MAGNETIC RESONANCE IMAGING FOR THE EARLY DETECTION OF BREAST CANCER IN WOMEN AT HIGH RISK:

A SYSTEMATIC REVIEW OF THE EVIDENCE

PREPARED BY THE NATIONAL BREAST CANCER CENTRE

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DEPARTMENT OF HEALTH AND AGEING

Magnetic resonance imaging for the early detection of breast cancer in women at high risk: A systematic review of the evidence

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Acc	Accuracy
ANZHSN	Australia and New Zealand Horizon Scanning Network
AUC	Area under curve
BI-RADS	Breast imaging reporting and data systems
BSE	Breast self-examination
CBE	Clinical breast examination
CE	Contrast-enhanced
CI	Confidence interval
DCIS	Ductal carcinoma *in situ*
FDA	Food and Drug Administration
HTAi	Health Technology Assessment International
LCIS	Lobular carcinoma *in situ*
M	Mammography
MARIBS	Magnetic resonance imaging breast screening
MRI	Magnetic resonance imaging
MRISC	Magnetic resonance imaging screening
NK	Not known
NLR	Negative likelihood ratio
NPV	Negative predictive value
PLR	Positive likelihood ratio
PPV	Positive predictive value
ROC	Receiver-operator characteristic
Sens	Sensitivity
Spec	Specificity
US	Ultrasound
XRM	X-ray mammography

EXECUTIVE SUMMARY

The research question addressed by the systematic review was:

Does the use of magnetic resonance imaging (MRI) instead of, or in addition to, other modalities improve the diagnosis of breast cancer during screening of asymptomatic women at high risk of breast cancer?

Where possible, the review also investigated the impact of age and risk factor subgroup upon the relative diagnostic performance of MRI. This review did not relate to the role of MRI for the diagnosis of breast cancer in symptomatic women. The review included common screening interventions currently used by high-risk asymptomatic women as the comparator (ie clinical examination, ultrasound or mammography), but investigated MRI's role as an alternative to, or an addition to, other screening techniques.

THE POPULATION

Women were considered to be at potentially higher risk of developing breast cancer if they met at least one of the following criteria:[1]

- past breast or ovarian cancer, including a diagnosis of ductal carcinoma *in situ* (DCIS) or lobular carcinoma *in situ* (LCIS)
- two first- or second-degree relatives on one side of the family diagnosed with breast or ovarian cancer **plus** one or more of the following features on the same side of the family:
    - additional relative(s) with breast or ovarian cancer
    - breast cancer diagnosed before age 40
    - bilateral breast cancer
    - breast **and** ovarian cancer in the same woman
    - Ashkenazi Jewish ancestry
    - breast cancer in a male relative
- one first- or second-degree relative diagnosed with breast cancer at age 45 or younger **plus** another first- or second-degree relative on the same side of the family with sarcoma (bone/soft tissue) at age 45 or younger
- member of a family in which the presence of a high-risk breast cancer gene mutation has been established
- at potentially high risk for ovarian cancer (see Appendix A)
- evidence of atypical hyperplasia.

THE TECHNOLOGY

MRI involves the use of a strong magnetic field to allow the detailed visualisation of tissues within the body. The superconducting magnet is the most common type of magnet used in MRI. The magnetic field is generated by passing a current through coils of wire which are bathed in liquid helium at –269.1 °C. The main magnet creates a stable magnetic field while three gradient magnets (which are very low strength) are used to create a variable field. These three gradient magnets are what allow the MRI scanner to image in three different planes (axial, sagittal and coronal) while the patient remains in one position. In comparison, computed tomography (CT) scanning is limited to the axial plane; while with x-ray, patients have to be continually moved to obtain images in different planes. For the purpose of performing MRI on breast tissue, it is best that a dedicated breast coil is used. This improves comfort for the patient, as well as the quality of the images obtained.

The main benefits of MRI relate to the quality and resolution of the images that can be obtained (including the ability to image in different planes), and the fact that the contrast materials used in MRI have a very low incidence of side effects. The radiographer and radiologist's previous experience with breast MRI has considerable impact upon the quality of the images and their interpretation, and therefore adequate training is required.

METHODOLOGY

The current literature search covered the period up to July 2005, and encompassed Medline and EMBASE (via EMBASE.com); Cochrane Library; and international HTA agencies. After the removal of duplicate citations, and addition of further citations sourced from the reference lists of recent key publications, a total of 417 unique citations remained. After application of the predefined inclusion/exclusion criteria, a total of 11 articles were included in the review (six systematic reviews and five articles presenting results of four original studies).

Methodological information relating to the study population, the nature of the diagnostic intervention and the definition of outcomes was extracted from the included studies. Particular attention was paid to methodological factors known to influence the quality of diagnostic and screening studies.

RESULTS

A variety of studies had been included in the six identified systematic reviews. The majority had small patient numbers and differing definitions of high-risk women; these did not meet the inclusion criteria for the current review. Nevertheless, the results suggested that MRI alone had higher sensitivity and lower specificity than mammography alone, in a high-risk population.

The final reports of several large original studies[2–4] have recently been published and therefore were not included in the existing systematic reviews. The results of these original studies were considered together with one eligible original study identified via the existing systematic reviews.[5] Three of the four studies were of a prospective design, and all included women who received both MRI and mammography screening. The fourth study was retrospective, and only 75 of the cohort received both MRI and mammography. One study specifically included only women who were known *BRCA1/2* mutation carriers. The other three studies included a wider population of women considered to be at high risk (eg relatives who were known mutation carriers, family history of breast cancer). All four studies presented results relating to the

diagnostic performance of MRI compared with mammography. One study presented quality of life data. None of the studies were designed to investigate survival.

All four studies used a scoring system for the level of certainty of diagnosis, however this was ultimately dichotomised to calculate diagnostic performance. All scoring systems were the same as, or equivalent to, that of the American College of Radiology Breast Imaging Reporting and Data Systems (BI-RADS). The sensitivity and specificity results are highly dependent upon the cut-point used for the dichotomisation (specifically whether BI-RADS 3 'probably benign' is categorised as positive or negative; and the categorisation of BI-RADS 0 'equivocal, more imaging required').

When compared to mammography alone, the pooled results of the original studies suggested that MRI alone was approximately twice as sensitive (77% vs 40%) and <10% less specific (87% vs 94%), when used for screening women at high risk of developing breast cancer. This was the case in all women considered to be at high risk and the subgroup of women who had *BRCA1* or *BRCA2* mutations.

The addition of MRI to mammography for the screening of women at high risk of breast cancer resulted in different diagnostic performance, depending upon the definition of a positive result. When a positive result was defined as either test being positive, the sensitivity was approximately 94%, comparing favourably with mammography alone (~40%). Understandably, combining the MRI and mammography tests in this way does result in a sacrifice in specificity (77% vs 94%). Results were similar between all women at high risk and the subgroup of women with *BRCA1/2* mutations. When a positive result depended upon both tests being positive, the resulting sensitivity fell to 23% for all women at high risk and 56% for the subgroup of women with *BRCA1/2* mutations. For this definition of a positive result, specificity was high (98% in all women at high risk and 90% in the subgroup of women with *BRCA1/2* mutations).

In general terms, the findings of the current review are similar to those of the existing systematic reviews; that is, MRI alone shows a higher sensitivity and slightly lower specificity when compared with mammography alone. The inclusion of larger, well-designed studies in the current review allows this conclusion to be drawn with more certainty. It had also been suggested previously that MRI may have a particular role among younger women at higher risk of developing breast cancer. However, the current systematic review was unable to identify evidence that specifically supports the targeting of MRI screening to younger women, relative to high-risk women in general.

Studies of MRI screening for women at high risk of breast cancer are limited to the assessment of the diagnostic performance of MRI versus other screening modalities. To date studies have not evaluated whether improvements in sensitivity translate into improved long-term health outcomes for patients such as survival.

INTRODUCTION

The aim of this systematic review was to summarise the evidence relating to the value of **magnetic resonance imaging (MRI) in screening asymptomatic women considered to be at high risk of developing breast cancer.** In Australia, mammography is the imaging modality typically used in this setting.

THE POPULATION

Women were considered to be at potentially higher risk of developing breast cancer if they met at least one of the following criteria:[1]

- past breast or ovarian cancer, including a diagnosis of ductal carcinoma *in situ* (DCIS) or lobular carcinoma *in situ* (LCIS)
- two first- or second-degree relatives on one side of the family diagnosed with breast or ovarian cancer **plus** one or more of the following features on the same side of the family:
    - additional relative(s) with breast or ovarian cancer
    - breast cancer diagnosed before age 40
    - bilateral breast cancer
    - breast **and** ovarian cancer in the same woman
    - Ashkenazi Jewish ancestry
    - breast cancer in a male relative
- one first- or second-degree relative diagnosed with breast cancer at age 45 or younger **plus** another first- or second-degree relative on the same side of the family with sarcoma (bone/soft tissue) at age 45 or younger
- member of a family in which the presence of a high-risk breast cancer gene mutation has been established
- at potentially high risk for ovarian cancer (see Appendix A)
- evidence of atypical hyperplasia.

THE TECHNOLOGY

MRI involves the use of a strong magnetic field to allow the detailed visualisation of tissues within the body. The superconducting magnet is the most common type of magnet used in MRI. The magnetic field is generated by passing a current through coils of wire, which are bathed in liquid helium at –269.1 °C. The main magnet creates a stable magnetic field while three gradient magnets (which are very low strength) are used to create a variable field. These three gradient magnets are what allow the MRI scanner to image in three different planes (axial, sagittal and coronal) while the patient remains in one position. In comparison, computed tomography (CT) scanning is limited to the axial plane; while with x-ray, patients have to be continually moved to obtain images in different planes. For the purpose of performing MRI on breast tissue, it is best that a dedicated breast coil is used. This improves comfort for the patient, as well as the quality of the images obtained.

The main benefits of MRI relate to the quality and resolution of the images that can be obtained (including the ability to image in different planes), and the fact that the contrast materials used in MRI have a very low incidence of side effects. The radiographer and radiologist's previous experience with breast MRI has considerable impact upon the quality of the images and their interpretation, and therefore adequate training is required.

While MRI is generally very safe there are a number of issues which must be taken into account when considering patients for MRI:

- The magnetic field used in MRI is generally of the order of 0.5–2.0 Tesla. Due to the strength of the field, it is important that metal objects are not taken into the room with the MRI scanner, and that the patient informs the clinician/technician of any metal or other implants present within the body. Of particular concern are metallic fragments in the eye (as the eye does not form scar tissue that can hold the fragments in place), pacemakers (which can malfunction even if the patient goes near the scanner) and aneurysm clips (as movement may cause tearing of the artery).
- Being placed inside the MRI scanner can be a problem for people with claustrophobia and larger people. It should be noted that as new MRI scanners are developed, the machines per se are becoming smaller and are able to handle larger sized patients.
- The machine is very noisy. Earplugs or headphones are used to minimise the discomfort.
- Patients must remain very still for extended periods (eg 20–90 minutes) as even a slight movement can distort the image.
- While there are no known biological hazards to humans, at this stage pregnant women are generally not scanned unless the benefit exceeds any potential risk.

METHODS

The research question addressed by the systematic review was:

> *Does the use of MRI instead of, or in addition to, other modalities improve the diagnosis of breast cancer during screening of asymptomatic women at high risk of breast cancer?*

In addition, the review investigated the impact of age and risk factor subgroup upon the relative diagnostic performance of MRI, where possible. This review did not relate to the role of MRI for the diagnosis of breast cancer in symptomatic women.

For the purpose of this review the following definitions applied:

POPULATION

Asymptomatic women considered to be at a high risk of developing breast cancer due to personal or family history or presence of a genetic mutation.

TEST

Magnetic resonance imaging

Contrast-enhanced imaging using a gadolinium-chelate containing contrast agent.

COMPARATOR

Any other screening modality

Modalities commonly used for breast cancer screening include mammography, ultrasound (US) and clinical breast examination (CBE).

OUTCOMES

Diagnostic test performance

- Sensitivity (Sens) — how good is this test at identifying people who have the condition?
- Specificity (Spec) — how good is this test at correctly excluding people without the condition?
- Positive predictive value (PPV) — if a person tests positive, what is the probability that she has the condition?
- Negative predictive value (NPV) — if a person tests negative, what is the probability that she does not have the condition?
- Accuracy (Acc) — what proportion of all tests has given the correct result (ie true positive or true negative)?
- Likelihood ratio of a positive test (PLR) — how much more likely is a positive test to be found in a person with, as opposed to without, the condition?
- Likelihood ratio of a negative test (NLR) — how much more likely is a negative test to be found in a person without, as opposed to with, the condition?

- Receiver-operator characteristic (ROC) curve — what is the trade-off between sensitivity and specificity at different possible cut points of a diagnostic test? The area under the ROC (AUC ROC) curve is a measure of test accuracy.

Other outcomes

Tumour characteristics, adverse events, quality of life, survival.

LITERATURE SEARCH

A search of the medical literature identified original studies that investigated and reported the effectiveness of MRI for screening women at a high risk of breast cancer. The intention of the review was to investigate the role of MRI as an addition or alternative to other screening techniques. Therefore, to answer the review questions in an unbiased fashion, studies must have reported results for MRI screening compared with at least one of the diagnostic modalities below, in the same patients:

- mammography
- ultrasonography
- clinical breast examination.

The current literature search covered the period up to July 2005. The search strategy is presented in Appendix B. Any relevant additional papers identified from the bibliographies of included publications were also included.

Searches were conducted of the following databases/sources:

- Medline 1966 to 5 July 2005 (via EMBASE.com)
- EMBASE 1980 to 5 July 2005 (via EMBASE.com)
- Cochrane Library Issue 2 2005
- international HTA agencies (see Appendix B).

After the removal of duplicate citations, and addition of further citations sourced from the reference lists of recent key publications, a total of 417 unique citations remained. The abstracts of these citations were then assessed in accordance with the following exclusion criteria. For those citations where insufficient detail was provided in the abstract, the full paper was retrieved and assessed.

EXCLUSION CRITERIA

The following exclusion criteria were applied to the title/abstracts:

- **Not original clinical study**
  - publications not reporting the findings of one or more original clinical studies (ie non-systematic reviews, editorials, opinion pieces and letters) were excluded, as were methodological, technical, prognostic studies or animal studies.

- **Inappropriate population**
  - studies in asymptomatic women not considered to be at 'high risk'
  - studies conducted in a symptomatic or referred population rather than a screening population
  - studies conducted in men
  - studies conducted in children or adolescents.

- **Inappropriate intervention**
  - studies not involving MRI.

- **Inappropriate outcomes**
  - studies not reporting (or providing insufficient information to calculate) relevant diagnostic outcomes (sensitivity, specificity, PPV, NPV, PLR, NLR, diagnostic accuracy and diagnostic odds ratio) or other relevant outcomes (ie tumour characteristics, adverse events, quality of life, survival).

