



Australia and New Zealand Horizon Scanning Network

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# **National Horizon Scanning Unit**

## **Horizon scanning report**

# **MRI Screening for Breast Cancer in Genetically High-Risk Women**

**May 2004**



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ISBN 0 642 82611 0

ISSN

Publications Approval Number: 3598

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The production of this *Horizon scanning report* was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments; MSAC and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

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## Introduction

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The National Horizon Scanning Unit, Department of Public Health, University of Adelaide, on behalf of the Medical Services Advisory Committee (MSAC), has undertaken an Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the introduction and use of magnetic resonance imaging (MRI) screening for breast cancer in genetically high-risk women (Horizon Scanning Register number: 0000062).

MRI is currently utilised in Australia as an imaging modality for the soft tissues of the body such as muscles, nerves, brain, discs and ligaments. It is offered through major public and private hospitals in Australia, however MRI for breast screening is not readily available in Australia and is regarded as a complementary imaging modality to conventional mammography and ultrasound.

This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of MRI screening for breast cancer, its present use, the potential future application of the technology, and its likely impact on the Australian health care system.

This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with MRI screening for breast cancer.

## Background

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### Description of the technology

#### *The procedure*

MRI was first used to image breast tissue in the early 1980s. In the mid 1980s contrast enhanced MR imaging was introduced using gadolinium-diethylenetriamine penta-acetic acid (Gd-DTPA), which exploits the property that cancerous lesions tend to be highly vascularised compared to benign lesions and may take up the contrast agent more rapidly (Coons 1996).

A MRI scanner produces a strong magnetic field. Pulsed oscillating magnetic fields (radio-frequency energy) are used to organise the intrinsic magnetic behaviour of hydrogen nuclei in the body, causing a change in their alignment so that they are oscillating perpendicular to the main field direction, (excitation). Tuned receiver coils detect these magnetic field oscillations through electromagnetic induction (personal communication, Mr Greg Brown<sup>1</sup>). Once the pulse is removed, the nuclei realign or relax at different rates depending on the surrounding environment. The relaxation time is

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<sup>1</sup> Greg Brown is the Senior Radiographer in MRI Research and Development Radiology in the Royal Adelaide Hospital

referred to as T1. In addition to relaxation time, MRI assesses the spin property of nuclei. When the radio-frequency pulse is applied, the nuclei align and the spins come into phase. When the pulse is removed, the spins of the nuclei “de-phase” and the signal decreases. When the spins are completely at random again the MR signal disappears. The time taken for the spins to de-phase is referred to as T2 (FASEB 2002).

Spatial localisation of the MR signal is achieved by the application of “gradient” magnetic fields at specific stages of the MR sequence, causing a predictable relationship between location and resonant frequency that can be resolved. The excitation/ receive cycle is repeated with varying spatial encoding to deliver an array of coded signals that are reconstructed into a set of images with Fourier Transformation mathematics (personal communication, Greg Brown).

Hydrogen nuclei in blood and cerebrospinal fluid have a long relaxation time, compared to those nuclei in tissues, with hydrogen nuclei in fat cells having the shortest relaxation time of approximately 300 milliseconds (FASEB 2002). Gd-DTPA preferentially enters malignant tissue, changing the water properties and therefore the T1 and T2 rates, and this modulates the MRI signal (Furman-Haran et al 2002). The differences in realignment and spin times appear as differences in brightness on the MR image. A series of consecutive two-dimensional images or slices are compiled and assembled by a computer programme to produce a final three-dimensional image (FASEB 2002).

### *Intended purpose*

MRI is primarily used for the investigation of neurological and musculoskeletal disorders such as multiple sclerosis, strokes and tendonitis and is used to image soft tissues such as the brain, muscles, tendons and ligaments. MRI has been of limited use in the detection of cancers (Warren 2001a). MRI may be used as a breast imaging modality, providing additional information to conventional mammography.

The aim of MRI is to provide early detection of breast cancer and to increase the number of therapeutic options available to women at high-risk of breast cancer. Currently women at high-risk of developing breast cancer may opt for increased clinical surveillance, prophylactic mastectomy or chemoprevention. Models suggest that a 30 year old woman who undergoes a prophylactic mastectomy may gain three to five years of life expectancy, however this benefit declines with age with minimal benefit at age 60 years (NHMRC 1999). Prophylactic mastectomy may reduce the risk of breast cancer by at least 90% but doesn't completely eliminate the risk of breast cancer. Women considered to be at high-risk of breast cancer were enrolled in a randomised controlled trial in the United States, which compared breast cancer development in women allocated to receive tamoxifen or placebo, after a follow-up of four years (Forrest & Anderson 1999). Tamoxifen reduced the risk of invasive breast cancer by 49% (two-sided  $P < 0.00001$ ), with cumulative incidence through 69 months of follow-up of 43.4 versus 22.0 per 1000 women in the placebo and tamoxifen groups, respectively (Fisher et al 1998).



Figure 1 Patient undergoing MRI scan of the breast (Printed with permission: Siemens Ltd)

MRI may be especially useful in clinical situations where mammography is considered less accurate or difficult to perform, such as for the examination and imaging of women:

- at increased familial or genetic risk of breast cancer;
- with dense breast tissue;
- following breast surgery, allowing differentiation between carcinoma and scar tissue;
- prior to surgery to assess the size and number of malignant lesions;
- following tumour lysis and prior to surgery as mammography may be impaired by fibrosis induced by tumour lysis;
- with prostheses;
- with unknown primary cancer metastases; and
- young women previously treated for Hodgkin's disease (Ikeda et al 2000; Del Maschio et al 2002; Blue Cross Blue Shield 2003).

Following an MRI scan of the breast, an abnormal finding may require biopsy. If the abnormality cannot be visualised by any means other than MRI, this may require a more invasive procedure, as few, if any, sites in Australia have the appropriate MR-compatible biopsy equipment (personal communication Susan Nicols<sup>2</sup>).

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<sup>2</sup> Susan Nicols is the Manager of the QA program, The Royal Australian & New Zealand College of Radiologists

As MRI does not utilise ionising radiation it has been proposed as a safer option for women with BRCA1 and 2 gene mutations, as these women may be more susceptible to radiation damage (Warren 2001b).

MRI is contraindicated in patients with cardiac pacemakers, automatic cardiac defibrillators, intracranial ferromagnetic aneurysm clips, implanted neurostimulators or bone growth stimulators, intraocular ferromagnetic foreign bodies, breast tissue expanders, cochlear implants, who are pregnant or have allergies to gadolinium (ICSI 2003).

*Clinical need and burden of disease*

In Australia, breast cancer is the most common registrable cancer in females. There were 11,314 new cases of breast cancer and 2,521 deaths from breast cancer reported in Australia for the year 2000. Australian women have an approximate life time risk of one in eleven of developing breast cancer before the age of 75 years (AIHW and AACR 2003; NHMRC 1999). The age specific mortality rates for breast cancer in Australia are shown in Table 1.

Table 1 Age-specific mortality rates <sup>a</sup> for breast cancer in Australia, 1998-2001

Age group <sup>b</sup>													
20-24	25-29	75-79	35-39	75-79	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
0.2	0.7	3.2	8.5	17.9	29.2	42.1	53.7	63.1	66.5	86.9	101.3	129.2	186.7

<sup>a</sup> Rate per 100,000 women, <sup>b</sup> No mortality was recorded for women aged <20 years (AIHW and DHA 2003)

In New Zealand, the number of new female breast cancer registrations was 2,306 and the number of registered female breast cancer deaths was 622, for the year 2000. The age standardised incidence and mortality for breast cancer is 89.4 and 21.1 per 100,000 respectively (New Zealand Health Information Service<sup>3</sup>) New Zealand women have an approximate life time risk of one in ten of developing breast cancer. The risk is similar for Maori and non-Maori women (BreastScreen Aotearoa 2003).

