results were verified and the fact that not all studies provided data on specificity. Some further analysis of specificity and the investigation of reasons for heterogeneity may have helped determine the extent of false-positive MRI findings. The authors' conclusions are supported by the data presented but should be interpreted with some degree of caution given the possibility of publication bias, especially given the small number of included studies.

**Implications of the review for practice and research**
Practice: The authors stated that if a policy of using MRI to screen young high-risk women is adopted, it would be essential to provide counselling and information about the uncertainty surrounding potential findings and the higher risk of false-positive findings.

Research: The authors stated that evidence is needed about the effects of early detection of breast cancer on mortality in young women at high-risk of breast cancer. Due to problems in conducting a randomised controlled trial (RCT) for this outcome, an RCT could compare screen-detected tumour stage and interval cancer rates (shorter term outcomes) for screening strategies with and without MRI.

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