After application of the inclusion/exclusion criteria to abstracts/titles, 28 citations remained. Reasons for exclusion of citations are summarised in Table 1 and are listed for individual citations in Appendix C.

Table 1. Reasons for exclusion

Total unique publications	**Exclusion based on title/abstract N=417**
Not an original clinical study	305
Wrong patient group	64
Wrong test	13
Wrong outcomes	3
Other[a]	4
Included publications	**28**

NB. Many papers met more than one exclusion criterion. Only one was assigned in the order presented above.
[a] Reasons for classification as other included: describing protocol/study design only; duplicate data and insufficient citation details to enable identification of study.

Full articles were retrieved for the remaining 28 citations and each was assessed for inclusion in the review. In total, 11 articles were included in the review: six systematic reviews and five articles presenting results of four original studies. The citation details of the full papers assessed, and their inclusion/exclusion status, is shown in Table 2. A decision was made to exclude studies from the review if they detected less than 10 cancers, for two reasons. Firstly, diagnostic performance results based on the detection of so few cancers are potentially unreliable, and secondly, the final results of a number of large screening studies had recently been published. Brief details of the studies excluded due to the detection of less than 10 cancers are provided in Appendix D.

Table 2. Full papers assessed for inclusion and inclusion/exclusion status

Citation	Status
Australia and New Zealand Horizon Scanning Network. MRI screening for breast cancer in genetically high-risk women. Commonwealth of Australia. Canberra, May 2004.[6]	**Included. Systematic review/horizon scanning**
Blue Cross Blue Shield. Magnetic resonance imaging of the breast in screening women considered to be at high genetic risk of breast cancer. TEC bulletin (Online). 2003;20(3):12–14.[7]	**Included. Systematic review.**
Brekelmans CTM, Seynaeve C, Bartels CCM, *et al*. Effectiveness of breast cancer surveillance in *BRCA1/2* gene mutation carriers and women with high familial risk. J Clin Oncol. 2001;19(4):924–930.[8]	Excluded. Looked at screening in general. No data on MRI presented separately.
Calderon-Margalit R, Paltiel O. Prevention of breast cancer in women who carry *BRCA1* or *BRCA2* mutations: A critical review of the literature. Int J Cancer. 2004;112(3):357–364.[9]	**Included. Systematic review.**
Cilotti A, Caligo MA, Cipollini G, *et al*. Breast MR imaging screening in eight women proved or suspected to be carriers of *BRCA1&2* gene mutations. J Exp Clin Cancer Res. 2002;21 3 Suppl:137–140.	Excluded. < 10 cancers detected (see Appendix D).
Elmore JG, Armstrong K, Lehman CD, Fletcher SW. Screening for breast cancer. J Am Med Assoc. 2005;293(10):1245–1256.[10]	**Included. Systematic review.**
Gilhuijs KGA, Deurloo EF, Muller SH, *et al*. Breast MR imaging in women at increased lifetime risk of breast cancer: Clinical system for computerized assessment of breast lesions — Initial results. Radiology. 2002;225(3):907–916.	Excluded. Not assessing screening.
Hartman AR, Daniel BL, Kurian AW, *et al*. Breast Magnetic Resonance Image Screening and Ductal Lavage in Women at High Genetic Risk for Breast Carcinoma. Cancer. 2004;100(3):479–489.[11]	Excluded. < 10 cancers detected (see Appendix D).
Institute for Clinical Systems Improvement. Magnetic resonance imaging (MRI) for the detection of breast abnormalities. 2003.[12]	**Included. Systematic review.**
Irwig L, Houssami N, Van Vliet C. New technologies in screening for breast cancer: A systematic review of their accuracy. Br J Cancer. 2004;90(11):2118–2122.[13]	**Included. Systematic review.**
Kriege M, Brekelmans CTM, Boetes C, *et al*. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med. 2004;351(5):427–437+519.[3]	**Included. Original study.**
Kuhl CK, Schmutzler RK, Leutner CC, *et al*. B reast MR imaging screening in 192 women proved or suspected to be carrier of a breast cancer susceptibility gene: Preliminary results. Radiology. 2000;215(1):267–279.[14]	Excluded. < 10 cancers detected in asymptomatic patients (see Appendix D).
Leach MO, Eeles RA, Turnbull LW, *et al*. The UK national study of magnetic resonance imaging as a method of screening for breast cancer (MARIBS). J Exp Clin Cancer Res. 2002;21 Suppl 3:107–114.[15]	Excluded. Duplicate data from MARIBS study.[2]
Leach MO. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: A prospective multicentre cohort study (MARIBS). Lancet. 2005;365(9473):1769–1778.[2]	**Included. Original study.**
Lehman CD, Blume JD, Weatherall P, *et al*. Screening women at high risk for breast cancer with mammography and magnetic resonance imaging. Cancer. 2005;103(9):1898–1905.	Excluded. < 10 cancers detected (see Appendix D).
Liberman L, Morris EA, Benton CL, Abramson AF, Dershaw D. Probably benign lesions at breast magnetic resonance imaging preliminary experience in high-risk women. Cancer. 2003;98(2):377–388.[16]	Excluded. < 10 cancers detected (see Appendix D).
Morris EA, Liberman L, Ballon DJ, *et al*. MRI of occult breast carcinoma in a high-risk population. AJR Am J Roentgenol. 2003;181(3):619–626.[17]	Excluded. Wrong outcomes. Examining diagnostic performance of biopsy not MRI.

Citation	Status
Podo F, Sardanelli F, Canese R, *et al*. The Italian multi-centre project on evaluation of MRI and other imaging modalities in early detection of breast cancer in subjects at high genetic risk. J Exp Clin Cancer Res. 2002;21 Suppl 3:115–124.[18]	Excluded. < 10 cancers detected (see Appendix D).
Rijnsburger AJ, Essink-Bot, ML, Van Dooren S, *et al*. Impact of screening for breast cancer in high-risk women on health-related quality of life. Br J Cancer. 2004;91(1):69–76.[19]	**Included. Original study.**
Sim LSJ, Hendriks JHCL, Fook-Chong SMC, *et al*. Breast ultrasound in women with familial risk of breast cancer. Ann Acad Med Singapore. 2004;33(5):600–606.	Excluded. Subset of data from Stoutjesdijk study.[5]
Stoutjesdijk M, Boetes C, Jager GJ, *et al*. Magnetic resonance imaging and mammography in women with a hereditary risk of breast cancer. J Natl Cancer Inst. 2001;93(14):1095–1102.[5]	**Included. Original study.**
Tilanus-Linthorst MMA, Bartels CCM, Obdeijn AIM, Oudkerk M. Earlier detection of breast cancer by surveillance of women at familial risk. Eur J Cancer. 2000;36(4):514–519.[20]	Excluded. < 10 cancers detected (see Appendix D).
Tilanus-Linthorst MMA, Obdeijn IMM, Bartels KCM, De Koning HJ, Oudkerk M. First experiences screening women at high risk for breast cancer with MR imaging. Breast Cancer Res Treat. 2000;63(1):53–60.[21]	Excluded. < 10 cancers detected. Duplicate data from Tilanus-Linthorst *et al.* (2000a).[20]
Trecate G, Vergnaghi D, Bergonzi S, *et al*. BMRI in early detection of breast cancer in patients with increased genetic risk: Our preliminary results. J Exp Clin Cancer Res. 2002;21 Suppl 3:125–130.[22]	Excluded. < 10 cancers detected (see Appendix D).
Trecate G, Vergnaghi D, Bergonzi S, *et al*. Breast MRI screening in patients with increased familial and/or genetic risk for breast cancer: A preliminary experience. Tumori. 2003;89(2):125–131.	Excluded. < 10 cancers detected. Subset of data from Podo *et al*. (2002).[18]
Warner E, Plewes DB, Shumak RS, *et al*. Comparison of breast magnetic resonance imaging, mammography, and ultrasound for surveillance of women at high risk for hereditary breast cancer. J Clin Oncol. 2001;19(15):3524–3531.23	Excluded. Duplicate data from Warner *et al.* (2004).[4]
Warner E, Plewes DB, Hill KA, *et al*. Surveillance of *BRCA1* and *BRCA2* mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. J Am Med Assoc. 2004;292(11):1317–1325.[4]	**Included. Original study.**
Warren RML, Pointon L, Caines R, *et al*. What is the recall rate of breast MRI when used for screening asymptomatic women at high risk? Magnetic Resonance Imaging. 2002;20(7):557–565.[24]	Excluded. Duplicate data from MARIBS[2] study.

DATA EXTRACTION AND QUALITY ASSESSMENT

Methodological information relating to the study population, the nature of the diagnostic intervention and the definition of outcomes was extracted from the included studies. Particular attention was paid to methodological factors known to influence the quality of diagnostic/screening studies.

A detailed assessment of study quality was undertaken using a modification of the diagnostic-specific checklist published by the Cochrane Screening and Diagnostic Tests Methods group.[25] Context-specific notes relating to the use of the checklist are provided in Appendix E. Quality assessment was undertaken on the basis of the information clearly enunciated in the published paper. No attempt was made to contact authors to seek clarification.

Outcomes were extracted from included publications by one reviewer and checked for accuracy by a second reviewer. Data relating to sensitivity, specificity, PPV, NPV, accuracy, PLR, NLR and AUC ROC curve were extracted. If the results were also reported in the publication using an alternative dichotomisation (ie different cut-point between positive and negative), these results were also extracted. If available, data were also extracted by age group (ie <40; <50; ≥50) and various subgroups with respect to high-risk factors.

This review aimed to identify studies, review their quality and then summarise the evidence relating to the effectiveness of screening women at high risk of developing breast cancer using MRI. Therefore, where patient population, test techniques and interpretation, and study quality were suitably consistent, it was the intention to meta-analyse the results to calculate pooled estimates of the key diagnostic performance measures. To do so the test results of both imaging techniques would be considered to be truly dichotomous rather than continuous in nature, in accordance with the interpretation of these tests in routine clinical practice. Therefore, meta-analyses would be conducted by pooled weighted proportions, rather than summarised in ROC curve space.

RESULTS

INCLUDED SYSTEMATIC REVIEWS

Six systematic reviews were identified that assessed screening of women at increased risk of developing breast cancer using MRI. A summary of the main characteristics of these reviews is shown in Table 3. While all of the reviews have searched the MEDLINE database, only one has searched EMBASE. Each review will be considered in turn.

Elmore *et al.* (2005)[10]

The objective of this review was to evaluate breast cancer screening, especially in the community, and to examine evidence about new screening modalities. Screening modalities that were examined included screening mammography, full-field digital mammography and computer-aided detection programs, clinical breast examination (CBE), breast self-examination (BSE), MRI and ultrasound (US). National screening guidelines, the benefits and harms of screening and issues surrounding communication with patients were also examined.

MEDLINE, The Cochrane Library, the National Guideline Clearinghouse web site, the US Preventive Services Task Force recommendations and reviews, and the International Agency for Research on Cancer Handbook of Cancer Prevention were searched for relevant English-language publications. No date range for the search has been provided. Search terms included those relating to mass screening and breast, in conjunction with more specific terms relating to each of the screening modalities under review.

Six non-randomised studies were identified which provided data on test characteristics of MRI in women at high risk of developing breast cancer. Of the six identified studies, five were prospective and were carried out in the Netherlands, Canada, Italy and Germany,[3,4,14,21] while the remaining study was retrospective and was carried out in the United States.

The number of women in the studies ranged from 105 to 1909, while the proportion of women known to be mutation carriers (eg *BRCA1/2*) varied from 5% to 100%. Sensitivities ranged from 71% to 100%, while the PPV of biopsies performed based on MRI results ranged from 24% to 89%.

The authors note that while sensitivity of MRI in a high-risk population is higher than for mammography, specificity tends to be lower. The authors stated that “the high cost of MRI (approximately 10 times the cost of mammography) and its relatively low specificity (compared with mammography) probably prohibit its routine use for screening general populations”.

Table 3. Summary of characteristics of included systematic reviews

Citation	Patient population	Intervention	Comparator	Outcomes	Included studies[a]
Elmore et al (2005)[10]	Not specified	Breast cancer screening in the community (including MRI)	Not specified	Not specified	Kriege et al (2004)[3] Warner et al (2004)[4] Morris et al (2003)[17] Podo et al (2002)[18] Tilanus-Linthorst et al (2000)[21] Kuhl et al (2000)[14]
ANZHSN 2004[6]	Women who are at genetically high risk of developing breast cancer	MRI breast cancer screening	Mammography	Effectiveness Safety	Hartman et al (2004)[11] Kriege et al (2003)[b26] Kuhl et al (2003)[27] Liberman et al (2003)[16] Morris et al (2003)[17] Robson et al (2003)[28] Kuhl et al (2002)[29] Leach et al (2002)[15] Podo et al (2002)[18] Trecate et al (2002)[22] Warren et al (2002)[24] Stoutjesdijk et al (2001)[5] Warner et al (2001)[b23] Kuhl et al (2000)[14] Tilanus-Linthorst et al (2000)[21]
Calderon-Margalit and Paltiel (2004)[9]	Women with *BRCA1/2* mutations	Surveillance for early detection (including MRI), bilateral prophylactic mastectomy, prophylactic oophorectomy and chemoprevention	Not specified	Not specified	Brekelmans et al (2001)[8] Stoutjesdijk et al (2001)[5] Warner et al (2001) [b23] Kuhl et al (2000)[14] Tilanus-Linthorst et al (2000)[21]

Irwig et al (2004)[13]	Asymptomatic women considered to be at high risk of breast cancer because of genetic predisposition or those in whom mammography may be less accurate because they are younger or have radiologically dense breast tissue	New technologies in breast cancer screening (including MRI)	Not specified	Accuracy	Warner et al (2001)[b23] Stoutjesdijk et al (2001)[5] Tilanus-Linthorst et al (2000a,b)[20,21] Kuhl et al (2000)[14]
Blue Cross Blue Shield (2003)[7]	Women considered to be at high genetic risk of breast cancer due to (i) confirmed *BRCA1/2* mutation; (ii) known *BRCA1/2* in relative; or (iii) pattern of breast cancer history in multiple first-degree relatives consistent with a high probability of harbouring *BRCA* mutations or other hereditary breast cancer	MRI breast cancer screening	Mammography	Sensitivity Specificity	Trecate et al (2002)[22] Warren et al (2002)[24] Warner et al (2001)[b23] Kuhl et al (2000)[14] Tilanus-Linthorst et al (2000)[21]
ICSI (2003)[12]	Not specified	MRI for the detection of breast abnormalities (including screening high-risk patients)	Not specified	Not specified	Morris et al (2003)[17] Podo et al (2002)[18] Kuhl et al (2000)[14] Warner et al (2001)[b23] Tilanus-Linthorst et al (2000)[21]

Note: Underlined studies have been included in this current review.