Women may be described as being at high risk of developing breast cancer if they have one or more of the following criteria:

- breast or ovarian cancer diagnosed in three or more first- or second-degree relatives on the same side of the family; or
- two or more 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)
  - bilaterality
  - onset of breast cancer before the age of 40
  - onset of ovarian cancer before the age of 50
  - breast and ovarian cancer in one individual
  - Jewish ancestry
  - breast cancer in a male relative; or

<sup>3</sup> New Zealand Health Information Service, Ministry of Health (2004), Wellington, New Zealand

- one first- or second-degree relative diagnosed with breast cancer at age 45 years or younger, plus another first- or second-degree relative on the same side of the family with bone or soft tissue sarcoma at age 45 or younger; or
- a demonstrated germline mutation in a high-risk breast cancer-associated gene such as BRCA1, BRCA2 or Tp53 by genetic testing (NHMRC 1999).

It has been estimated that this group would be less than one per cent of the total female population of Australia, and although this group has a higher risk than the general population, the majority will *not* go on to develop breast cancer (NHMRC 1999).

The BRCA1 and 2 mutations were identified as being associated with breast cancer in the mid 1990s (Miki et al 1994; Wooster et al 1995). The BRCA1 gene is mapped to chromosome 17q21 and encodes for a protein with several functional domains including a transcriptional co-activator. The BRCA2 gene maps to chromosome 13q12 and encodes for a protein that is twice the size of that produced by BRCA1, but has no well-defined functional domains. The role of BRCA1 and 2 is unclear, however, it is thought that they play a role in DNA repair, the regulation of gene expression and embryogenesis. The BRCA genes are highly heterogenous and by 2002 the National Human Genome Research Institute had identified 864 distinct nucleotide variants in BRCA1 and 882 in BRCA2. The Tp53 gene is one of the most common mutations and is associated with malignancies such as soft tissue and bone sarcomas, brain tumours, leukaemias, adrenocortical tumours, breast cancer and Li-Fraumeni syndrome. Tp53 gene products have many biological functions, including checking the control of the cell cycle after DNA damage (Marsh et al 2001). Several methods are available to identify mutations, however, precise characterisation requires direct sequencing, which makes screening for these mutations a difficult and expensive task (NHMRC 1999; Radice 2002). Research is also in progress for several other gene variants that are yet to be identified (Mote et al 2004).

Genetic screening for BRCA1 and 2 is available in only a few laboratories within Australia but currently does not have a Medicare Benefits Schedule (MBS) item number and is only available for women who have been referred by a familial cancer service, after extensive counselling (National Breast Cancer Centre 2000). In Australia, the number of women tested for BRCA mutations is small, with less than 70 women tested in South Australia during 2003 (see Figure 2). Similar figures would apply for other Australian states, with adjustment for differences in population sizes.

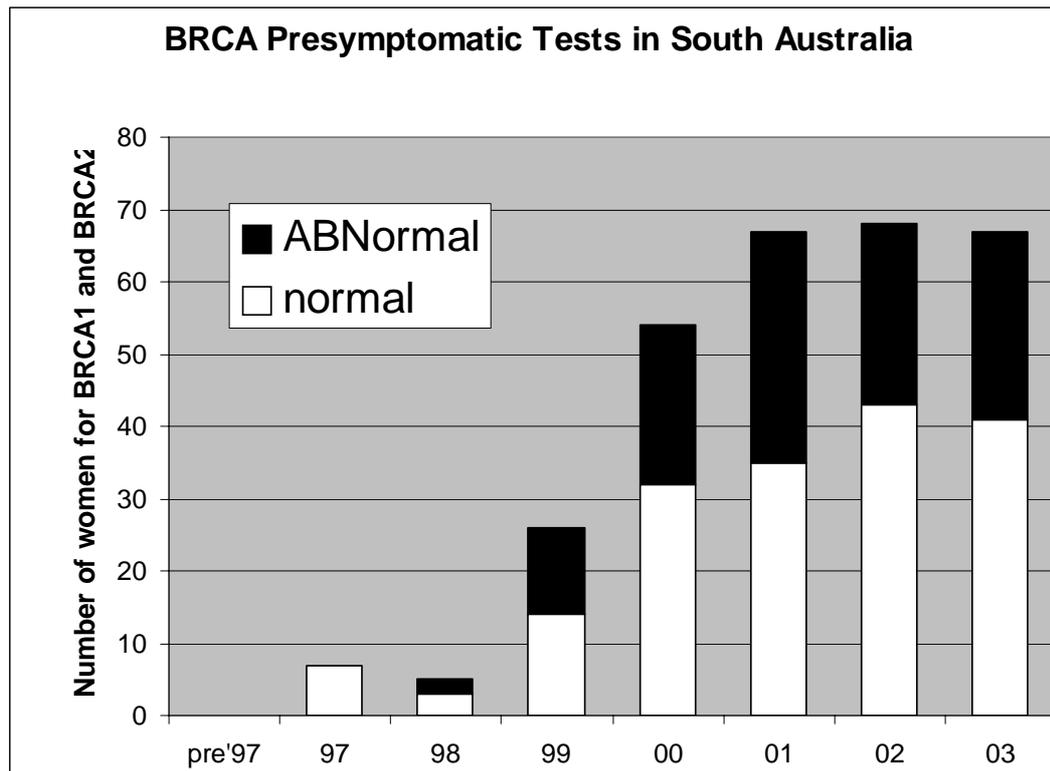


Figure 2 Number of familial, asymptomatic high-risk women tested for BRCA1 and BRCA2 in South Australia (Printed with permission: Professor G Suthers, South Australian Familial Cancer Service)

In 1999, Southey et al conducted a population-based, case-control family study of early onset breast cancer in Australia and the incidence of the BRCA1 mutation. Two groups of women with breast cancer were chosen for BRCA1 sequencing by random stratified sampling: 47 women who reported a familial history of breast cancer and 44 women with no family history. Of the 47 women with a family history, only 1/47 (2%) had a protein-truncating BRCA1 mutation compared to 2/42 (5%) in the group of women without a family history. Overall, Southey et al (1999) estimated the proportion of Australian women with diagnosed breast cancer before the age of 40 who carry a germline mutation in the BRCA1 gene was 3.8 per cent [95% CI 0.3%, 12.6%]. In addition 67 women without breast cancer were sequenced, none of whom carried the protein truncating mutation. However, a number of polymorphisms and rare variants were detected in both cases and controls (Southey et al 1999). Similar results were reported in the United Kingdom, where 1,220 samples from women with breast cancer were sequenced fully. This study found 0.7 per cent and 1.3 per cent of women with breast cancer carried the BRCA 1 and BRCA2 mutations, respectively (Anglian Breast Cancer Study Group 2000). The Australian study by Marsh et al (2001) analysed 71 familial breast cancer patients and 143 control individuals for the Tp53 mutation, G13964C, and found 3/71 (4.2%; 95% CI [0%, 8.9%]) of the familial breast cancer group and 5/143 (3.5%; 95% CI [0.6%, 6.4%]) of controls with this mutation (Marsh et al 2001).

The frequency of these mutations in the female population of Australia are described in Table 2. Women who carry the BRCA1 or 2 mutations have a 40-

80% lifetime risk of developing breast cancer. In addition, more than half of these patients will develop breast cancer before the age of 50 and a significant number before the age of 35 (Kuhl 2002). The lifetime risk of developing breast cancer is summarised in Table 3.