[a] Only those included studies examining MRI are included here.

[b] Later versions of these studies have been included in the current review.

Australia and New Zealand Horizon Scanning Network (ANZHSN) (2004)[6]

The aim of this Horizon Scanning Report was to provide preliminary evidence regarding the safety, effectiveness and cost-effectiveness of MRI screening for breast cancer, as well as a consideration of ethical issues.

Both an electronic database and internet search were carried out to April 2004. Databases searched included (but were not limited to) Pre-MEDLINE/MEDLINE, EMBASE, Current Contents, The Cochrane Library and PsychInfo. Internet sites searched included, among others, the Current Controlled Clinical Trials metaRegister, Health Technology Assessment International (HTAi) and the Food and Drug Administration (FDA). In total 15 relevant publications were identified. One publication provided level 1b evidence,[21] while the remaining 14 publications provided level 3b evidence.[5,11,14–18,22–24,26–30]

According to the authors, based on the results of the included studies, "MRI appears to have improved sensitivity, comparable false positive rates and improved false negative rates when compared to mammography, for young, at risk women." However, on the basis of the data shown by the authors, it is not possible to draw conclusions relating to age group, and to do so has the potential to be misleading.

The authors note the small number of breast cancers detected in the included studies, as well as the low number of screening rounds.

Calderon-Margalit and Paltiel (2004)[9]

The aim of this study was to review various preventive strategies for women with *BRCA1/2* mutations, who were at high risk of developing breast cancer. The preventive strategies under review included early surveillance (mammography and MRI), bilateral prophylactic mastectomy, prophylactic oophorectomy and chemoprevention.

MEDLINE and PubMed were searched from 1998 to 2004 using search terms for the gene mutations, breast cancer, prevention and the specific modalities being assessed. Five identified studies related to early surveillance and included an assessment of MRI. These included two retrospective cohorts,[5,8] one non-randomised trial,[14] one cross-sectional study[23] and one cohort study.[21]

Sensitivities for MRI alone were 100% in three of the studies, and 74% in another that assessed a screening program (including CBE, BSE, mammography and optional MRI). PPVs for MRI ranged from 26% to 64%. The authors noted that the studies substantially differed in their study populations and their choice of gold standard. The authors concluded that, if indeed the sensitivity of MRI proves to be about 100% in detecting occult breast cancer, clear criteria should be defined as to who should receive MRI screening in order to increase its PPV, reduce unnecessary procedures and control costs.

Irwig et al (2004)[13]

The aim of this review was to examine the accuracy of new technologies proposed for breast cancer screening. The tests under examination were US, MRI, full-field digital mammography and computer-aided detection.

MEDLINE was searched using terms relating to breast neoplasms, sensitivity and specificity, mass screening and specific terms for each of the technologies under review. The date span of the search was 1966 to December 2002. The search was supplemented with a search of reference lists of relevant articles and targeted MEDLINE searches.

Four studies were identified that were relevant to the assessment of MRI screening for breast cancer.[5,14,20,21,23] All studies included women at high risk of developing breast cancer. Less than 40 cancers were identified across the four studies. The authors state that the results suggest that MRI is more sensitive than mammography in selected populations, but may also have a lower specificity.

The authors concluded that MRI had not been evaluated as a screening test in unselected populations, and its potential role in screening (if any) was in women at high risk of breast cancer.

Blue Cross and Blue Shield Association (2003)[7]

The specific research question addressed by this review was “what is the comparative sensitivity and specificity between screening MRI and screening mammography among women considered to be at high genetic risk of breast cancer?”

A search of MEDLINE (via PubMed) to November 2003 was conducted using key search terms such as “magnetic resonance imaging”, “high risk”, “screening”, “breast neoplasm” and “genetic”. The search was supplemented with searches of Current Contents, key journals, reference lists and contacting known experts in the field. Specific inclusion criteria were formulated for included studies.

Five studies met the inclusion criteria for the review,[14,21–24] while two abstracts were included as supplemental evidence.[26,27] Sensitivity and specificity were calculated in two of the studies, with the sensitivity of MRI compared with mammography being 100% and 33% respectively.[14,23] However, the authors note that these calculations are based on very small numbers of detected cancers (<10 in each study). Similarly high sensitivities were seen for MRI in the two studies reported as abstracts (96% and 71%), while specificities were 95% and 88%.

The authors concluded that the findings of reasonably performed comparative studies demonstrate probable superiority and definite non-inferiority of MRI in terms of sensitivity for detecting breast cancer in high genetic-risk women. The specificity of MRI was equal to mammography in the study by Kuhl,[14] but worse in the other studies. In addition they concluded that the possibly inferior specificity of MRI might be considered acceptable in the setting of screening high genetic-risk subjects who may accept this level of specificity because of the high value they place on sensitive test performance.

Institute for Clinical Systems Improvement (2003)[12]

The topic under review was MRI for the detection of breast abnormalities. The potential uses assessed for MRI included: (i) local staging of recently diagnosed breast cancer; (ii) monitoring

response to neoadjuvant therapy; (iii) problem solving situations including a questionable lesion on mammogram/US, a focal area of clinical concern with negative mammogram and US, questions of recurrence and a palpable axillary lymph node metastasis from presumed primary breast tumour with negative mammogram and clinical breast exam; (iv) screening high risk patients; and (v) evaluation of silicone implants.

A literature search was conducted of the MEDLINE database and supplemented a search of the bibliographies of retrieved articles and key article identified by members of a working group. The date range of the search is not provided. With regards to screening in high risk patients, five studies were included.[14,17,18,21,23]

While the results of the included screening studies are described in some detail, the only relevant finding reported for this indication is that MRI screening of high risk patients (previous personal or strong family history of breast cancer or carriers of a breast cancer susceptibility gene) is currently being studied in several multicentre studies.

SUMMARY

A variety of studies had been included in the six published systematic reviews described here, and the majority of these did not meet the inclusion criteria for our review. While studies had small numbers and differing definitions of high-risk women, in general, the results suggested that MRI had higher sensitivity and lower specificity than mammography in a high-risk population.

As stated in the Blue Cross Blue Shield[7] review, showing effectiveness of screening tests usually requires demonstration that the test is sensitive and specific enough to detect preclinical disease without excess morbidity that might be caused by acting on false positive tests. In addition it should be shown that health outcomes are improved as a result of the earlier detection. A number of the reviews noted that studies of MRI screening for women at high risk of breast cancer were limited to the assessment of the diagnostic performance of MRI versus other screening modalities, and did not evaluate whether improvements in sensitivity translated into improved outcomes for patients such as survival.

INCLUDED ORIGINAL STUDIES

The final reports of large studies examining the effectiveness of MRI screening for women at high risk of breast cancer had been published since the publication of the six systematic reviews described above.[2–4] These, and one study included in three of the six identified systematic reviews[5] met the inclusion criteria for this review. The main reason that studies included in the systematic reviews failed to be included in this review was the fact that less than 10 cancers had been detected.

CHARACTERISTICS OF THE STUDIES

Table 4 briefly summarises the four studies included in the current review. The patient characteristics, the nature of the diagnostic interventions and the definitions of outcomes are presented for each study, with an emphasis on mammography as the main comparator. The reader is referred to the original publications for further detail of MRI and mammography techniques and interpretation.

Table 4. Characteristics of included studies

Author, year **Study acronym**	**Country**	**Setting**	**Patient cohort**	**Mammography and MRI results reported for same patients?** **Approach for combined result**	**Nature of MRI** **Categorisation of positive and negative** **Treatment of equivocal results**	**Nature of mammography** **Categorisation of positive and negative** **Treatment of equivocal results**
Leach et al, 20052 MARIBS	UK	Accredited screening centre or familial breast cancer clinics (22)	Asymptomatic women at high risk of breast cancer aged 35–49 who fulfilled the following criteria: (i) known carriers of BRCA1, BRCA2 or Tp53 mutation; (ii) first degree relative of someone with known mutation (~ 35%); (iii) strong family history of breast or ovarian cancer (~ 65%); (iv) family history consistent with classic Li-Fraumeni syndrome. Women who had subsequent genetic testing and were found to be negative were excluded from the study Mean age 40 (31–55) years 120 BRCA carriers (82 BRCA1/38 BRCA2) No patients with prior breast cancer Prospective N=649 women/1881 screens (mean 2.9 screening rounds per woman) 2–7 years follow-up	Yes (women who did not receive both were excluded from analysis) Mammography performed annually and, by preference, on the same day as the MRI (74%). Results reported for: MRI alone M alone MRI + M (either +ve) MRI + M (both +ve)	Contrast-enhanced MRI Contrast agent Gd-DTPA 0.2 mmol/kg Field strength of 1.0–1.5 Tesla with a dedicated breast coil (GE Medical Systems, Marconi Medical Systems, Philips Medical Systems, Siemens Medical Solutions) Each screening study read by two radiologists unaware of results of other tests Assigned a score on 4 point scale: A=malignant B=equivocal C=benign N=normal -ve result = C, N +ve result = A, B	Two-view or one-view (mediolateral oblique) Each screening study read by two radiologists unaware of results of other tests Assigned a score on a 5-point scale: M1=benign/normal M2=probably benign M3=indeterminate M4=suspicious M5=malignant -ve result = M1, M2 +ve result = M3, M4, M5
Kriege et al, 20043 MRISC	Netherlands	Familial cancer clinics (6)	Women with a high genetic risk of breast cancer as follows: (i) a cumulative lifetime risk of ≥ 15% based on modified tables of Claus and aged 25–70; or (ii) women aged < 25 years if they had a family history of breast cancer diagnosed before the age of 30. Women with a history of breast cancer, or with current breast cancer symptoms were excluded Mean age 40 (19–72) years 354 BRCA carriers (276 BRCA1/77 BRCA2/1 BRCA1/2) No patients with prior breast cancer Prospective N=1952 women (1909 included in analysis)/4169 screens (mean of 2.2 per woman) Median follow-up 2.9 years	Yes (for mammography and MRI) Tests to be performed either same day or within the same timeframe (ie day 5–15 of menstrual cycle) MRI alone M alone CBE alone	Contrast-enhanced MRI Gadolinium-containing contrast medium Scans performed yearly. No further details of MRI provided. Assigned a score on a 5-point scale: 0=need additional imaging evaluation 1=negative 2=benign 3=probably benign 4=suspicious abnormality 5=highly suggestive of malignancy -ve result = 1, 2 +ve result = 0, 3, 4, 5	Scans performed yearly. No further details of mammography provided Assigned a score on a 5-point scale: 0=need additional imaging evaluation 1=negative 2=benign 3=probably benign 4=suspicious abnormality 5=highly suggestive of malignancy -ve result = 1, 2 +ve result = 0, 3, 4, 5

Warner et al, 2004[4]	Canada	Familial cancer clinics in Southern Ontario and Montreal Screening performed at single centre	Women aged 25–65 who were known carriers of the *BRCA1/2* mutations. Women with a past history of breast cancer could be included if the contralateral breast was intact. Women with bilateral breast cancer, currently undergoing chemotherapy or with known metastatic disease were excluded. Women weighing > 91 kg were excluded for technical reasons Mean age 46.6 (26–65) years 236 *BRCA* carriers (137 *BRCA1*/99 *BRCA2*) 30% previous breast cancer Prospective N=236 women/457 screens (mean of 1.9 screens per woman) All women had one round of screening, 58% had two rounds and 36% had three rounds Minimum follow-up after last screening was 1 year	Yes MRI, mammography, CBE and US performed on same day For premenopausal women was performed during second week of menstrual cycle Results reported as: M alone MRI alone US alone M+CBE+MRI+US combined M+US combined Does not state how a +ve combined test was assigned, but is assumed to be that any of the modalities was +ve	Simultaneous bilateral MRI with 1.5 T magnet. During the first year used a single turn elliptical coil; subsequently used a phased coil arrangement 0.1 mmol/kg gadolinium-diethylenetriamine used as contrast medium For cases which were potentially suspicious (ie MRI +ve but not other modalities), a diagnostic MRI was performed Assigned a score on a 5-point scale: 0=need additional imaging evaluation 1=negative 2=benign 3=probably benign 4=suspicious abnormality 5=highly suggestive of malignancy +ve result = 4, 5 -ve result = 1, 2, 3 Unclear whether 0 resulted in further imaging or biopsy	Conventional 4-view film/screen mammograms. No further details reported. Assigned a score on a 5-point scale: 0=need additional imaging evaluation 1=negative 2=benign 3=probably benign 4=suspicious abnormality 5=highly suggestive of malignancy +ve result = 4, 5 -ve result = 1, 2, 3 Unclear whether 0 score resulted in further imaging or biopsy

Stoutjesdijk et al, 2001[5]	Netherlands	University Medical Centre, Nijmegen	Women (no age range reported) at risk of early onset breast cancer. Inclusion criteria were as follows: (i) lifetime risk > 15% based on *BRCA1/2* gene mutation, or family history of breast or ovarian cancer; (ii) no personal history of breast cancer; (iii) adequate follow-up data for confirmation of findings (ie histology or imaging at least 2 years later) Retrospective chart review N=179 women(40 with mammography only, 49 with MRI only, 75 with both within 4 months at least once and 15 with both greater then 12 months apart) Analysis in this review limited only to the 75 women who received both MRI and mammography within 4 months of each other. Only the latest screening for each of these women was included in the study Follow-up 2 years	**No,** but results were available for a subgroup who had both (n=75) Results reported for: M alone (all subjects; not shown here) MRI alone (all subjects; not shown here) M alone (subjects with both) MRI alone (subjects with both)	1.5 T system (Magnetron Vision, Siemens) with a standard bilateral dedicated breast coil Both pre-and post-contrast images taken. Contrast agent 0.2 mmol/kg gadopentatate dimeglumine Images taken during 2nd week of menstrual cycle for pre-menopausal women Images classified as: 0 = additional imaging required 1 = negative 2 = benign 3 = probably benign 4 = suspicious abnormality 5 = highly suggestive of malignancy +ve test = 4, 5 -ve test = 1,2 Score of 3 resulted in recommendation for follow-up testing at 3–6 months (but included as positive in study calculations of diagnostic performance)	Mammomat 3000 (Siemens) or Senographe 2000D (GE Medical Systems) Images taken during 2nd week of menstrual cycle for pre-menopausal women Images classified as: 0 = additional imaging required 1 = negative 2 = benign 3 = probably benign 4 = suspicious abnormality 5 = highly suggestive of malignancy +ve test = 4, 5 -ve test = 1,2 Score of 3 resulted in recommendation for follow-up testing at 3–6 months (but included as positive in study calculations of diagnostic performance)

Abbreviations: CBE, clinical breast examination; M, mammography; MARIBS, Magnetic Resonance Imaging Breast Screening; MRI, magnetic resonance imaging; MRISC, Magnetic Resonance Imaging Screening; US, ultrasound.

OBJECTIVES AND POPULATIONS OF STUDIES

According to the published protocol,[31] the aim of the Magnetic Resonance Imaging Breast Screening (MARIBS) study was to "test the hypothesis that Magnetic Resonance Imaging (MRI) can be used with equal or better sensitivity then X-ray Mammography (XRM) with an acceptable false positive rate for the screening of premenopausal women at high genetic risk of developing breast cancer". The outcomes to be assessed in the study included sensitivity and specificity, optimum image analysis methodology, biopsy rate, size and stage of tumours identified, interval cancers and psychological aspects of screening. The included paper by Leach and collegues[2] presents results relating to the sensitivity and specificity of MRI compared with mammography, recall and biopsy rates and tumour characteristics.

The aims of the Dutch MRI Screening (MRISC) study[3] were to investigate (i) the value of regular surveillance in women at high risk for breast cancer due to familial predisposition; (ii) the efficacy of MRI compared with mammography; (iii) quality of life effects of regular screening; and (iv) the cost-effectiveness of regular screening.[32] In this study, participating women were stratified into one of three groups based on their level of risk – *BRCA1/2* mutation carriers; women at high risk (30–50% cumulative lifetime risk); and women at moderate risk (15–30% cumulative lifetime risk). The primary endpoint of the study was to be the percentage and incidence of advanced tumours compared with earlier stage tumours. Intermediate outcomes included the incidence and stage distribution of tumours at first (prevalent) and continued (incident) screening; the ratio, stage distribution and time since last screening of interval carcinomas; the sensitivity, specificity and PPV of the different screening modalities; and quality of life, including the physical, psychological and social effects of screening. Two papers describing results from this study were included in this review. The paper by Kreige *et al*.[3] presented results relating to characteristics of identified tumours, interval tumours and diagnostic performance. The paper by Rijnsburger and collegues[19] presented the quality of life results.

The objective of the study presented by Warner *et al.*[4] was to compare the sensitivity and specificity of four methods of breast cancer surveillance (mammography, ultrasound, MRI, and CBE) in women with hereditary susceptibility to breast cancer due to a *BRCA1/2* mutation. Preliminary results of this study were presented previously,[23] however, only the final results[4] are included in this review.

The study presented by Stoutjesdijk *et al.*[5] aimed to compare the sensitivity of MRI and mammography in women at high hereditary risk of breast cancer, and also to determine whether MRI could play a role in the early detection of breast cancer in these women. The data used for this retrospective study came from reports of breast cancer surveillance examinations that used MRI or mammography between 1994 and 2001. In an initial cohort of 179 women, 75 had received both MRI and mammography within 4 months of each other. Results were presented separately for this subgroup.

In summary, the four included studies differed in a number of aspects including design, population and outcomes assessed. Three of the four studies were of a prospective design, and all included women who received both MRI and mammography screening. The fourth study was retrospective, and only 75 of the cohort received both MRI and mammography. One study specifically included only women who were known *BRCA1/2* mutation carriers. The other three studies included a wider population of women considered to be at high risk (eg relatives who were known mutation carriers, family history of breast cancer). All four studies presented results relating to the diagnostic performance of MRI compared with mammography. One study presented quality of life data.

SCORING AND DEFINITION OF A POSITIVE RESULT

All four studies used a scoring system for the level of certainty of diagnosis, however this was ultimately dichotomised to calculate diagnostic performance. All scoring systems were the same as, or equivalent to, that of the American College of Radiology Breast Imaging Reporting and Data Systems (BI-RADS). This system includes the following:

- BI-RADS 1 = negative
- BI-RADS 2 = benign
- BI-RADS 3 = probably benign
- BI-RADS 4 = suspicious abnormality
- BI-RADS 5 = highly suggestive of malignancy
- BI-RADS 0 = additional imaging required

The MARIBS[2] study used a four-point scale for the MRI results: A, malignant (BI-RADS 5); B, suspicious (equivalent to BI-RADS 0, 3, 4); C, benign (BI-RADS 2) and N, negative (BI-RADS 1). For the mammography results, Leach *et al.* used the following classifications: M1 (BI-RADS 1); M2 (BI-RADS 2); M3 (BI-RADS 0, 3); M4 (BI-RADS 4) and M5 (BI-RADS 5). The other three studies used an unmodified version of the BI-RADS system.

There were some differences in the manner in which studies dichotomised their results into positive and negative (see Table 5). Both the MARIBS[2] and MRISC[3] studies included BI-RADS 3 (probably benign) as a positive result, while the Warner[4] study include BI-RADS 3 as a negative result. A BI-RADS 3 in the Stoutjesdijk[5] study led to a recommendation for follow-up testing in 3–6 months, however it was included as a positive result in the diagnostic performance calculations. The MRISC[3] and Stoutjesdijk[5] studies provided results separately for each of the BI-RADS classifications so the data could be presented at different cut-offs (ie positive result ± BI-RADS 3).

Table 5. Dichotomisation of MRI and mammography results into positive and negative

Study	BI-RADS 1	BI-RADS 2	BI-RADS 3	BI-RADS 4	BI-RADS 5	BI-RADS 0
MARIBS Leach (2005)[2]	–	–	+	+	+	+
MRISC Kriege (2004)[3]	–	–	+	+	+	+
Warner (2004)[4]	–	–	–	+	+	?
Stoutjesdijk (2001)[5]	–	–	+ (Follow-up testing at 3–6 months)	+	+	?

QUALITY ASSESSMENT

The quality of the included studies was assessed using a modification of the diagnostic-specific checklist of the Cochrane Screening and Diagnostic Tests Methods group[25] (see Appendix E). Methodological and reporting characteristics influencing the quality of each of the individual included trials are summarised in Table 6.

The included prospective studies[2–4] were of reasonable methodological quality for the following reasons: (i) reading of the images was carried out without knowledge of the reference standard, or of the results of the alternate imaging modality; (ii) the vast majority of MRI and mammography scans were performed on the same day or within a restricted time period; and (iii) all included subjects received both MRI and mammography. In addition, in all three studies the data were presented in a manner such that the data could be easily extracted in a format that allowed recalculation of diagnostic parameters.

The included retrospective study by Stoutjesdijk *et al.*[5] was also of reasonable methodological quality, for the same reasons outlined above. It should be noted that in this study, MRI and mammography results were re-read prospectively, blinded to the results of the alternate scan.

Similar disease prevalence was seen in the three prospective studies. In the MARIBS[2] study disease was detected in 1.9% of screenings for all women at high risk. In the MRISC[3] study, the rate of detection for all women at high risk was 9.5 per 1000 woman-years, or 1.1% of screenings. A much higher disease prevalence (16.5%) was seen in the subgroup analysis of 75 women who had both MRI and mammography within four months in the retrospective Stoutjesdijk[5] study. This much higher rate likely reflected the highly selected population included in this analysis.

In the MARIBS[2] study, disease was seen in 3.4% and 4.9% of screenings conducted in women with *BRCA1* and *BRCA2* mutations, respectively. These values are comparable to what is seen in women with *BRCA1/2* mutations in the Warner[4] study, when data from all screening rounds are combined (4.8% of screenings). When analysed by individual screening rounds (one, two and three), disease was detected in 5.5%, 5.1% and 2.4% of women, respectively. In the MRISC[3] study, the rate of detection in mutation carriers was 26.5 per 1000 woman-years at risk. Data were not available to allow calculation of the percentage of screenings at which disease was detected.

The similar prevalence seen across the three prospective studies gives reassurance that the populations within the three studies were comparable. Therefore, the pooled results are likely to be generalisable to the high-risk population in the wider community.

Table 6. Study quality for included studies

Author (date)	Reference standard adequate?	Tests and reference standard measured independent of each other? (avoid measurement bias)	Were all patients assessed by the reference standard? (avoid verification bias)	Test diagnosis made independent of other clinical information?	Reference standard measured before treatment started? (avoid treatment paradox)	M result determined independent of MRI result?	MRI result determined independent of M result?	Were M & MRI measured at similar point in time?	Consecutive patients at high risk presenting for screening?	Was a representative spectrum of disease captured? Were patients with more advanced or recurrent disease included? Was the disease prevalence indicative of the target population?
Leach et al, 2005[2]	Adequate. Histology result or presence or absence of interval cancer in the year after examination. Interval cancers ascertained by follow-up questionnaire to participants and contacting study sites	MRI and M made without knowing reference standard but not vice versa	No. Screening study so only those with positive M or MRI underwent further assessment	Yes. Radiologists were unaware of the results of other tests	Probably	Yes. Radiologists unaware of results of other tests	Yes. Radiologists unaware of results of other tests	Mostly. Same day for 76%. 4% more than a month apart	Not stated	Yes. Tumours ranging from Grades 1–3 were identified Study reported prevalence of disease: First screening round – 27 per 1000 women Subsequent screening rounds – 13 per 1000 women Prevalence calculated from data in study: All women at high risk – 1.9% of screenings Women with *BRCA1* – 3.4% of screenings Women with *BRCA2* – 4.9% of screenings

Author (date)	Reference standard adequate?	Tests and reference standard measured independent of each other? (avoid measurement bias)	Were all patients assessed by the reference standard? (avoid verification bias)	Test diagnosis made independent of other clinical information?	Reference standard measured before treatment started? (avoid treatment paradox)	M result determined independent of MRI result?	MRI result determined independent of M result?	Were M & MRI measured at similar point in time?	Consecutive patients at high risk presenting for screening?	Was a representative spectrum of disease captured? Were patients with more advanced or recurrent disease included? Was the disease prevalence indicative of the target population?
Kriege et al, 2004[3]	Adequate. Diagnosis of malignant tumour based on histology. No details provided regarding how interval cancers were detected	MRI and M made without knowing reference standard but not vice versa	No. Screening study so only those with positive CBE, M or MRI underwent further assessment	MRI and M readings made independent of each other but not stated if tests assessed blinded to other clinical information	Probably	Yes. Results blinded so that two examinations were not linked	Yes. Results blinded so that two examinations were not linked	Probably. State that it was to be same day or within same timeframe (ie days 5–15 of menstrual cycle)	Not stated	Yes. Tumours of various sizes and grades were identified Study reported prevalence (rate of detection): All women at high/moderate risk – 9.5 per 1000 woman-years at risk Mutation carriers – 26.5 per 1000 woman-years at risk High-risk group – 5.4 per 1000 woman-years at risk Moderate-risk group – 7.8 per 1000 woman-years at risk Prevalence calculated from data in study: 1.1% of screenings

Author (date)	Reference standard adequate?	Tests and reference standard measured independent of each other? (avoid measurement bias)	Were all patients assessed by the reference standard? (avoid verification bias)	Test diagnosis made independent of other clinical information?	Reference standard measured before treatment started? (avoid treatment paradox)	M result determined independent of MRI result?	MRI result determined independent of M result?	Were M & MRI measured at similar point in time?	Consecutive patients at high risk presenting for screening?	Was a representative spectrum of disease captured? Were patients with more advanced or recurrent disease included? Was the disease prevalence indicative of the target population?
Warner et al, 2004[4]	Adequate. Diagnosis based on histology. Patients were also followed-up annually by questionnaire to determine whether any cancers had been diagnosed since the last screening interval	MRI and M made without knowing reference standard but not vice versa	No. Screening study so only those with positive CBE, M, MRI or US underwent further assessment	Radiologists blinded to results of CBE	Probably	Each imaging study read and scored independentl y by a different radiologist	Each imaging study read and scored independentl y by a different radiologist	Yes. Performed on same day	Not stated	Yes. Tumours of various sizes detected Prevalence calculated from data in study (women with *BRCA1/2* mutations): Screening round 1 – 5.5% of subjects Screening round 2 – 5.1% of subjects Screening round 3 – 2.4% of subjects All screening rounds – 4.8% of screenings
Stoutjesdijk et al, 2001[5]	Adequate Diagnosis based on histology or follow-up testing at ≥ 2 years	MRI and M made without knowing reference standard but not vice versa	No. Screening study so only those with positive imaging underwent further assessment	MRI and M readings made independent of each other but not stated if tests assessed blinded to other clinical information	Probably	Yes. Mammogram s were prospectively interpreted by one of three radiologists who were blinded to MRI results	Yes. MRIs prospectively interpreted by one of two radiologists who were blinded to mammograp hy results	In the subjects who received both MRI and M, 75 received them both within a 4 month interval. Possible for interval cancers to have arisen between M and MRI screens	Probably not. Retrospective study. Data included here are from a selected, non-consecutive group of women who had both tests	Yes, tumours of various grades and receptor status identified Prevalence calculated from data in study: 16 per 100 subjects

Abbreviations: CBE, clinical examination; M, mammography; MRI, magnetic resonance imaging; US, ultrasound.

DIAGNOSTIC PERFORMANCE RESULTS

The observed diagnostic test and disease status results, and the calculated diagnostic performance for each of the included studies, are presented in Tables 5–9. While all studies assessed the diagnostic performance of MRI alone and mammography alone, only the UK MARIBS study[2] and the Canadian study by Warner *et al.*[4] examined the effect of adding MRI to mammography/other screening modalities.

There are two important points to note. First, diagnostic performance results were specific to the definitions of positive and negative used in the study and cannot be extrapolated to different cut-points. For the purpose of this review, where possible, data were analysed using different cut-points to show the effect on diagnostic performance. Second, many of the results presented in the included studies related to multiple screening rounds and were likely to underestimate the diagnostic performance of the first round of screening. Where information on the first round of screening was available, this has been noted.

MARIBS Study[2]

The results of the MARIBS[2] study are shown in Table 7. It should be noted that these results relate to all screening rounds combined; women had between one and seven rounds of screening (mean 2.9 per patient).

When all women considered to be at high risk are assessed, the sensitivity of screening using either MRI alone, or in combination with mammography (assuming a positive result in either test gives a positive combined result) was higher than for mammography alone. On the other hand, specificity was highest with mammography alone, compared with MRI alone or MRI in combination with mammography (see Table 7). The AUC ROC curve was 0.85 (95% CI 0.84, 0.87) for MRI and 0.70 (95% CI 0.68, 0.72) for mammography. When the analysis was limited to the first round of screening, the sensitivity and specificity of MRI was 75% and 82%, while the sensitivity and specificity of mammography was 40% and 93%. When all subsequent rounds of screening were considered the sensitivity and specificity for MRI was 80% and 81%, while for mammography it was 40% and 90%. Two interval cancers were detected: one between the first and second round, and one between the fifth and sixth rounds. One was identified as benign on mammography (round 1) while the other was identified as being benign on MRI (round 5).