Table 2 Genes associated with an inherited predisposition to breast cancer

Gene	Mutation frequency	Major sites at risk	Risk to age 75 in mutation carriers
BRCA1	~ 1/1,000	breast ovary	40-80% 10-60%
BRCA2	~ 1/1,000	breast ovary	40-80% 10-40%
Tp53	~ 1/10,000	breast bone or soft tissue	50% < 10- 50%

(National Breast Cancer Centre 2000)

Table 3 Lifetime risk of developing breast cancer

General population	High-risk women	BRCA1, BRCA2 or Tp53 carriers
1 in 11 (9%)	1 in 8 (11.5%) and up to 1 in 4 (25%) Risk is 1.5 to 3-fold higher than the population average	1 in 4 (25%) and up to 1 in 2 (50%) Risk is more than 3-fold higher than the population average

(National Breast Cancer Centre 2000)

Women at high-risk of breast cancer tend to develop disease at a significantly younger age and are usually pre-menopausal. These women tend to have dense breast tissue and mammography, the gold standard for breast screening, has been demonstrated to be insensitive in the presence of dense breast tissue. Breast cancers in younger patients also tend to be more aggressive, high-grade (see Appendix A) and receptor negative, making early diagnosis critical (Kuhl 2002; Blue Cross Blue Shield 2003). There is limited evidence that mammographic screening offers any survival benefit to women with a family history of breast cancer (The Royal College of Radiologists 2003).

#### *Stage of development*

MRI for breast screening is not readily available in Australia and is regarded as a complementary imaging modality, providing additional information to mammography (NHMRC 1999). MRI does not currently receive MBS funding for this indication. It is not recommended for the screening of all women in the population due to its high cost and the lack of knowledge in respect to the sensitivity and specificity of MRI in screening the general population (Coons 1996). Currently there are no agreed standard interpretation criteria for evaluating breast MRI images and a lack of standardisation of technique (Del Maschio et al 2002). Some malignancies, such as lobular carcinoma and ductal carcinoma in situ (DCIS), may not demonstrate appreciable enhancement with MRI. In addition, hormonal fluctuations may affect contrast enhancement and it has been recommended that MRI screening of breast tissue be conducted during the first two weeks of the menstrual cycle (Blue Cross Blue Shield 2003). Uptake of MRI for breast screening should only be considered for women at high-risk of developing breast cancer.

In New Zealand, MRI screening for breast cancer in high-risk women is done on an ad hoc basis and is not used as a tool in an organised population screening programme. MRI is costly and not funded by District Health Boards in the public system. No data are available on the numbers of women screened in this manner.

MRI in New Zealand is almost always used as a diagnostic tool for breast cancer. It is undecided whether or not MRI for high-risk women should be used as a screening tool in New Zealand until the results of the UK MRI breast screening study (MARIBS) are known. At this stage the low specificity, lack of MRI compatible biopsy equipment in NZ and high cost prevent it being widely promoted as a screening tool (personal communication, Dr Madeline Wall<sup>4</sup>).

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## Treatment Alternatives

### Existing comparators

The current gold standard in Australia for breast cancer detection is the mammogram, which consists of a set of two-dimensional X-rays of the breast. The patient's breasts are placed between two plates, which firmly compress the breast, flattening and pulling the breast tissue away from the chest wall. The standard mammographic examination includes two sets of low-dose X-rays, one taken from the side (medio-lateral oblique) and one from the top view (cranio-caudal) resulting in a two-dimensional radiographic representation of the breast. The procedure takes approximately 20 minutes. Double readings of screening mammograms is mandatory in Australia (Forrest & Anderson 1999; President and Fellows of Harvard College 2003).

The risk of breast cancer development associated with a standard mammogram is extremely small. However, the risk to women with a genetic predisposition to breast cancer after repeated exposure to the radiation of a mammogram is unknown. The harm of radiation exposure in these potentially susceptible women must be weighed up against the potential diagnostic benefits. The use of ionising radiation limits the age of patients who can undergo a mammogram and the frequency with which mammograms can be used. The radiation dose used for a mammogram will depend on the breast size, thickness and density of the tissue (Warren 2001b).

The initial mammogram serves as a baseline reference to enable the radiologist and clinicians to track any changes in the breast that may occur over time. On a mammogram of normal breast tissue, fat will appear as grey and the denser breast tissue as white. Abnormalities are easier to identify in older, post-menopausal women as their breasts have proportionally greater amounts of fat. Mammography may not be as sensitive in older women who are taking hormone replacement therapy, which will result in denser breast tissue. Mammographic screening can detect cancer of the breast in its preclinical

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<sup>4</sup> Dr Madeleine Wall, Clinical Leader BreastScreen Aotearoa, NZ Ministry of Health.

phase, detecting abnormalities as small as 5mm, which would not be detectable by palpation. Mammograms will detect microcalcifications, of which 80 per cent are harmless and will not lead to cancer. Microcalcifications that are dispersed evenly throughout the breast are likely to be benign whereas those that are clustered may be cancerous. On finding an abnormality, the radiologist may recommend a repeat mammogram, additional magnified X-rays or a biopsy (Forrest & Anderson 1999; President and Fellows of Harvard College 2003).

Breast screening was introduced as a national program in Australia in 1991 and is known as BreastScreen Australia. The program aims to provide mammographic screening at two-year intervals for asymptomatic women aged 50-69 years, however women aged 40-49 and over 70 years of age are eligible to attend free of charge (National Breast Cancer Centre 2002; Forrest & Anderson 1999). Diagnostic mammographic examinations are available under the MBS (item numbers 59300 and 59303) for women with symptoms. The total number of mammogram examinations conducted in Australia during 2001 is shown in Table 4. In the year 2000-2001 BreastScreen Australia screened 1,567,544 women as part of their ongoing program. Of these 1,063,479 (68%) were in their target group of 50-69 years of age. The participation rate for all women in Australia for this target group was 56.9 per cent (AIHW and DHA 2003). Current data suggests that screening 10,000 women aged 50-69 years of age, over 10 years, will prevent approximately 18 deaths, compared to preventing seven deaths in 10,000 women aged 40-49 years of age (National Breast Cancer Centre 2002).

Table 4 Number of mammogram examinations, by age, in Australia for the year 2001<sup>a</sup>

Frequency of mammogram	Age (years)						
	18-29	30-39	40-49	50-59	60-69	70+	Total
Annually	9.9	28.8	144.4	227.2	118.0	72.1	600.5
>1, up to 2 years	2.4	18.4	195.3	510.3	363.7	214.7	1,304.8
>2 years apart		6.1	12.8	9.3	6.3	7.9	42.5
Not stated			4.6	13.6	6.7	9.3	34.3
Total	12.4	53.3	357.2	760.5	494.7	304.0	1,982.1

<sup>a</sup> Number of females '000 (AIHW and DHA 2003)

## Clinical Outcomes

### Effectiveness

*MRI vs mammograms in asymptomatic women with no prior history of breast cancer*

Two full text studies and one abstract study described the results of screening asymptomatic women at high-risk of developing breast cancer, who had *no previous history* of breast cancer (Table 5). The low quality study by Leach (2002) described the results from the multi-centre British MRI screening trial

(level 3b diagnostic evidence). This study screened 415 asymptomatic women who underwent a total of 1,236 examinations by both MRI and mammography. Leach reported that a total of 15/415 (3.6%) were diagnosed with breast cancer but failed to report how many were diagnosed by MRI alone, mammography alone, or by both modalities. The largest screening study to date, the Dutch National Screening Study, comprises 1,848 asymptomatic women. Preliminary results for this screening trial were presented by Kriege et al (2003), in an abstract to the American Society of Clinical Oncology. Sensitivity was reported as 71, 36 and 16 per cent and specificity was 88, 95 and 97 per cent for MRI, mammography and clinical examination respectively (DCIS and invasive carcinoma). In addition, this study reported on the sensitivity for MRI and mammography to detect invasive cancers, which was 83 and 26 per cent respectively.