When only women in the *BRCA1* group were considered, the sensitivity and specificity of MRI alone were 92% and 79% compared with 23% and 92% for mammography alone. When MRI and mammography were combined (with either test positive resulting in a combined positive result) the sensitivity was 92% and the specificity was 74%. When only women from the *BRCA2* group were considered, the sensitivity and specificity of MRI alone was 58% and 82%, compared with 50% and 92% for mammography alone. When MRI and mammography were combined (with either test positive resulting in a combined positive result) the sensitivity was 92% and the specificity was 78%.

Exclusion of women with *BRCA1* from the overall group of women at high risk resulted in sensitivities of 68% with MRI and 50% with mammography. Exclusion of women with *BRCA2* from the overall group of women at high risk resulted in sensitivities of 87% for MRI alone and 35% for mammography alone. Combined results after exclusion of women with *BRCA1/2*

mutations were not reported. When DCIS-only cancers were excluded (n=6), the sensitivity of MRI alone was 86% compared with 31% for mammography alone (combined result not reported).

It is important to note that testing for *BRCA1/2* was restricted to women with breast cancer and, as such, the sensitivities for these subgroups refer to women definitely known to have the mutation, the specificities do not. Diagnostic performance results were not reported by age group or family history subgroup.

The authors conclude that “the gain in sensitivity of contrast-enhanced (CE) MRI over mammography was greatest in women with either a germline mutation for *BRCA1* or with a first-degree relative with such a mutation. Since these women also have a higher absolute risk in the age range studied [< 50] than the other risk groups, CE MRI screening might be particularly productive in this group”. However, the reader must bear in mind that no age group analyses were actually undertaken.

Table 7. Observed diagnostic results and calculated diagnostic performance: MARIBS study[2]

	Test result	Disease +ve	Disease -ve	Total	Sens	Spec	PPV	NPV	Acc	PLR	NLR
All women at high risk											
Mammography result	Test +ve	14	121	135	40%	93%	10%	99%	92%	6.1	0.6
	Test –ve	21	1725	1746							
	Total	35	1846	1881							
MRI result	Test +ve	27	344	371	77%	81%	7%	99%	81%	4.1	0.3
	Test –ve	8	1502	1510							
	Total	35	1846	1881							
Combined result (M + MRI; either positive)	Test +ve	33	428	461	94%	77%	7%	100%	77%	4.1	0.1
	Test –ve	2	1418	1420							
	Total	35	1846	1881							
Combined result (M + MRI; both positive)	Test +ve	8	37	45	23%	98%	18%	99%	97%	11.4	0.8
	Test –ve	27	1809	1836							
	Total	35	1846	1881							
Women with BRCA1											
Mammography result	Test +ve	3	30	33	23%	92%	9%	97%	89%	2.8	0.8
	Test –ve	10	335	345							
	Total	13	365	378							
MRI result	Test +ve	12	95	88	92%	79%	14%	100%	80%	4.4	0.1
	Test –ve	1	270	290							
	Total	13	365	378							
Combined result (M + MRI; either positive)	Test +ve	12	95	107	92%	74%	11%	100%	75%	3.5	0.1
	Test –ve	1	270	271							
	Total	13	365	378							
Combined result (M + MRI; both positive)	Test +ve	3	11	14	23%	97%	21%	97%	94%	7.7	0.8
	Test –ve	10	354	364							
	Total	13	365	378							
Women with BRCA2											
Mammography result	Test +ve	6	13	19	50%	94%	32%	97%	92%	8.9	0.5
	Test –ve	6	219	225							
	Total	12	232	244							
MRI result	Test +ve	7	41	48	58%	82%	15%	97%	81%	3.3	0.5
	Test –ve	5	191	196							
	Total	12	232	244							
Combined result (M + MRI; either positive)	Test +ve	11	51	62	92%	78%	18%	99%	79%	4.2	0.1
	Test –ve	1	181	182							
	Total	12	232	244							
Combined result (M + MRI; both positive)	Test +ve	2	3	5	17%	99%	40%	96%	95%	12.9	0.8
	Test –ve	10	229	239							
	Total	12	232	244							
Women with BRCA1* or *BRCA2											
Mammography result	Test +ve	9	43	52	36%	93%	17%	97%	91%	5.0	0.7
	Test –ve	16	554	570							
	Total	25	597	622							
MRI result	Test +ve	19	136	15	76%	77%	12%	99%	77%	3.3	0.3
	Test –ve	6	461	467							
	Total	25	597	622							
Combined result (M + MRI; either positive)	Test +ve	23	146	169	92%	76%	14%	100%	76%	3.8	0.1
	Test –ve	2	451	453							
	Total	25	597	622							
Combined result (M + MRI; both positive)	Test +ve	14	62	76	56%	90%	18%	98%	88%	5.4	0.5
	Test –ve	11	535	546							
	Total	25	597	622							

Abbreviations: Acc, accuracy; M, mammography; MRI, magnetic resonance imaging; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

MRISC study[3]

The results of the MRISC[3] study are shown in Table 8. The main results relate to all screening rounds combined, resulting in a mean of 2.2 tests per subject.

As reported in the study, the sensitivity and specificity of MRI alone when BI-RADS 0, 3, 4 and 5 were considered positive were 71% and 90% respectively. The corresponding values for mammography alone were 40% and 95%. When BI-RADS 3 (probably benign) was classified as negative instead of positive (*post-hoc* analysis for this review), the sensitivity and specificity of MRI alone were 64% and 96% respectively, with the corresponding values for mammography alone being 33% and 99%.

For the first screening round in isolation, the sensitivity of MRI was 79% compared with 38% for mammography. For subsequent screening rounds the sensitivity of MRI was 62% compared with 43% for mammography. The corresponding specificities were not reported. ROC curves were generated for all patients and the AUCs were 0.83 for MRI compared with 0.69 for mammography, resulting in a difference of 0.14 (95% CI 0.02, 0.26; $p<0.05$).

When the analysis was limited to invasive tumours only, the sensitivity of MRI was 79.5% compared with 33.3% for mammography. When the analysis was limited to DCIS, the sensitivity of MRI compared with mammography was 17% vs 83% respectively.

Four interval cancers were detected during the study: three were symptomatic and one was detected in a sample from a prophylactic mastectomy. Two of the three symptomatic cancers were detected seven months after screening imaging, while the other was detected three months after screening imaging. Diagnostic performance results were not reported by gene mutation group, age group or family history subgroup.

Table 8. Observed diagnostic results and calculated diagnostic performance: MRISC study[3]

	Test result	Disease +ve	Disease –ve	Total	Sens	Spec	PPV	NPV	Acc	PLR	NLR
All women at high risk											
Positive result based on BI-RADS 0, 3, 4, 5											
CBE result[a]	Test +ve	3	3	6	7%	100%	50%	99%	99%	86.7	0.9
	Test –ve	42	3897	3939							
	Total	45	3900	3945							
Mammography result	Test +ve	18	207	225	40%	95%	8%	99%	94%	8.0	0.6
	Test –ve	27	3917	3944							
	Total	45	4124	4169							
MRI result	Test +ve	32	420	452	71%	90%	7%	100%	90%	7.0	0.3
	Test –ve	13	3704	3717							
	Total	45	4124	4169							
Positive result based on BI-RADS 0, 4, 5[b]											
CBE result[c]	Test +ve	8	75	83	18%	98%	9%	99%	97%	8.4	0.8
	Test –ve	37	3825	3862							
	Total	45	3900	3945							
Mammography result	Test +ve	15	40	55	33%	99%	27%	99%	98%	34.4	0.7
	Test –ve	30	4084	4114							
	Total	45	4124	4169							
MRI result	Test +ve	29	148	177	64%	96%	14%	100%	96%	15.1	0.4
	Test –ve	16	3976	3991							
	Total	45	4124	4169							

Abbreviations: Acc, accuracy; CBE, clinical breast examination; M, mammography; MRI, magnetic resonance imaging; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

[a] Positive result based on classification of suspicious only.

[b] *Post-hoc* analysis.

[C] Positive result based on classification of suspicious or probably benign.

Warner et al (2004)[4]

The results of the Warner[4] study are summarised in Table 9. This study was limited to women who were known *BRCA1/2* mutation carriers. Therefore, this represents a more restricted population than that of the other three included studies. In addition, while this study examined multiple rounds of screening, the results for each round are presented separately, allowing for an examination of the effect of repeated screening on diagnostic performance. In contrast with the other studies, BI-RADS 3 was classified as a negative result.

During the first screening round of the study, the sensitivity and specificity of MRI alone was 85% and 93%, compared with 38% and 100% for mammography alone and 25% and 95% for US alone. During the second year the sensitivity and specificity of MRI alone was 71% and 97%, while in the third year it was 50% and 99%. For mammography alone, sensitivity and specificity were 43% and 100% during the second year and 0% and 100% during the third year. For US alone, sensitivity and specificity were 57% and 96% for the second year and 0% and 100% for the third year. It should be noted that only seven cancers were detected during the second round of screening, while only two cancers were detected during the third round. As such, these results should be treated with caution.

When all three rounds were combined together (*post-hoc* analysis for this review), the sensitivity and specificity of MRI alone was 77% and 95%, compared with 36% and 100% for mammography alone and 33% and 96% for US alone. The AUC ROC curve was 0.89 for MRI alone, 0.77 for mammography alone, 0.65 for US alone and 0.48 for CBE alone (sensitivity and specificity were not reported for this modality). The sensitivities and AUC ROC curve for different combinations of the screening modalities examined (including CBE) are shown in Table 10.

One interval cancer was detected during the study, seven months after the third round of screening. The authors note that, in retrospect, the tumour could be seen on both the MRI and mammography scans. One other woman, who had a bilateral mastectomy after a cancer was detected, was found to have a tumour in the contralateral breast that was not detected by screening. Diagnostic performance results were not reported by age group or family history subgroup.

The authors note that a disadvantage of the use of MRI is its high cost and relatively low specificity. However, they showed that the recall rate for MRI decreased substantially with each progressive round of screening (26%, 13% and 10% for rounds 1, 2 and 3 respectively), and that specificity and PPV improved with successive rounds (Table 9). They conclude that their results "support the position that MRI-based screening is likely to become the cornerstone of breast cancer surveillance for *BRCA1* and *BRCA2* mutation carriers". However, they also note the importance of showing that these improvements in diagnostic performance translate into improvements in breast cancer mortality before it can be recommended for general use.

Table 9. Observed diagnostic results and calculated diagnostic performance: Warner[4] study

	Test result	Disease +ve	Disease -ve	Total	Sens	Spec	PPV	NPV	Acc	PLR	NLR
Women with BRCA1/2 (Year 1)											
Mammography result	Test +ve	5	1	6	38%	100%	83%	97%	96%	85.8	0.6
	Test –ve	8	222	230							
	Total	13	223	236							
US result	Test +ve	3	10	13	25%	95%	23%	96%	92%	5.4	0.8
	Test –ve	9	207	216							
	Total	12	217	229							
MRI result	Test +ve	11	15	26	85%	93%	42%	99%	93%	12.6	0.2
	Test –ve	2	208	210							
	Total	13	223	236							
Women with BRCA1/2 (Year 2)											
Mammography result	Test +ve	3	0	3	43%	100%	100%	97%	97%	NA	0.6
	Test –ve	4	129	133							
	Total	7	129	136							
US result	Test +ve	4	5	9	57%	96%	44%	98%	94%	14.7	0.4
	Test –ve	3	124	127							
	Total	7	129	136							
MRI result	Test +ve	5	4	9	71%	97%	56%	98%	96%	23.0	0.3
	Test –ve	2	125	127							
	Total	7	129	136							
Women with BRCA1/2 (Year 3)											
Mammography result	Test +ve	0	0	8	0%	100%	NA	98%	98%	NA	1.0
	Test –ve	2	83	85							
	Total	2	83	85							
US result	Test +ve	0	2	2	0%	98%	0%	98%	95%	0.0	1.0
	Test –ve	2	81	83							
	Total	2	83	85							
MRI result	Test +ve	1	1	2	50%	99%	50%	99%	98%	41.5	0.5
	Test –ve	1	82	83							
	Total	2	83	85							
Women with BRCA1/2 (All years)[a]											
Mammography result	Test +ve	8	1	9	36%	100%	89%	97%	97%	158.2	0.6
	Test –ve	14	434	448							
	Total	22	435	457							
US result	Test +ve	7	17	24	33%	96%	29%	97%	93%	8.4	0.7
	Test –ve	14	412	426							
	Total	21	429	450							
MRI result	Test +ve	17	20	37	77%	95%	46%	99%	95%	16.8	0.2
	Test –ve	5	415	420							
	Total	22	435	457							

Abbreviations: Acc, accuracy; M, mammography; MRI, magnetic resonance imaging; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value; Sens, sensitivity; Spec, specificity; US, ultrasound.

[a] *Post-hoc* analysis.

Table 10. Sensitivity and AUC ROC curve of different combinations of screening modalities: Warner study[4]

Imaging combination	Sensitivity	AUC ROC curve
MRI + mammography + US + CBE	95%	0.93
MRI + mammography + CBE	86%	0.94
MRI + US + CBE	NR	0.91
Mammography + US + CBE	64%	0.81
Mammography + CBE	45%	0.77

Data source: Warner,[4] p1321 and Figure 1. NB. BI-RADS 3 classified as negative result

Abbreviations: AUC ROC, area under the receiver-operator characteristic; CBE, clinical breast examination; MRI, magnetic resonance imaging; NR, not reported; US, ultrasound.

Stoutjesdijk et al (2001)[5]

The results of the Stoutjesdijk[5] study are summarised in Table 11. The results presented in this review relate to the subgroup of 75 women who received both MRI and mammography within a four-month period. Only the most recent screening round was included for each women was included in the analysis. As such, it is important to note that women within this group may have previously been through multiple rounds of screening.

In the post-hoc analysis conducted for this review, in which BI-RADS 3, 4 and 5 were considered positive, the sensitivity and specificity of MRI alone was 100% and 86% respectively, while for mammography alone it was 42% and 89%. In the study analysis in which BI-RADS 4 and 5 were considered positive, the sensitivity and specificity of MRI was 92% and 95%, compared with 42% and 97% for mammography. The AUC ROC curve for the subset of 75 women who had both MRI and mammography within a four-month period was 0.99 (95% CI 0.96, 1.0) for MRI and 0.80 (95% CI 0.70, 0.90) for mammography. The difference was 0.19 (95% CI 0.09, 0.29; p=0.05). The authors note that these results are similar to those shown for the whole cohort of women included in the study (data not shown here).

For 10 of the 12 cancers identified, the second imaging performed was for diagnosis and not screening. For seven of these cases mammography was performed first, while for the remaining three cases MRI was performed first. The authors state that any possible bias on the results of the study were minimised due to the fact that images were ‘re-read’ prospectively for this retrospective study. While it is stated in the methodology section that MRI and mammography images were re-read independently of each other, it is not clear if they were re-read independent of other clinical information, including disease status or test results. Diagnostic performance results were not reported by gene mutation subgroup, age group or family history subgroup.