As previously mentioned, breast cancers in younger patients tend to be aggressive and high-grade (Kuhl 2002; Blue Cross Blue Shield 2003). The three studies by Leach et al (2002), Stoutjesdijk et al (2001) and Kriege et al (2003) all reported the majority of breast cancers detected as invasive or grade III (see Appendix A).

Table 5 MRI vs mammography for the diagnosis of breast cancer in *asymptomatic* women at high-risk of developing breast cancer, with *no previous history* of breast cancer

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Leach (UK MRI breast screening study -MARIBS) (2002), United Kingdom	3b	Cross-classification of patients on MRI and mammography	415 asymptomatic women at >50% familial risk of developing breast cancer and no previous history of breast cancer Median age 41 years, range 35-49 years	415 women underwent 1,236 examinations 15/415 (3.6%) women diagnosed with breast cancer (8 grade III, 3 grade II, 1 grade I) 3/15 (20%) = DCIS 12/15 (80%) = invasive cancer Of the 15 women, 2/15 (13%) had known BRCA1 or BRCA2 mutations, 10/15 (67%) were from families with known history
Stoutjesdijk et al (2001), The Netherlands	3b	Cross-classification of patients on MRI, mammography and compared to core-needle and/or excisional biopsy	75 asymptomatic women with family history of breast or ovarian cancer, BRCA1 or BRCA2 mutation and no personal history of breast cancer, at high-risk of developing breast cancer  Age range 21-71 years of age MRI and mammogram conducted within 4 months of each other	13/75 (17%) women diagnosed with breast cancer (6 grade III, 5 grade II, 1 grade I, 1 grade not stated) 2/13 (15%) women had known BRCA1 mutations Diagnostic accuracy (area under the curve, AUC) <b>Mammography</b> 0.70 [95%CI 0.60, 0.80] <b>MRI</b> 0.98 [95%CI 0.95, 1.0] <b>Difference in AUC</b> 0.28 [95%CI 0.17, 0.39], p=0.02 <sup>a</sup>

Kriege et al (2003), (Dutch National Screening Study, MRISC), The Netherlands Abstract	3b	Cross-classification of patients on MRI, CBE and mammography, compared to histology	<p>1,848 asymptomatic woman at high-risk of developing breast cancer (&gt;15% risk of breast cancer due to familial or genetic disposition and no previous history of breast cancer)</p> <p>294/1848 (16%) with known BRCA1 or BRCA2 mutation</p> <p>Mean age 41 years, range 19-70 years</p>	<p>Detected 30/1848 (1.6%) of women with breast cancer</p> <p>Average incidence rate = 0.9% per year</p> <p>6/30 (20%) of these diagnosed with DCIS</p> <p>24/30 (80%) = invasive cancer</p> <p><b>MRI</b></p> <p>Sensitivity 71%</p> <p>Specificity 88%</p> <p>Sensitivity for invasive tumours 83%</p> <p><b>Mammography</b></p> <p>Sensitivity 36%</p> <p>Specificity 95%</p> <p>Sensitivity for invasive tumours 26%</p> <p><b>CBE</b></p> <p>Sensitivity 16%</p> <p>Specificity 97%</p> <p>Sensitivity for invasive tumours 20%</p>
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MRI = magnetic resonance imaging, CBE = clinical breast examination, DCIS = ductal carcinoma in situ, <sup>a</sup> author's statistical analysis using the z-score test

### *MRI vs mammograms in asymptomatic women who may or may not have a prior history of breast cancer*

Eight of the full text studies and one abstract study reported on MRI compared to mammography in asymptomatic women, who may or may not have had a previous history of breast cancer (Table 6). Of these studies, the two papers by Liberman et al (2003) and Morris et al (2003) reported on the same study. Kuhl et al reported preliminary results for the same good quality (level 3b diagnostic evidence) study at three separate time points (2000, 2002 and 2003 (abstract)), with an increasing number of women participating (105, 192 and 462 women respectively). There were minor fluctuations in the values of specificity and sensitivity for MRI, mammography and ultrasound over this period of time, however overall trends were maintained. Kuhl et al (2003) reported positive predictive values of 57, 38 and 18 per cent for MRI, mammography and ultrasound respectively. A positive predictive value of 57 per cent indicates that out of 100 women who test positive, then 57 were correctly identified as being positive. These results were contradicted by the study by Warner et al (2001) (level 3b diagnostic evidence) who reported positive predictive values for MRI and mammography of 26 and 66 per cent, respectively. Reassuringly, however these two studies reported the same negative predictive value for MRI (100%) and a similar value for mammography (95-98%). A negative predictive value of 95 per cent indicates that out of 100 women who test negative, then 95 were correctly identified as being negative. Of concern are the remaining five women who would assume they were disease free when in fact they were not. Values for the specificity and sensitivity for MRI (both high) and mammography (greatly reduced sensitivity) were similar in both of these studies. In addition, Kuhl et al (2000)

reported that of the nine women detected with breast cancer 4/9 (44%) were less than the age of 40. Warner et al (2001) reported that the age of all women detected with cancer in their study ranged between 33-53 years of age. The poor sensitivity of mammography in this population may be related to the young age of the women and the density of their breast tissue, which decreases with age. Of the six invasive breast cancers detected by Warner et al (2001), four of the women were characterised as having high-density breast tissue and two as having low density. Only those women with low-density breast tissue had breast cancer detected by mammography, whereas MRI detected all six cases. However, mammography was the only imaging modality to detect the one case of ductal carcinoma in situ (DCIS). The studies by Podo et al (2002), Trecate et al (2002), Liberman et al and Morris et al (2003) (level 3b diagnostic evidence) did not report the specificity or sensitivity of MRI or mammography for the screening of high-risk women. They did, however report the number of breast cancers detected by each modality. Detection with mammography ranged from 0 to 12.5 per cent, and detection by MRI ranged from 88 to 100 per cent. However, in the single study reported by both Liberman et al and Morris et al (2003) a degree of uncertainty exists as to whether the cancers detected could be attributed to cancers missed by mammography or if they were interval cancers, as MRI scans were conducted within six months of an occult mammogram.

Table 6 MRI vs mammography for the diagnosis of breast cancer in *asymptomatic* women at high-risk of developing breast cancer, who *may have had a previous history of* breast cancer

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Hartman et al (2004), United States	3b	Cross-classification of patients on MRI, CBE and mammography, compared to core-needle and/or excisional biopsy.	41 asymptomatic women at high-risk of developing breast cancer 24/41 (58.5%) with known BRCA1 or BRCA2 mutation 12/41 (29.3%) with a previous history of breast cancer Median age 42.5 years, range 27-72 years	<b>MRI</b> Abnormal finding in 25/41 (61%) Recommended 6-month follow-up in 14/41 (34.1%) 95%CI [19.6%, 48.6%] Recommended biopsy in 11/41 (26.8%) 95%CI [13.3%, 40.4%] Of these women 1/11 (9%) diagnosed with DCIS 2/11 (18%) diagnosed with atypical lobular hyperplasia 1/11 (9%) diagnosed with papilloma 2/11 (18%) had radial scars <b>Mammography</b> Detected 1/41 (2.4%) woman with atypical lobular hyperplasia

Kuhl et al (2000), Germany <sup>a</sup>	3b	Cross-classification of women on MRI, US and mammography, compared to core-needle and/or excisional biopsy	<p>192 asymptomatic women with a personal or family history of breast cancer, or a confirmed BRCA1 or BRCA2 mutation</p> <p>Mean age 39 ± 9 years, median 38 years, range 18-65 years</p> <p>Validation of screening was only available in 105 women (preliminary results)</p>	<p>9/105 (8.6%) women diagnosed with breast cancer (6 grade III, 1 "high grade", 1 grade II, 1 grade not stated)</p> <p><b>MRI</b> Sensitivity 100% (9/9) Specificity 95% (91/96) PPV 64% (9/14) NPV 100% (91/91) Diagnostic accuracy 95% (100/105)</p> <p><b>Mammography</b> Sensitivity 33% (3/9) Specificity 92% (89/96) PPV 30% (3/10) NPV 94% (89/95) Diagnostic accuracy 88% (92/105)</p> <p><b>Ultrasound</b> Sensitivity 33% (3/9) Specificity 80% (77/96) PPV 14% (3/22) NPV 93% (77/83) Diagnostic accuracy 76% (80/105)</p>
Kuhl (2002), Germany <sup>a</sup>	3b	Cross-classification of women on MRI, US and mammography, compared to core-needle and/or excisional biopsy	<p>192 asymptomatic women with a personal or family history of breast cancer, or a confirmed BRCA1 or BRCA2 mutation</p> <p>Mean age 39 ± 9 years, median 38 years, range 18-65 years</p>	<p><b>Asymptomatic women only</b> 9/192 (4.7%) women diagnosed with breast cancer</p> <p><b>MRI</b> Sensitivity 100% (9/9) Specificity 94% PPV 75% Diagnostic accuracy 95%</p> <p><b>Mammography</b> Sensitivity 44% Specificity 92% PPV 50% Diagnostic accuracy 85%</p> <p><b>Ultrasound</b> Sensitivity 44% Specificity 78% PPV 27% Diagnostic accuracy 73%</p> <p><b>Combined mammography and ultrasound</b> Sensitivity 53%</p> <p><b>Symptomatic and asymptomatic women</b> 15/198 (7.5%) women diagnosed with breast cancer</p> <p>Cancers detected by Mammography 7/15 (46.7%) Ultrasound 7/15 (46.7%) MRI 15/15 (100%)</p>

<p>Liberman et al (2003) and Morris et al (2003), USA <sup>b</sup></p>	<p>3b</p>	<p>Cross-classification of patients on MRI and mammography, compared to core-needle and/or excisional biopsy</p>	<p>367 asymptomatic women with previous breast cancer, biopsy proven lobular carcinoma in situ or family history of breast carcinoma, at high-risk of developing breast cancer  Median age 50 years, range 23-82 years  355/367 (95%) women had a mammogram performed within 6 months of MRI</p>	<p>Mammograms were occult at the time they were conducted.  64/367 (17%) of women recommended a biopsy  59/367 (16%) underwent biopsy  PPV = 14/59 (24%) of women who underwent biopsy  14/367 (3.8%) women diagnosed with breast cancer  8/14 (57%) = DCIS  6/14 = infiltrating carcinoma (2 grade II, 3 grade I, 8 grade 0, 1 grade not stated)</p>
<p>Podo et al (2002), Italy</p>	<p>3b</p>	<p>Cross-classification of patients on MRI, US and mammography, compared to core-needle and/or excisional biopsy</p>	<p>105 asymptomatic women with a personal or family history of breast cancer, or a confirmed BRCA1 or BRCA2 mutation, at high-risk of developing breast cancer (40/105 (38%) had previous breast cancer) or family history  Mean age 46 years, median age 51 years, range 25-77 years</p>	<p>First round screening detected 7/105 (6.7%) women with breast cancer  Second round screening detected 1/14 (7.1%) women with breast cancer  Overall incidence of breast cancer 8/105 (7.6%)  5/8 (63%) of these women had a previous history of breast cancer  Cancers detected by  MRI 7/8 (88%)  Ultrasound 1/8 (12.5%)  Mammography 1/8 (12.5%)  MRI had one false positive  2/8 (25%) = invasive ductal carcinoma  2/8 (25%) = invasive lobular carcinoma  1/8 (12.5%) = invasive ductal carcinoma + invasive lobular carcinoma  2/8 (25%) = multifocal DCIS  1/8 (12.5%) = DCIS + LCIS</p>

Trecate et al (2002), Italy	3b	Cross-classification of patients on MRI, US and mammography, compared to histology	<p>23 asymptomatic women with a proven or suspected mutation in BRCA1 or BRCA2</p> <p>Age range 30-61 years</p> <p>5/23 (21.7%), 2/23 (8.7%) and 1/23 (4.3%) had previous breast, ovarian and breast and ovarian cancer, respectively</p>	<p>4/23 (17.4%) women diagnosed with breast cancer</p> <p>3/4 (75%) of these women had a previous history of breast cancer</p> <p>Cancers detected by</p> <table border="0"> <tr> <td>Mammography</td> <td>0/4 (0%)</td> </tr> <tr> <td>Ultrasound</td> <td>2/4 (50%)</td> </tr> <tr> <td>MRI</td> <td>4/4 (100%)</td> </tr> </table>	Mammography	0/4 (0%)	Ultrasound	2/4 (50%)	MRI	4/4 (100%)																																		
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Warner et al (2001), Canada	3b	Cross-classification of patients on MRI, US, CBE and mammography, compared to biopsy	<p>196 asymptomatic women with a proven or suspected mutation in BRCA1 or BRCA2, or family history of breast cancer.</p> <p>55/196 (28%) women had a previous history of breast cancer and 34/55 (62%) had a known BRCA1 or BRCA2 mutation</p> <p>Mean age 43 years, range 26-59 years</p>	<p>33/196 (16.8%) women underwent biopsy for suspected abnormality</p> <p>7/196 (3.6%) women diagnosed with Stage I breast cancer</p> <p>6/7 (86%) were invasive cancers</p> <p>1/7 (14%) was a DCIS</p> <p><b>MRI</b></p> <p>Detected 6/6 (100%) of cancers</p> <table border="0"> <tr> <td>Sensitivity</td> <td>100% (6/6)</td> </tr> <tr> <td>Specificity</td> <td>91% (173/190)</td> </tr> <tr> <td>PPV</td> <td>26% (6/23)</td> </tr> <tr> <td>NPV</td> <td>100% (173/173)</td> </tr> <tr> <td>Diagnostic accuracy</td> <td>91% (179/196)</td> </tr> </table> <p><b>Mammography</b></p> <p>Detected 2/6 (33%) of cancers</p> <table border="0"> <tr> <td>Sensitivity</td> <td>33% (2/6)</td> </tr> <tr> <td>Specificity</td> <td>99.5% (189/190)</td> </tr> <tr> <td>PPV</td> <td>66% (2/3)</td> </tr> <tr> <td>NPV</td> <td>98% (189/193)</td> </tr> <tr> <td>Diagnostic accuracy</td> <td>97% (191/196)</td> </tr> </table> <p><b>Ultrasound</b></p> <p>Detected 3/5(60%) of cancers °</p> <table border="0"> <tr> <td>Sensitivity</td> <td>50% (3/6)</td> </tr> <tr> <td>Specificity</td> <td>93% (167/180)</td> </tr> <tr> <td>PPV</td> <td>19% (3/16)</td> </tr> <tr> <td>NPV</td> <td>98% (167/170)</td> </tr> <tr> <td>Diagnostic accuracy</td> <td>91% (170/186)</td> </tr> </table> <p><b>CBE</b></p> <p>Detected 6/6 (100%) cancers</p> <table border="0"> <tr> <td>Sensitivity</td> <td>33% (2/6)</td> </tr> <tr> <td>Specificity</td> <td>99.5% (189/190)</td> </tr> <tr> <td>PPV</td> <td>66% (2/3)</td> </tr> <tr> <td>NPV</td> <td>97% (189/193)</td> </tr> <tr> <td>Diagnostic accuracy</td> <td>97% (191/196)</td> </tr> </table>	Sensitivity	100% (6/6)	Specificity	91% (173/190)	PPV	26% (6/23)	NPV	100% (173/173)	Diagnostic accuracy	91% (179/196)	Sensitivity	33% (2/6)	Specificity	99.5% (189/190)	PPV	66% (2/3)	NPV	98% (189/193)	Diagnostic accuracy	97% (191/196)	Sensitivity	50% (3/6)	Specificity	93% (167/180)	PPV	19% (3/16)	NPV	98% (167/170)	Diagnostic accuracy	91% (170/186)	Sensitivity	33% (2/6)	Specificity	99.5% (189/190)	PPV	66% (2/3)	NPV	97% (189/193)	Diagnostic accuracy	97% (191/196)
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Kuhl (2003), Germany <sup>a</sup> Abstract	3b	Cross-classification of women on MRI, US and mammography, compared to core- needle and/or excisional biopsy	462 asymptomatic women with a personal or family history of breast cancer, or a confirmed BRCA1 or BRCA2 mutation  Mean age 39 ± 9 years, median 38 years, range 18-65 years	45/462 (9.7%) women diagnosed with 51 breast cancers  <b>MRI</b> Sensitivity 96% (49/51) Specificity 95% PPV 57% (49/86) NPV 100%  <b>Mammography</b> Sensitivity 43% (21/49) Specificity 94% PPV 38% (21/55) NPV 95%  <b>Ultrasound</b> Sensitivity 47% (24/51) Specificity 88% PPV 18% (24/137) NPV 97%
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MRI = magnetic resonance imaging, CBE = clinical breast examination, US = ultrasound, DCIS = ductal carcinoma in situ, LCIS = lobular carcinoma in situ, PPV = positive predictive value, NPV = negative predictive value