The authors noted a number of potential limitations of their study. These included: (i) the fact that this population of women who *opted* for annual surveillance may not be representative of women who are invited to take part in a screening program; (ii) the mix of screening versus surveillance imaging (as noted above); (iii) the small number of breast cancers detected; and (iv) the retrospective nature of the study. The authors concluded that their study “shows that annual screening with breast MRI is more accurate than mammography in the early detection of malignant tumours in women with a hereditary risk of breast cancer”. However, they also noted that this finding needs to be confirmed in large prospective studies, such as the MRISC[3] and MARIBS[2] studies, which were underway at the time of publication.

Table 11. Observed diagnostic results and calculated diagnostic performance: Stoutjesdijk study[5]

	Test result	Disease +ve	Disease -ve	Total	Sens	Spec	PPV	NPV	Acc	PLR	NLR
All women receiving both tests											
Positive result based on BI-RADS 3, 4, 5											
Mammography result	Test +ve	5	7	12	42%	89%	42%	89%	81%	3.8	0.7
	Test –ve	7	56	63							
	Total	12	63	75							
MRI result	Test +ve	12	9	21	100%	86%	57%	100%	88%	7.0	0
	Test –ve	0	54	54							
	Total	12	63	75							
Positive result based on BI-RADS 4, 5											
Mammography result	Test +ve	5	2	7	42%	97%	71%	90%	88%	13.1	0.6
	Test –ve	7	61	68							
	Total	12	63	75							
MRI result	Test +ve	11	3	14	92%	95%	79%	98%	95%	19.3	0.1
	Test –ve	1	60	61							
	Total	12	63	75							

Abbreviations: Acc, accuracy; M, mammography; MRI, magnetic resonance imaging; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

Note: Only results from the subgroup of 75 women who underwent both MRI and mammography within a four-month period are included here. Results relate only to the most recent screening round for each of the included women.

DISCUSSION OF DIAGNOSTIC PERFORMANCE RESULTS

A summary of the sensitivity and specificity results for mammography alone, MRI alone and combined mammography + MRI is shown in Table 12, Figures 1 and 2. Where data from more than one study were available, these were pooled. Results are shown separately for (i) all women at high risk of developing breast cancer ; and (ii) women with *BRCA1* or *BRCA2* mutations.

The sensitivity and specificity of each of the modalities was similar in both women at high risk and the subgroup of women with *BRCA1/2* mutations. The sensitivity of MRI alone was approximately twice that of mammography alone (ie approximately 77% vs 40%). On the other hand, specificity was <10% higher for mammography alone than for MRI alone (approximately 94% vs 87%).

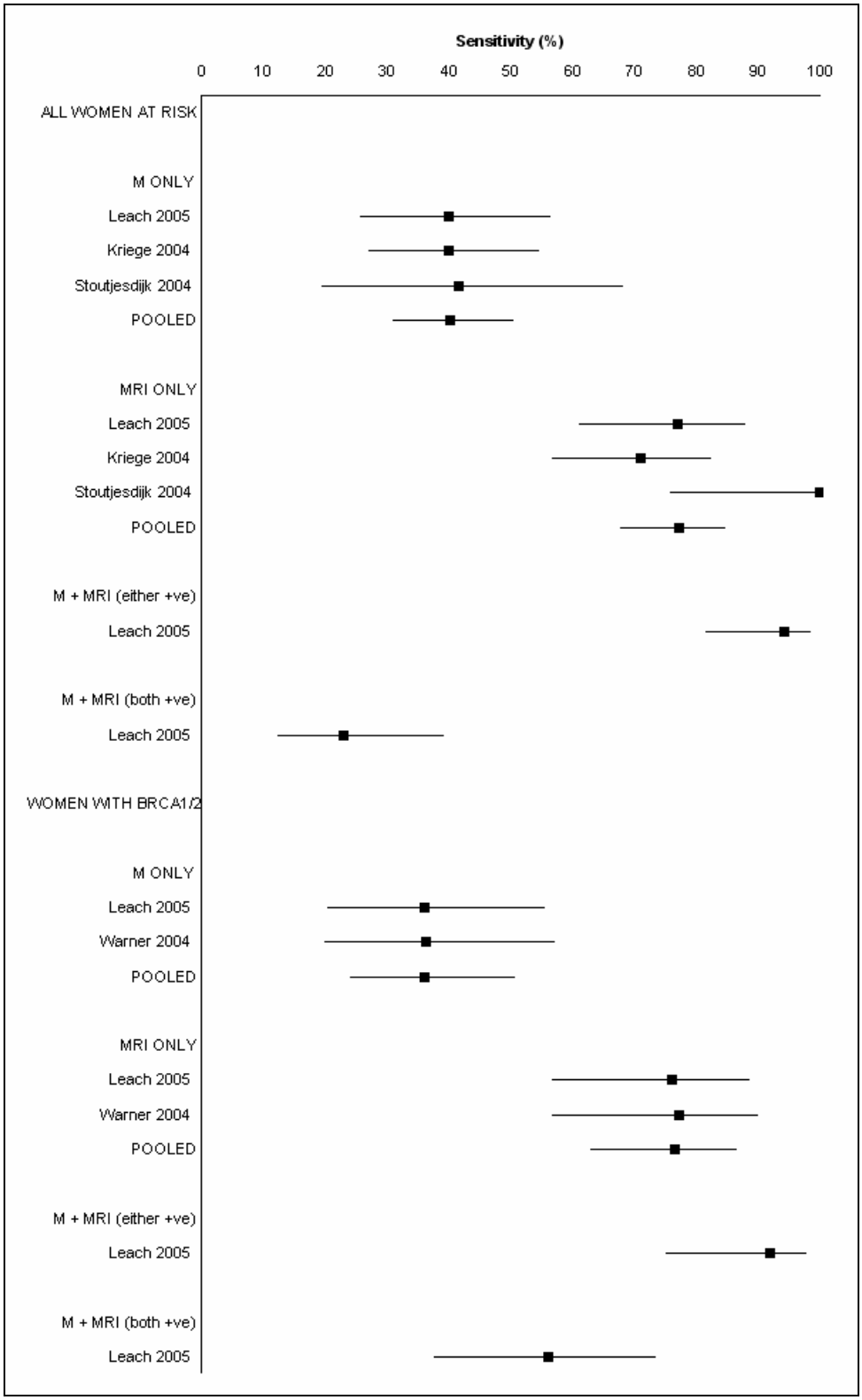
When the modalities were combined, and a positive result in either test constituted a positive result overall, sensitivity was significantly improved – approximately 94% for the combined modalities compared with 77% for MRI alone. However, the trade-off for combining the tests in this way was that the specificity of the combination of mammography + MRI was lower than that of MRI alone (approximately 77% vs 87%).

Table 12. Summary of sensitivity and specificity of mammography and MRI in all women at high risk and women with *BRCA1/2* mutations

Study	Sensitivity % (95% CI)	Specificity % (95% CI)
ALL WOMEN AT HIGH RISK		
Mammography only		
MARIBS[2]	40.0 (25.6, 56.4)	93.4 (92.2, 94.5)
MRISC[3]	40.0 (27.0, 54.5)	95.0 (94.3, 95.6)
Stoutjesdijk[5]	41.7 (19.3, 68.0)	88.9 (78.8, 94.5)
Pooled estimate	***40.2(30.8, 50.4)***	***94.4(93.8, 95.0)***
MRI only		
MARIBS[2]	77.1 (61.0, 87.9)	81.4 (79.5, 83.1)
MRISC[3]	71.1 (56.6, 82.3)	89.8 (88.9, 90.7)
Stoutjesdijk[5]	100 (75.7, 100)	85.7 (75.0, 92.3)
Pooled estimate	***77.2 (67.6, 84.6)***	***87.2 (86.3, 88.0)***
Mammography + MRI (either test +ve)		
MARIBS[2]	94.3 (81.4, 98.4)	76.8 (74.8, 78.7)
Pooled estimate	***94.3 (81.4, 98.4)***	***76.8 (74.8, 78.7)***
Mammography + MRI (both tests +ve)		
MARIBS[2]	22.9 (12.1, 39.0)	98.0 (97.2, 98.5)
Pooled estimate	***22.9 (12.1, 39.0)***	***98.0 (97.2, 98.5)***
WOMEN WITH *BRCA1* OR *BRCA2* MUTATION		
Mammography only		
MARIBS[2]	36.0 (20.2, 55.5)	92.8 (90.4, 94.6)
Warner[4]	36.4 (19.7, 57.0)	99.8 (98.7, 100)
Pooled estimate	***36.2 (24.0, 50.5)***	***95.7 (94.3, 96.8)***
MRI only		
MARIBS[2]	76.0 (56.6, 88.5)	77.2 (73.7, 80.4)
Warner[4]	77.3 (56.6, 89.9)	95.4 (93.0, 97.0)
Pooled estimate	***76.6 (62.8, 86.4)***	***84.9 (82.6, 86.9)***
Mammography + MRI (either test +ve)		
MARIBS[2]	92.0 (75.0, 97.8)	75.5 (71.9, 78.8)
Pooled estimate	***92.0 (75.0, 97.8)***	***75.5 (71.9, 78.8)***
Mammography + MRI (both tests +ve)		
MARIBS[2]	56.0 (37.4, 73.3)	89.6 (86.9, 91.8)
Pooled estimate	***56.0 (37.4, 73.3)***	***89.6 (86.9, 91.8)***

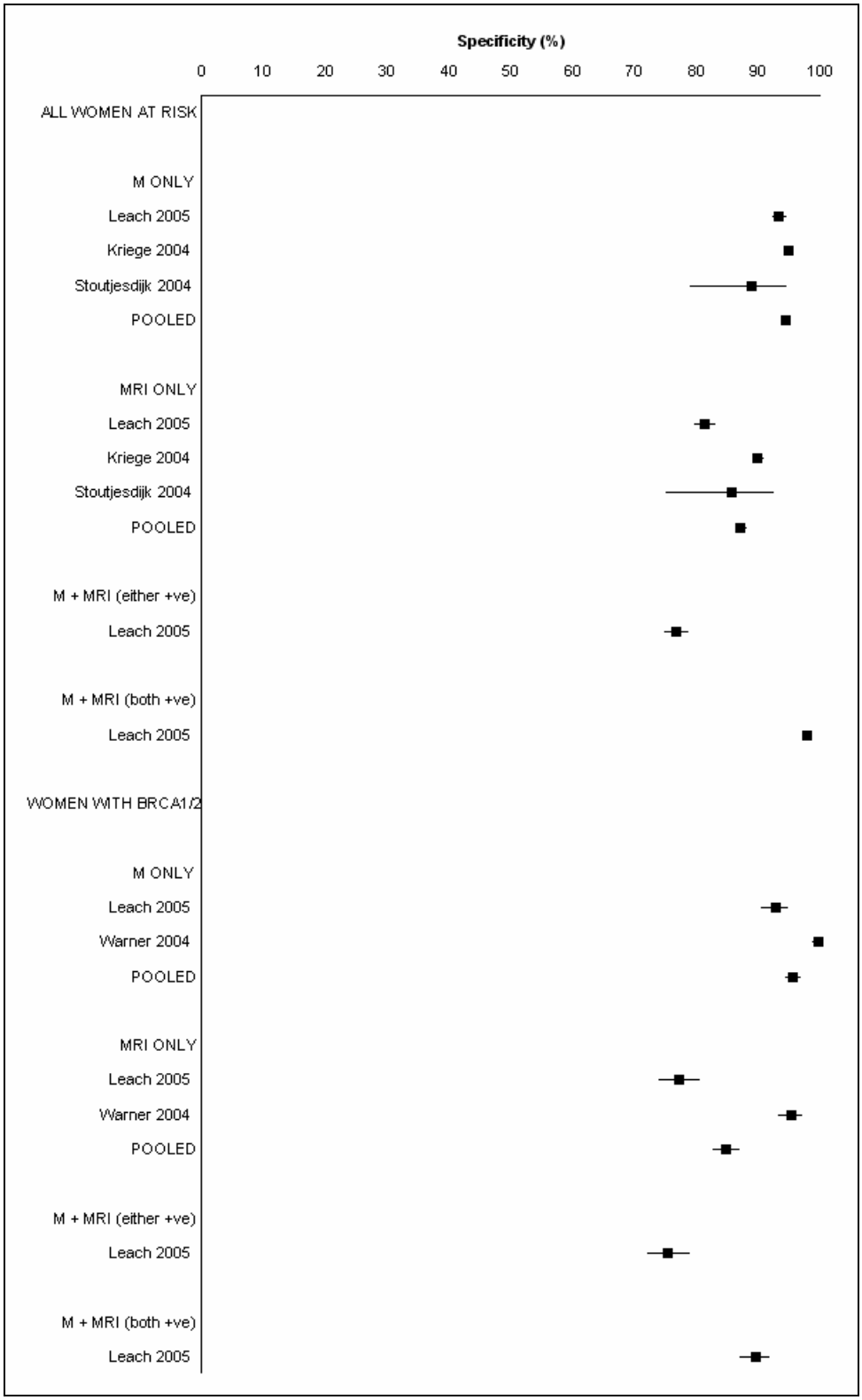
NB. In Warner[4] BI-RADS 3 was classified as negative result (in contrast to, MARIBS,[2] MRISC,[3] Warner,[4] Stoutjesdijk[5] where classified as positive)

Figure 1. Summary of sensitivity of mammography and MRI in all women at high risk and women with *BRCA1/2* mutations



NB. Leach[2] refers to the MARIBS[2] study, Kriege[3] refers to the MRISC[3] study. In Warner[4] BI-RADS 3 was classified as negative result (in contrast to Leach,[2] Kriege,[3] Stoutjesdijk[5] where classified as positive)

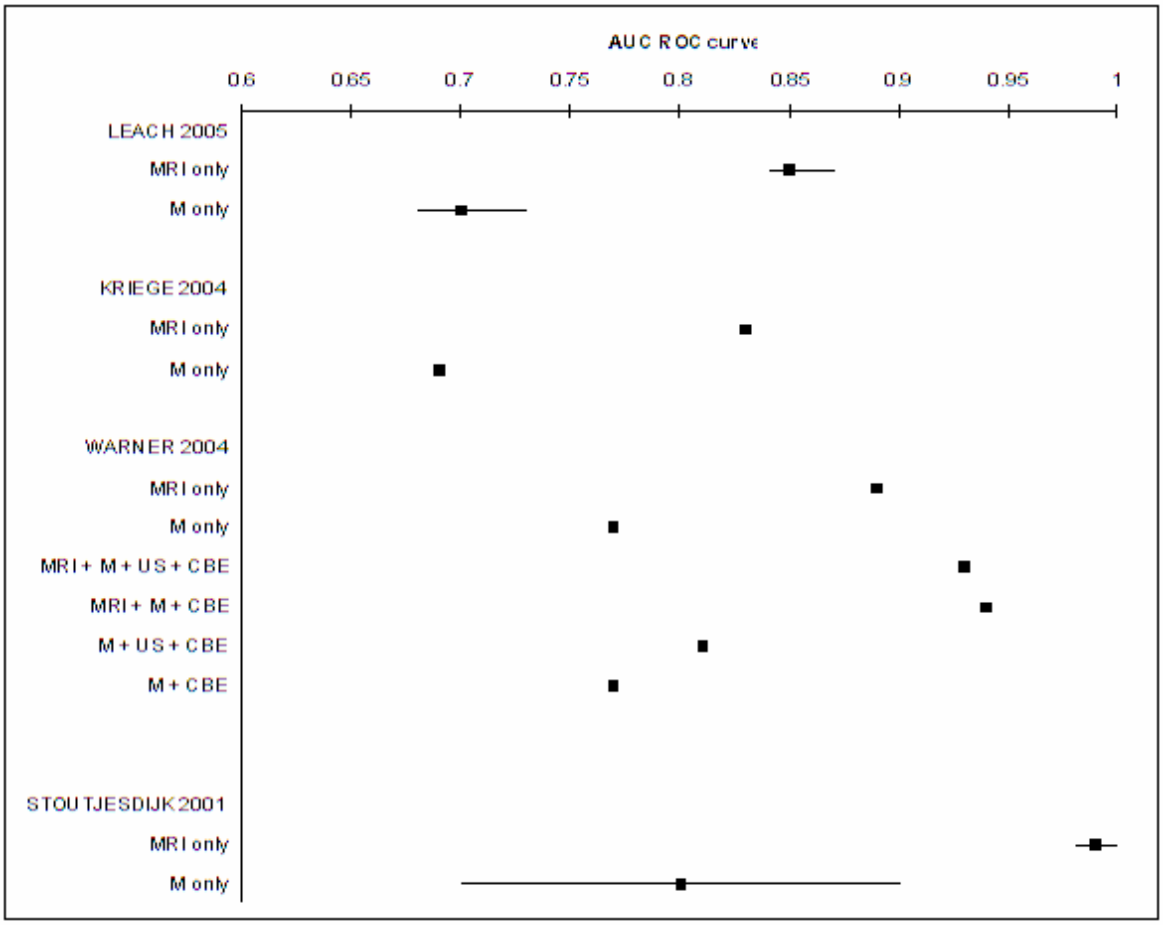
Figure 2. Summary of specificity of mammography and MRI in all women at high risk and women with *BRCA1/2* mutations



NB. Leach[2] refers to the MARIBS[2] study, Kriege[3] refers to the MRISC[3] study. In Warner[4] BI-RADS 3 was classified as negative result (in contrast to Leach,[2] Kriege,[3] Stoutjesdijk[5] where classified as positive)

A summary of the AUC ROC curves is shown in Figure 3. These results suggested that MRI alone was significantly more accurate than mammography alone at detecting breast cancer during screening of women at high risk. Accuracy was significantly improved when MRI was used in combination with other modalities. For example, the AUC ROC curve for a combination of MRI, mammography and CBE was 0.94, while for a combination of MRI, mammography, US and CBE it was 0.93.

Figure 3. Summary of AUC ROC curves for the included studies



NB. The results reported for the MARIBS,[2] MRISC,[3] Stoutjesdijk[5] studies relate to all women at high risk. The results for the Warner[4] study relate only to women with *BRCA1/2* mutations. AUC ROC of combined MRI + M was not reported in MARIBS.[2] NB. In Warner[4] BI-RADS 3 was classified as negative result (in contrast to MARIBS,[2] MRISC,[3] Stoutjesdijk[5] where classified as positive)

One of the issues that had arisen in the literature since the publication of the included studies was the fact that while women participating in these studies were usually undergoing screening MRI for the first time, they may have had screening mammography in the past. This had the potential to artificially inflate the difference in sensitivity between MRI and mammography during the first round of screening.

Altundag *et al.*[33] wrote in response to the MRISC[3] paper that the mammography results might have been confounded as the majority of women had undergone prior mammography, but not MRI. As such, a higher yield of breast cancers detected by MRI would be expected during the initial screening round. Kriege and collegues[3] reply that while this was the case with the initial round of screening, MRI was also more sensitive than mammography during subsequent screening rounds (76.5% vs 29.4% respectively).

Helvie and collegues[34] wrote of the same issue in response to the Warner[35] study. Warner *et al.*[35] replied, noting that in the period of follow-up since the publication of the study, an additional seven cancers were identified: all seven were detected by MRI, while only two were detected by mammography, also suggesting that even during later rounds of screening, MRI was substantially more sensitive than mammography.

OTHER RELEVANT RESULTS

AGE

A summary of the age characteristics of the women in the four included studies is shown in Table 13. All had a mean age between 40 and 50 years. Whilst the MARIBS[2] study attempted to only include women between 35 and 49 years, in fact the age range was 31–55 years and the mean age was 40 years. Furthermore, given the heterogeneity between patients, diagnostic reporting, study designs and quality, it would be incorrect to attempt to draw any conclusions about diagnostic performance by age by indirectly comparing the results of this study with the others.

Table 13. Age characteristics in the included studies

	MARIBS[2]	MRISC[3]	Warner[4]	Stoutjesdijk[5]
Age inclusion criteria	35–49	25–70	25–65	-
Actual age range	31–55	19–72	26–65	-
Mean age	40	40	46.6	-
Age categories				
≤ 30	-	-	-	7/75 (9%)
31–40	-	-	-	23/75 (31%)
41–50	-	-	-	35/75 (47%)
≥ 51	-	-	-	10/75 (13%)

Table 14 shows a summary of the number of tumours detected for different age categories in the MRISC[3] study. These results suggest that women who are known mutation carriers or at high-risk tend to be diagnosed at a younger age than women who are at moderate risk. However, this result could also be due to differing numbers of subjects within the age categories for each of the risk groups. As this cannot be ruled out, these results should be interpreted with caution. Furthermore, these results in no way address the question of the relative diagnostic performance of MRI and mammography in younger high-risk women versus high-risk women in general.

Table 14. Breast cancers detected in the three risk groups by age categories: MRISC study[3]

Age at diagnosis	Mutation carriers	High-risk group	Moderate-risk group	Total
All ages	23	16	11	50
20–29 years	2 (8.7%)	0	0	2 (4.0%)
30–39 years	13 (56.5%)	5 (31.3%)	1 (9.1%)	19 (38.0%)
40–49 years	6 (26.1%)	7 (43.7%)	7 (63.6%)	20 (40.0%)
50–69 years	2 (8.7%)	4 (25.0%)	3 (27.3%)	9 (18.0%)

In the Stoutjesdijk[5] study, the mean age at detection of breast cancer was 42.3 ± 7.0, while the age range was 31–50. As mentioned previously, the AUC ROC curves for the subgroup of 75 women who received mammography and MRI within four months were 0.70 for mammography and 0.98 for MRI. When multivariate analyses were used to adjust for age and risk categories, the resulting AUC ROC curves were 0.80 for mammography and 0.99 for MRI.

In the Warner[4] study, the mean age at detection of breast cancer was 47.4 (SD 7.7), while the age range was 33–63.

As stated in the diagnostic results section above, none of these studies reported the diagnostic performance characteristics of MRI (or the comparator) by age group. Therefore, on the basis of the currently available data, it is not possible to reach a conclusion regarding the relative diagnostic performance of MRI in different age groups.

TUMOUR CHARACTERISTICS

The characteristics of tumours identified in the MRISC[3] study were examined and compared to tumour characteristics from two control populations: (1) derived from all women who had breast cancers diagnosed in the Netherlands in 1998; and (2) based on unselected patients, who had received a diagnosis of breast cancer in Leiden or Rotterdam between 1996 and 2002 and who were participating in a prospective study of the prevalence of gene mutations. A number of differences in tumour characteristics were seen between women in the screening study compared with the two control groups. Significantly more women in the screening study had tumours less than 10 mm (43.2%) compared with those in control group 1 (14.0%; p<0.001) or control group two (12.5%; p=0.04). In addition, the rates of node-positive tumours were lower in the screening study women (21.4%), compared with control group 1 (52.4%; p<0.001) and control group two (56.4%; p=0.001). The authors concluded that “MRI screening did indeed contribute to the early detection of hereditary breast cancer”. They also noted that tumours greater than 2 cm were found more often in known mutation carriers than the other two risk groups (ie high risk and moderate risk) and that as such, “more frequent screening is needed for women with these mutations”. A list of the characteristics of all tumours found in the MARIBS,[2] Warner,[4] Stoutjesdijk[5] studies is shown in Appendix F.

QUALITY OF LIFE

The publication by Rijnsburger and colleagues[19] describes the quality of life data collected in the Dutch MRI study. Women participating in the MRISC[3] study at one of the study sites were invited to participate in a health-status study. Of the 519 women invited, 334 agreed to participate. Health-status data were collected at baseline (two months prior to screening; N=329), time of screening (N=316) and post screening (one or four weeks; N=288). The questionnaire used in the study included a generic health profile measure (SF-36), a generic

preference-based measure of quality of life (EQ-5D), the somatic subscale of the SCL-90, self-developed screen-specific items and other measures (not reported in this publication). In addition, details of patient characteristics, demographics and patient and family disease history were collected. Women were divided into subgroups according to risk categories (*BRCA1/2* mutation carriers, high risk and moderate risk), screening modality (CBE alone or in combination with MRI and mammography) and whether they had additional diagnostic evaluation after screening (yes or no).

Based on their results, the authors made the following observations:

- the study sample showed better health-related quality of life compared to the general population
- there were no significant changes in health-related quality of life or distress over time
- the impact of screening on health status did not differ between risk categories
- more women considered mammography to be more painful than MRI, while more women experienced anxiety due to MRI compared with mammography.

The authors note that the results do not provide evidence for a distress-raising effect of screening and conclude that screening for breast cancer in high-risk women does not have an unfavourable impact on short-term generic health-related quality of life and general distress. However, it may be possible that the short duration of any impairment in quality of life and the insensitivity of the quality of life instruments lead to an inability to detect any differences.

DISEASE-FREE AND OVERALL SURVIVAL

In the MRISC[3] study, none of the 50 patients diagnosed with breast cancer had died within 87.6 woman-years of follow-up (mean of 1.5 years per patient). Contralateral breast cancer occurred in one patient. A patient with non-Hodgkin's lymphoma died. However, none of the studies were designed to investigate the impact of MRI screening upon patient survival.

ONGOING STUDIES

In order to identify ongoing studies of MRI screening for women at high risk of breast cancer, a number of clinical trial websites were searched including Current Controlled Trials (http://www.controlled-trials.com), Clinicaltrials.gov (http://clinicaltrials.gov/ct) and the National Cancer Institute (http://cancernet.nci.nih.gov/clinicaltrials). Only one relevant ongoing trial was identified,[36] as summarised in Table 15.

Table 15. Ongoing MRI breast cancer screening study: National Cancer Institute Clinical Trial[36]

Title	Study type and location/s	Objectives	Participants
Pilot screening study of breast imaging outcome measures in women at high genetic risk of breast cancer	Screening Bethseda, USA	• To assess whether imaging procedures such as MRI and PET scans improve the ability to detect cancer in women who have a high genetic risk for breast cancer • In addition, a self-administered questionnaire will be used to assess a number of issues, including the psychosocial impact of participation in a high-risk screening program and the perceived burden (distress/pain/ discomfort) of the procedures used in the study (ductal lavage, MRI, PET)	• 25–56 years • *BRCA1/2* gene carrier • More than 5 years since breast or ovarian cancer • Received previous genetic counselling • No previous radiation therapy to both breasts • No previous surgery to remove both breasts or both ovaries • No breast implants

CONCLUSIONS

DIAGNOSTIC PERFORMANCE OF MRI AS AN ALTERNATIVE TO MAMMOGRAPHY

When compared to mammography alone, the results of the included studies suggest that MRI alone is approximately twice as sensitive (77% vs 40%) and <10% less specific, when used for screening women at high risk of developing breast cancer. This was the case in all women considered to be at high risk and the subgroup of women who had *BRCA1* or *BRCA2* mutations.

DIAGNOSTIC PERFORMANCE OF MRI IN ADDITION TO MAMMOGRAPHY

The addition of MRI to mammography for the screening of women at high risk of breast cancer resulted in different diagnostic performance depending upon the definition of a positive result. When a positive result was defined as either test being positive, the sensitivity was approximately 94%, comparing favourably with mammography alone (~ 40%). However, combining the MRI and mammography tests this way does result in a sacrifice in specificity when compared with mammography alone (77% vs 94%). Results were similar between all women at high risk and the subgroup of women with *BRCA1/2* mutations.

When a positive result depended upon both tests being positive, the resulting sensitivities were 23% for all women at high risk (compared with 40% for mammography alone) and 56% for the subgroup of women with *BRCA1/2* mutations (compared with 36% for mammography alone). For this definition of a positive result, specificity was 98% in all women at high risk and 90% in the subgroup of women with *BRCA1/2* mutations (compared with 94% and 96% respectively for mammography alone).

COMPARISON TO PREVIOUSLY PUBLISHED SYSTEMATIC REVIEWS

The results shown in this review are similar to those found in previously conducted systematic reviews which all noted the improved sensitivity and slightly lower specificity associated with MRI alone compared with mammography alone. [6,7,9,10,12,13]

It should be noted that the present review includes the final results of three prospective studies,[2–4] two of which have been included in only the most recent of the previous systematic reviews. The fourth study included in this review is a retrospective study,[5] which was included in three of the previously published reviews. The majority of studies included in the previously published reviews were excluded from this review due to the small number of cancers detected (ie < 10). In these smaller studies, in which less than 10 cancers were detected, the sensitivity of MRI has tended to be higher than in the more recent, larger studies.

It has been suggested in previous systematic reviews that MRI may have a particular role among younger women at higher risk of developing breast cancer. However, the current systematic review was unable to identify evidence that specifically supports the targeting of MRI screening to younger women, relative to higher risk women in general.

It should be noted that studies of MRI screening for women at high risk of breast cancer are limited to the assessment of the diagnostic performance of MRI versus other screening modalities. To date, studies have not evaluated whether improvements in sensitivity translate into improved long-term health outcomes for patients such as survival.