<sup>a</sup> the three papers by Kuhl (2000, 2002, 2003) are from the same study reported at different time points, <sup>b</sup> Liberman et al (2003) and Morris et al (2003) reported the same study, <sup>c</sup> ultrasound was not performed on one patient found to have breast cancer by other modalities

### *MRI for the diagnosis of breast cancer in asymptomatic women at high-risk of developing breast cancer*

One full text and one abstract study reported on MRI for screening women at high-risk of developing breast cancer, compared to biopsy alone (Table 7). The good quality study by Tilanus-Linthorst et al (2000) (level 1b diagnostic evidence) enrolled consecutive women with an occult mammogram conducted six months prior to the MRI examination. Therefore the results of MRI screening cannot be directly compared to the results of the mammogram as a degree of uncertainty exists as to whether the cancers detected could be attributed to cancers missed by mammography or if they were interval cancers.

Table 7 MRI for the diagnosis of breast cancer in *asymptomatic* women at high-risk of developing breast cancer

Study	Level of evidence	Study design	Population	Outcomes
Tilanus-Linthorst et al (2000), The Netherlands	1b	MRI compared to fine needle aspiration cytology	109 asymptomatic consecutive women with a family history of breast cancer or 50% density of breast tissue at mammography, at high-risk of developing breast cancer Mean age 42 years, range 22-68 years	Detected 3/109 (2.8%) of women with breast cancer. Mammograms were occult at the time they were conducted 6 months previously.
Robson et al (2003), United States Abstract	3b	MRI compared to biopsy	53 asymptomatic women at high-risk of developing breast cancer, with a confirmed BRCA1 or BRCA2 mutation	53 women underwent 115 examinations Detected 2/53 (3.8%) of women with DCIS (1 occult on mammogram) Sensitivity 100% Specificity 81% PPV 16.7% (2/12)

MRI = magnetic resonance imaging, DCIS = ductal carcinoma in situ, PPV = positive predictive value

## Safety

### *Rate of false positives and false negatives*

The obvious safety outcome of concern for MRI screening for women at high-risk of developing breast cancer is the number of false positives and negatives reported. False positive findings may result in patients undergoing unnecessary biopsies or surgery. False negatives give false reassurance to patients that they are disease free and therefore may have serious consequences in terms of their future treatment. Two of the full text and two of the abstract studies included for assessment reported sufficient data for false positive and negative values to be calculated (Table 8) (level 3b diagnostic evidence). Three of these studies were conducted on asymptomatic women with no previous history of breast cancer, however the study by Warner et al (2001) included asymptomatic women with and without a previous history of breast cancer. The low quality study by Kuhl et al (2000) reported false positive rates of 5, 7 and 2 per cent and false negative rates of 0, 67 and 67 per cent for MRI, mammography and ultrasound respectively for asymptomatic women. In 2003, Kuhl reported similar follow-up results of this screening trial on an increased number of women. False positive rates were 5, 6 and 12 per cent and false negative rates of 4, 57 and 53 per cent for MRI, mammography and ultrasound respectively. The study by Warner et al (2001) found that 7/17 (41%) of the false positive patients had fibroadenomas, which have micro-vessel densities similar to the

vasculature of tumours that are detected by MRI. The abstract study by Robson et al (2003) reported the highest false positive rate of 19 per cent for MRI when compared only to biopsy.

**Table 8** False positive and false negative rates of MRI and mammography

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Kuhl et al (2000), Germany <sup>a</sup>	3b	Cross-classification of women on MRI, US and mammography, compared to core-needle and/or excisional biopsy	192 asymptomatic women with a personal or family history of breast cancer, or a confirmed BRCA1 or BRCA2 mutation	<p><b>MRI</b></p> <p>False positive 5% (5/96)</p> <p>False negative 0% (0/9)</p> <p><b>Mammography</b></p> <p>False positive 7% (7/96)</p> <p>False negative 67% (6/9)</p> <p><b>Ultrasound</b></p> <p>False positive 20% (19/96)</p> <p>False negative 67% (6/9)</p>
Warner et al (2001), Canada	3b	Cross-classification of patients on MRI, US, CBE and mammography, compared to biopsy	196 asymptomatic women with a proven or suspected mutation in BRCA1 or BRCA2, or family history of breast cancer. 55/196 (28%) women had a previous history of breast cancer and 34/55 (62%) had a known BRCA1 or BRCA2 mutation	<p><b>MRI</b></p> <p>False positive 9% (17/190)</p> <p>False negative 0% (0/6)</p> <p><b>Mammography</b></p> <p>False positive 0.5% (1/190)</p> <p>False negative 67% (4/6)</p> <p><b>Ultrasound</b></p> <p>False positive 7% (13/180)</p> <p>False negative 50% (3/6)</p> <p><b>CBE</b></p> <p>False positive 0.5% (1/190)</p> <p>False negative 67% (4/6)</p>
Kuhl (2003), Germany <sup>a</sup> Abstract	3b	Cross-classification of women on MRI, US and mammography, compared to core-needle and/or excisional biopsy	462 asymptomatic women with a personal or family history of breast cancer, or a confirmed BRCA1 or BRCA2 mutation	<p><b>MRI</b></p> <p>False positive 5%</p> <p>False negative 4% (2/51)</p> <p><b>Mammography</b></p> <p>False positive 6%</p> <p>False negative 57% (28/49)</p> <p><b>Ultrasound</b></p> <p>False positive 12%</p> <p>False negative 53% (27/51)</p>

Robson et al (2003), United States Abstract	3b	MRI compared to biopsy	53 asymptomatic women at high-risk of developing breast cancer, with a confirmed BRCA1 or BRCA2 mutation	MRI False positive 19% False negative 0%
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MRI = magnetic resonance imaging, CBE = clinical breast examination, US = ultrasound

### Recall rate for mammography and MRI

One study reported on the recall rates of asymptomatic women screened for breast cancer using both MRI and mammography (Table 9). The recall rate is described as a screen, which returns a suspect, but not necessarily abnormal result, and therefore the patient is recalled for further testing. Patients recalled for further investigation may experience symptoms of undue stress and anxiety. The recall rate was higher for MRI (10%) compared to mammography (4%).

Table 9 The recall rate of MRI vs mammography after screening *asymptomatic* women for breast cancer

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Warren et al (2002), United Kingdom	3b	Cross-classification of patients on MRI and mammography.	415 asymptomatic women at >50% familial risk of developing breast cancer and no previous history of breast cancer Median age 41 years, range 35-49 years	Total recall rate 86/726 (11.8%) 95%CI [9.59%, 14.42%] Recall rate for MRI 73/716 (10.19%) 95%CI [8.08%, 12.65%] Recall rate for mammography 27/675 (4.0%) 95%CI [2.65%, 5.77%]

### Adverse events

Three studies reported on potential adverse events when MRI is used as a screening modality for breast cancer (Table 10). The good quality study by Tilanus-Linthorst et al (2000) and the study by Warner et al (2001) reported on women declining MRI examination due to claustrophobia, a common problem experienced by patients undergoing a MRI scan. In addition, the screening trial conducted by Warren et al (2002) reported 28/415 (7%) of women who had Li-Fraumeni syndrome and did not undergo the mammography arm of the trial due to the increased mutational risk associated with exposing these patients to excessive radiation.

Table 10 Adverse events associated with screening trials for breast cancer

Study	Study design	Population	Outcomes
Tilanus-Linthorst et al (2000), The Netherlands	MRI compared to fine needle aspiration cytology	109 asymptomatic consecutive women with a family history of breast cancer or 50% density of breast tissue at mammography, at high-risk of developing breast cancer	3 women declined MRI examination due to claustrophobia
Warner et al (2001), Canada	Cross-classification of patients on MRI, US, CBE and mammography, compared to biopsy	196 asymptomatic women with a proven or suspected mutation in BRCA1 or BRCA2, or family history of breast cancer	2 women did not participate in trial due to potential claustrophobia of MRI
Warren et al (2002), United Kingdom	Cross-classification of patients on MRI and mammography.	415 asymptomatic women at >50% familial risk of developing breast cancer and no previous history of breast cancer	28/415 (6.7%) women, representing 52/726 (7%) of screenings, were from families with Li Fraumeni syndrome and therefore did not undergo mammography due to radiation risk

Other safety issues associated with the use of MRI include the potential for an allergic reaction or anaphylactic shock from the use of the contrast agent, gadolinium. This is a rare event, occurring in approximately 1:10,000 patients (De Ridder et al 2001). The number of patients enrolled in the included studies are too small to record shock as an adverse event.

## Potential Cost Impact

### Cost Analysis

There are currently no cost-effectiveness data available for utilising MRI for the screening of women at high-risk of developing breast cancer. A framework for evaluating the cost-effectiveness of MRI for screening breast cancer was discussed by Plevritis but to date has not been conducted (Plevritis 2000). In addition, Hrungr et al (1999) conducted a cost-effectiveness evaluation for the use of MR imaging and core-needle biopsy in the preoperative work-up of suspicious lesions but not for the screening of high-risk women (Hrungr et al 1999).

The cost of a new MRI scanner is estimated to be approximately \$1.5-2.5 million depending on the options, specifications and building requirements. A dedicated breast coil is required for breast imaging, the cost of which is approximately \$30- 40,000. The appropriate software for assembling the three-dimensional MR breast images may cost between \$10-50,000. There are currently approximately 120 MRI scanners in Australia, situated in major private and public hospitals. A standard MRI image is covered under numerous item numbers on the MBS for a \$475 fee, however MRI of the breast is not currently covered by the MBS. Charges for MRI in a non-MBS

setting would range from \$250-600. The intravenous contrast agent required for MR imaging would cost approximately \$20 per scan (personal communication Susan Nicols).

Under the assumption that MRI equipment is under-utilised, a breast screening program may be able to employ existing MRI scanners. Therefore the only additional costs to the Australian health system would be the additional number of patients screened over and above those already being tested. The number of women considered to be at high-risk of developing breast cancer has been estimated to be less than one per cent of the total female population of Australia. This figure would equate to approximately 63,000 women, using the crude figure population estimate of 6.3 million females over the age of 25 years in Australia (Australian Bureau of Statistics 2002). If 63,000 women required an MRI this would be an additional cost to the Australian health system of approximately \$16-38 million per year (for annual screening). However, existing MRI units are mostly fully occupied, with many operating into the late evening and at weekends, leaving limited scope for additional MRI scans of high-risk women. Therefore the introduction of a breast-screening program may require the purchase of additional MRI units (personal communication Susan Nicols).

The UK National Health Service estimates the cost of targeted MRI screening as £350 (A\$860) per patient, per annum, and a cost per cancer detected of approximately £13,700 (A\$34,000). This compares with the current cost of population mammographic screening of between £5-8,000 (A\$12-20,000) per cancer detected (Brown et al 2000). Another study by Tilanus-Linthorst et al (2000) estimated the cost per cancer detected using MRI as €uro 13,930 (A\$23,000) compared to €uro 9,000 (A\$15,000) for conventional mammography. It is unclear how this data pertains to the Australian health system in the absence of a full cost effectiveness analysis in the Australian setting.

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## Ethical Considerations

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Women at high-risk of developing breast cancer are a small, vulnerable group in our society who are seeking certainty concerning their probability of developing breast cancer and their prognosis if breast cancer does occur. For these women, confidence in the veracity of the test result is perhaps even more important than it is for the general population. Therefore, care needs to be taken to ensure that women at high risk of developing breast cancer understand what test results mean. Two issues are of particular concern here. First, these women will want to be sure that a test result indicates whether disease is truly present or absent. Accurate information about the predictive value of MRI screening is essential, as is a concerted effort to help women understand the meaning of results. Positive predictive values for high-risk women range from 26 to 57 per cent for MRI, compared to 38 to 66 per cent for mammography. A positive predictive value of 57 per cent indicates that out of 100 women who test positive, then 57 were correctly identified as being positive. The remaining 43 women would need to undergo investigations such as biopsy or

surgery to confirm that they are in fact negative and have extra anxiety during this period. Reassuringly, negative predictive values for high-risk women for MRI were 100 per cent and 95-98 per cent for mammography (Kuhl et al 2003; Warner et al 2001). This suggests that women who are at genetically high risk for breast cancer may have every confidence that a negative test result indicates that the disease is truly absent.

Second, women offered the alternative screening modality of MRI must be informed of the uncertain benefits with respect to the impact of MRI screening on mortality. Despite the controversy surrounding population mammographic screening, a large body of evidence exists to support the belief that population mammographic screening has a beneficial effect on the reduction of the mortality rate for the target group of women aged 50-69 years. The long-term effect of MRI screening for high-risk women on mortality from breast cancer is unknown. The majority of screening studies are on-going and the only results currently available are short-term follow-up incident rates of breast cancer. Thus, it is currently unknown whether MRI detection of breast cancer is affected by *lead time bias*, meaning that although the disease is detected earlier, the progression of the disease and the eventual outcome may remain the same as if detected by conventional means. The concept of lead time bias, its implications for women's lives, and the uncertainties that surround it in this situation, need to be explained whenever consent is sought for MRI screening.