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APPENDIX A

RISK OF OVARIAN CANCER[1]

Women are considered to be at potentially higher risk of developing ovarian cancer if they meet at least one of the following criteria:

- previous ovarian or breast cancer
- one first-degree relative diagnosed with epithelial ovarian cancer in a family of Ashkenazi Jewish ancestry
- two first- or second-degree relatives on the same side of the family diagnosed with epithelial ovarian cancer, especially if one or more of the following features occurs on the same side of the family:
    - additional relative(s) with breast or ovarian cancer
    - breast cancer diagnosed before the age of 40
    - bilateral breast cancer
    - breast **and** ovarian cancer in the same woman
    - breast cancer in a male relative
- three or more first- or second-degree relatives on the same side of the family diagnosed with any cancers associated with hereditary non-polyposis colorectal cancer: colorectal cancer (particularly if diagnosed before the age of 50), endometrial cancer, ovarian cancer, gastric cancer and cancers involving the renal tract
- member of a family in which the presence of a high-risk ovarian cancer gene mutation has been established
- at potentially high risk for breast cancer.

APPENDIX B

LITERATURE SEARCH STRATEGY

EMBASE.com search strategy (encompassing Medline and Embase databases): 5 Jul 2005

No	Search terms	Hits
1	'breast cancer'/exp OR 'breast cancer'	151,006
2	('mri'/exp OR 'mri') OR ('magnetic resonance'/exp OR 'magnetic resonance')	361,236
3	screen OR ('screening'/exp or 'screening')	342,537
4	#1 AND #2 AND #3	470
5	#5 AND [english]/lim AND [humans]/lim	343

Cochrane Library search strategy: 5 Jul 2005

No	Search terms	Hits
1	*MRI* in All Fields or *magneric resonance* in All Fields in all products	3318
2	*Breast* in All Fields in all products	11553
3	*Screen* in All Fields or *screening* in All Fields in all products	11168
4	(#1 AND #2 AND #3)	18

Note: All Products encompass the following databases: the Cochrane Database of Systematic Reviews (CDSRs); the Database of Abstracts of Reviews of Effectiveness (DARE); The Cochrane Central Register of Controlled Trials (CENTRAL); The Cochrane Database of Methodology Reviews (Methodology Reviews); The Cochrane Methodology Register (CMR); Health Technology Assessment Database (HTA); and the NHS Economic Evaluation Database (NHS EED).

Health Technology Assessment and Guideline Groups internet search

Country	Acronym	Organisation	Website
Australia	CHPE/HEU	Centre for Health program Evaluation/Health Economics Unit	http://chpe.buseco.monash.edu.au/
	MSAC	Medicare Services Advisory Committee	http://www.health.gov.au/msac/
	ANZHSN	Australia and New Zealand Horizon Scanning Network	http://www.horizonscanning.gov.au/index.htm
Canada	AETMIS	Agence d'évaluation des technologies et des modes d'intervention en santé	http://www.aetmis.gouv.qc.ca/en/index.php?menu=1
	AHFMR	Alberta Heritage Foundation for Medical Research	http://www.ahfmr.ab.ca/
	CCOHTA	Canadian Coordinating Office Health Technology Assessment	http://www.ccohta.ca/entry_e.html
Finland	FinOHTA	Finnish Office for Health Care Technology Assessment	http://www.stakes.fi/finohta/e/
New Zealand	NZGG	New Zealand Guidelines Group	http://www.nzgg.org.nz/index.cfm?screensize=1024&ScreenResSet=yes
	NZHTA	New Zealand Health Technology Assessment	http://nzhta.chmeds.ac.nz/
Sweden	SBU	Statens Beredning för Medicinsk Utvärdering	http://www.sbu.se/www/index.asp
United Kingdom	CRD	Centre for Reviews and Dissemination	http://www.york.ac.uk/inst/crd/
	NCCHTA	National Coordinating Centre for Health Technology Assessment	http://www.hta.nhsweb.nhs.uk/
	NHS QIS	NHS Quality Improvement Scotland	http://www.nhshealthquality.org/nhsqis/qis_HomePage_New2.jsp?pContentID=43&p_applic=CCC&p_service=Content.show&
	NHSC	National Horizon Scanning Centre	http://www.publichealth.bham.ac.uk/horizon/
	NICE	National Institute for Clinical Excellence	http://www.nice.org.uk/
United States	AHRQ	Agency for Healthcare Research and Quality	http://www.ahrq.gov
	ECRI	Formerly the Emergency Care Research Institute	http://www.ecri.org/
	ICSI	Institute for Clinical Systems Improvement	http://www.icsi.org/index.asp
	OHPR	Oregon Health Policy and Research	http://www.ohppr.state.or.us/index.htm
	VATAP	Veterans Affairs Technology Assessment Program	http://www.va.gov/vatap/

APPENDIX C

LIST OF EXCLUDED CITATIONS AND REASONS FOR EXCLUSION

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Reason for exclusion: Title/abstract: Excluded. Not a clinical study.

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APPENDIX D

SUMMARY OF STUDIES EXCLUDED FOR DETECTING <10 CANCERS

Citation	Population	Number screened	Number of cancers detected
Lehman *et al.*	Previous breast cancer or ≥25% risk. Median age 42.5 (27–72) years.	390	4
Hartman *et al.*[11]	Documented *BRCA1/2* mutation or a > 10% risk of developing breast carcinoma at 10 years based on Claus model.	41	1
Liberman *et al.*[16]	Asymptomatic women with normal mammograms with high risk of developing breast cancer (ie previous breast cancer, biopsy-proven LCIS or atypia, or family history of breast cancer). Median age 50 (23–82) years.	367	9
Podo *et al.*[18]	Proven mutation carrier or first-degree relative with proven mutation. Mean age 46.0 (25–77) years.	105	8
Trecate *et al.*[22]	Suspected or proven to carry breast cancer susceptibility gene on the basis of personal or family history or genetic analysis. Age range 30–61 years.	23	4
Cilotti *et al.*	Proven or suspected *BRCA1/2* gene mutation. Age range 28–52 years.	8	1
Trecate *et al.*[22]	Note: subset of subjects from Podo et al (2003).[18] Proven mutation carrier or first-degree relative with proven mutation. Age range 30–61 years	23	4
Kuhl *et al.*[14]	Personal history or family history of breast cancer diagnosed before age 35; personal history or family history of ovarian cancer diagnosed before age 40; personal history or family history of bilateral breast cancer; personal history or family history of both breast and ovarian cancer; family history of at least relatives with breast or ovarian cancer diagnosed at or before 50 years; man with a personal or family history (male relative) of breast cancer. Mean age 39 ± 9 years.	192 asymptomatic women (also 6 symptomatic women not included here)	9 in asymptomatic women
Tilanus-Linthorst *et al.*[20,21]	Women at moderate or high risk based on tables of Houlston and Claus. Mean age: All women at high risk 42.9 (20-74) years. Subgroup of women with MRI (> 50% breast density on mammogram) 41.5 (22–68) years.	294 moderate risk and 384 high risk. 109 with > 50% breast density on mammogram had MRI.	3

APPENDIX E

QUALITY ASSESSMENT

Quality assessment of studies was undertaken using the considerations listed below (modified for the purposes of this review from the Cochrane Methods Group on Systematic Reviews of Screening and Diagnostic Tests: Recommended Methods)[25]

- Was the test compared with a valid reference measure?
- Were the test and the reference standard measured independently (blind) of each other (avoidance of measurement bias)?
- Were all patients assessed by the reference standard or was the choice of patients who were assessed by the reference standard independent of the test results (avoidance of verification bias)?
- Was the test performed independently of all other clinical information?
- Was the reference standard measured before any treatment interventions were started with knowledge of test results (avoidance of treatment paradox)?
- Were the MRI results independent of the mammography/other results?
- Were the mammography/other results independent of the MRI results?
- Were MRI and mammography/other measured at a similar time?
- Did the study include a consecutive sample of high-risk patients who were referred for screening?
- Was a representative spectrum of disease captured?
- Was the disease prevalence indicative of the target population?

APPENDIX F

TUMOUR CHARACTERISTICS

Screening round	Study	Detected by					Risk group			Age	Tumour type	DCIS size/invasive tumour size
		MRI	M	CBE	US	Interval	*BRCA1*	*BRCA2*	FH			
1	Leach 2005[2]	✓	✓	-	-	×		✓		NR	IDC + DCIS	NK/15 mm
1	Leach 2005[2]	✓	✓	-	-	×			✓	NR	IDC + DCIS	NK/12 mm
1	Leach 2005[2]	✓	✓	-	-	×	✓			NR	IDC + DCIS	4 mm/7 mm
1	Leach 2005[2]	✓	✓	-	-	×			✓	NR	DCIS	5 mm
1	Leach 2005[2]	✓	×	-	-	×	✓			NR	IDC + DCIS	NK/8 mm
1	Leach 2005[2]	✓	×	-	-	×	✓			NR	IDC + DCIS	NK/6 mm
1	Leach 2005[2]	×	✓	-	-	×		✓		NR	DCIS	9 mm
1	Leach 2005[2]	✓	×	-	-	×		✓		NR	IDC	22 mm
1	Leach 2005[2]	✓	×	-	-	×	✓			NR	IDC	31 mm
1	Leach 2005[2]	✓	×	-	-	×			✓	NR	IDC + DCIS	9 mm
1	Leach 2005[2]	✓	×	-	-	×	✓			NR	IDC + DCIS	16 mm
1	Leach 2005[2]	✓	×	-	-	×	✓			NR	IDC	21 mm
1	Leach 2005[2]	✓	×	-	-	×	✓			NR	IDC	18 mm
1	Leach 2005[2]	✓	×	-	-	×		✓		NR	IDC	20 mm
1	Leach 2005[2]	×	✓	-	-	×			✓	NR	DCIS	4 mm
1	Leach 2005[2]	×	✓	-	-	×			✓	NR	IDC	6 mm
1	Leach 2005[2]	×	✓	-	-	×			✓	NR	IDC + DCIS	NK/5 mm
1	Leach 2005[2]	×	×	-	-	✓	✓			NR	DCIS	6 mm
1	Warner 2004[4]	✓	×	×	×	×	✓			51	IDC	5 mm
1	Warner 2004[4]	×	✓	×	×	×		✓		51	DCIS	NR
1	Warner 2004[4]	✓	×	×	×	×	✓			46	IDC	5 mm
1	Warner 2004[4]	✓	×	✓	-	×		✓		49	IDC	10 mm
1	Warner 2004[4]	✓	✓	×	✓	×	✓			52	IDC	7 mm
1	Warner 2004[4]	✓	✓	×	✓	×	✓			33	IDC	10 mm
1	Warner 2004[4]	✓	✓	×	×	×	✓			48	IDC	10 mm
1	Warner 2004[4]	✓	✓	×	×	×		✓		46	DCIS	15 mm
1	Warner 2004[4]	✓	×	✓	×	×		✓		54	DCIS	30 mm
1	Warner 2004[4]	✓	×	×	×	×		✓		63	DCIS	40 mm
1	Warner 2004[4]	✓	×	×	×	×		✓		35	IDC	20 mm
1	Warner 2004[4]	✓	×	×	×	×	✓	·		50	IDC	15 mm
1	Warner 2004[4]	×	×	×	✓	×		✓		60	ILC	19 mm
1	Stoutjesdijk 2001[5]	✓	✓	-	-	-	✓			35	MDC	NR
1	Stoutjesdijk 2001[5]	✓	×	-	-	-	✓			31	MALT L	NR
1	Stoutjesdijk 2001[5]	✓	✓	-	-	-			✓	44	IDC	NR
1	Stoutjesdijk 2001[5]	✓	✓	-	-	-			✓	47	IDC	NR
1	Stoutjesdijk 2001[5]	✓	×	-	-	-			✓	50	IDC	NR
1	Stoutjesdijk 2001[5]	✓	×	-	-	-			✓	42	DCIS	NR
1	Stoutjesdijk 2001[5]	✓	✓	-	-	-			✓	30	DCIS	NR
1	Stoutjesdijk 2001[5]	✓	×	-	-	-			✓	46	ILC	NR
1	Stoutjesdijk 2001[5]	✓	×	-	-	-			✓	49	IDC + ILC	NR
1	Stoutjesdijk 20015	✓	✓	-	-	-			✓	40	IDC	NR
1	Stoutjesdijk 20015	✓	×	-	-	-			✓	44	IDC + ILC	NR

1	Stoutjesdijk 2001[5]	✓	×	-	-	-			✓	50	IDC + ILC	NR
2	Leach 2005[2]	✓	✓	-	-	×		✓		NR	DCIS	17 mm
2	Leach 2005[2]	✓	✓	-	-	×	✓			NR	IDC + DCIS	NK/31 mm
2	Leach 2005[2]	✓	×	-	-	×	✓			NR	IDC	10 mm
2	Leach 2005[2]	✓	×	-	-	×			✓	NR	IDC + DCIS	1 mm/15 mm
2	Leach 2005[2]	✓	×	-	-	×	✓			NR	IDC + DCIS	10 mm/20 mm
2	Leach 2005[2]	✓	×	-	-	×			✓	NR	IDC	11 mm
2	Warner 2004[4]	✓	×	×	✓	×		✓		47	IDC	7 mm
2	Warner 2004[4]	✓	✓	×	✓	×	✓			44	IDC	15 mm
2	Warner 2004[4]	×	✓	×	×	×		✓		38	DCIS	NR
2	Warner 2004[4]	✓	✓	×	×	×	✓			5450	IDC	20 mm
2	Warner 2004[4]	✓	×	×	×	×	✓			50	IDC	6 mm
2	Warner 2004[4]	×	×	×	✓	×	·	✓		39	IDC	15 mm
2	Warner 2004[4]	✓	×	×	✓	×	✓			53	IDC	10 mm
3	Leach 2005[2]	✓	✓	-	-	×			✓	NR	IDC + DCIS	NK/20 mm
3	Leach 2005[2]	✓	×	-	-	×			✓	NR	IDC	6 mm
3	Leach 2005[2]	✓	×	-	-	×		✓		NR	IDC + DCIS	NK/8 mm
3	Warner 2004[4]	×	×	-	×	✓	✓			40	IDC	17 mm
3	Warner 2004[4]	✓	×	×	×	×		✓		40	DCIS	60 mm
4	Leach 2005[2]	✓	✓	-	-	×	✓			NR	IDC + DCIS	NK/30 mm
4	Leach 2005[2]	✓	×	-	-	×	✓			NR	ILC	15 mm
4	Leach 2005[2]	×	✓	-	-	×		✓		NR	DCIS	18 mm
5	Leach 2005[2]	✓	×	-	-	×			✓	NR	IDC + DCIS	3 mm/10 mm
5	Leach 2005[2]	✓	×	-	-	×			✓	NR	IDC + DCIS	NK/8 mm
5	Leach 2005[2]	×	✓	-	-	×			✓	NR	IDC + DCIS	7 mm/6 mm
5	Leach 2005[2]	×	×	-	-	✓		✓		NR	IDC + DCIS	8 mm/8 mm

Abbreviations: DCIS, ductal carcinoma in-situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; MALT l, mucosa-associated lymphoid tissue lymphoma; MDC, medullary carcinoma.; NK, not known; NR, not reported.

[a] Represents the most recent screening round for each subject so may have been prior screening rounds.