## **Harms and Benefits**

Current BreastScreen mammography programs have a well-known track record for acknowledging and managing the sensitivities of women and the associated anxieties that may accompany a positive or equivocal result. MRI screens would be conducted as part of a radiology department's routine screening program. Specific programs to support women being screened for breast cancer are unlikely to be in place in these departments. There is no ethically acceptable reason to expose women at greater risk of breast cancer than the general population to potential harm by allowing them to be screened in an environment that does not acknowledge and address their specific issues. Accordingly, introducing MRI scanning as a screening tool for women at high risk of breast cancer must ensure that best practice standards for the delivery of breast cancer screening services are adopted.

## **Access Issues**

This technology is currently available in large public and private hospitals in Australia. Due to the expense of acquisition of MRI scanners, it is likely that they will only be purchased by these large tertiary hospitals and would not be made available in rural areas of Australia.

Women at genetically high risk of developing breast cancer who live in rural areas have already encountered access problems, as they must travel to tertiary centres for genetic testing and counselling services. These women would also need to travel to large regional centres to be screened, away from the support of family and friends. In addition, *annual* MRI screening is advised, compared with *biannual* screening for conventional mammography, which may present a

further emotional and financial burden for rural women. In this environment, rural women may be more likely to opt for mastectomy for pragmatic, financial, work, family and social reasons (National Breast Cancer Centre 2001).

The introduction of a new screening technology for one group of women inevitably raises questions in the public mind about the extension of this technology to a wider population. A rational approach to this issue requires information about the positive and negative predictive values for MRI in the general population. This information is currently unavailable. In its absence, women who are not at high risk may request access to MRI screening, basing their request on the experience of women in high-risk groups. A strategy for addressing this 'slippery slope' issue needs to be in place if MRI screening is introduced for high-risk women.

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## Training and Accreditation

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### Training

The Royal Australian and New Zealand College of Radiologists (RANZCR) conduct a training course for radiologists. For admission into the RANZCR training program, candidates must be a graduate of a recognised medical school, be fully registered as a medical practitioner and have completed two full years in an approved hospital as an intern or resident. In order to be recognised as a Specialist in Radiodiagnosis and Fellow of the College (FRANZCR), the trainee must complete Parts I and II of the FRANZCR examinations in radiodiagnosis and complete a minimum of five years practical training positions accredited by the RANZCR. The training program aims to provide experience and training in general radiology, computed tomography (CT), nuclear medicine, ultrasound, MRI, angiography and basic interventional techniques. A minimum of three months full-time MRI training, including image interpretation and appropriate protocol selection and modification is required, although registrars should receive ongoing training in this modality throughout their five years. Currently, in order to be recognised as a specialist in nuclear medicine, a holder of the FRANZCR must complete two years of full time training in Nuclear Medicine in Joint Specialist Advisory Committee (JSAC) approved centres. Advanced training in women's imaging, including breast imaging, neonatal ultrasound, CT and MRI, is available at the Royal Women's Hospital, Queensland. In addition, the RANZCR offer more a more detailed syllabus for graduates of the Part II examination, for breast imaging. There are 13 components in the extended syllabus, including "Other breast imaging modalities", which aims to contribute to the diagnosis of breast conditions by appropriate use of imaging techniques and to promote awareness of the current role of breast MRI examination in the evaluation of;

- the post treatment breast;
- implant evaluation; and
- preoperative extent of malignant disease.

Graduates should also be aware of the current issues in the use of breast MRI examination in the evaluation of breast disease including;

- the use of contrast agents;
- technique selection;
- sensitivity and specificity;
- availability; and
- cost.

Currently the Quality and Accreditation Program of the RANZCR requires that radiologists reporting on mammography view a minimum of 480 mammograms each year and that they document 15 hours of continuing professional development in mammography every three years (RANZCR 2003).

## **Clinical Guidelines**

In Australia, there are currently no clinical practice guidelines for breast screening using MRI. RANZCR promote and support population screening for breast cancer in asymptomatic women over the age of 40 using mammograms. RANZCR advocate the use of MRI as a complementary imaging modality, which can provide additional information to standard imaging by mammography (National Breast Cancer Centre 2002).

## **Limitations of the Assessment**

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Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon Scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

An Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, an Horizon Scanning Report is a 'state of play' assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of magnetic resonance imaging for women at high-risk of developing breast

cancer, its present and potential use in the Australian public health system, and future implications for the use of this technology.

## Search strategy used for the Report

The medical literature (Table 11) was searched utilising the search terms outlined in Table 12 to identify relevant studies and reviews, until April 2004. In addition, major international health assessment databases were searched.

Table 11 Literature sources utilised in assessment

Source	Location
<i>Electronic databases</i>	
AustHealth	University library
Australian Medical Index	University library
Australian Public Affairs Information Service (APAIS) - Health	University library
Cinahl	University library
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	University library
Current Contents	University library
Embase	Personal subscription
Pre-Medline and Medline	University library
ProceedingsFirst	University library
PsycInfo	University library
Web of Science – Science Citation Index Expanded	University library
<i>Internet</i>	
Current Controlled Trials metaRegister	<a href="http://controlled-trials.com/">http://controlled-trials.com/</a>
Health Technology Assessment international	<a href="http://www.htai.org">http://www.htai.org</a>
International Network for Agencies for Health Technology Assessment	<a href="http://www.inahta.org/">http://www.inahta.org/</a>
Medicines and Healthcare products Regulatory Agency (UK).	<a href="http://www.medical-devices.gov.uk/">http://www.medical-devices.gov.uk/</a>
National Library of Medicine Health Services/Technology Assessment Text	<a href="http://text.nlm.nih.gov/">http://text.nlm.nih.gov/</a>
National Library of Medicine Locator Plus database	<a href="http://locatorplus.gov">http://locatorplus.gov</a>
New York Academy of Medicine Grey Literature Report	<a href="http://www.nyam.org/library/greylit/index.shtml">http://www.nyam.org/library/greylit/index.shtml</a>
Trip database	<a href="http://www.tripdatabase.com">http://www.tripdatabase.com</a>
U.K. National Research Register	<a href="http://www.update-software.com/National/">http://www.update-software.com/National/</a>
US Food and Drug Administration, Center for Devices and Radiological Health.	<a href="http://www.fda.gov/cdrh/databases.html">http://www.fda.gov/cdrh/databases.html</a>
Websites of Specialty Organisations	Dependent on technology topic area

Table 12 Search terms utilised

Search terms
MeSH Breast neoplasms, magnetic resonance imaging
Text words Neoplasm*, cancer*, carcinoma*, tumour*, tumor*, breast*, magnetic resonance imag*, MRI, MR imag*
Limits Human, English, female

## Availability and Level of Evidence

Twelve full text papers and three abstract papers, which reported on ten studies, were included for assessment in this report (see Appendix B). One full text was included for the assessment of safety only. All studies included for assessment in this report were classified according to the levels of evidence for assessing diagnostic accuracy (Table 13). There was only one high-quality study by Tilanus-Linthorst et al (2000) (level 1b diagnostic evidence), who reported on the detection of breast cancer in consecutive women. Liberman et al (2003) and Morris et al (2003) reported the same findings of a retrospective cohort of women (level 3b evidence). Leach (2002) and Warren et al (2002) reported on different aspects (recall rate and diagnostic accuracy) of the same prospective cohort of women (level 3b diagnostic evidence). Two full text studies by Kuhl et al (2000) and Kuhl (2002), and one abstract study by Kuhl (2003) reported results from the same prospective cohort of women (level 3b diagnostic evidence), at different time points. All of the remaining papers were level 3b diagnostic evidence.

Table 13 Levels of evidence for assessing diagnosis <sup>a</sup>

Level of evidence	Study design
1a	SR (with homogeneity*) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centres
1b	Validating** cohort study with good† reference standards; or CDR tested within one clinical centre
1c	Absolute SpPins and SnNouts††
2a	SR (with homogeneity*) of Level ≥2 diagnostic studies
2b	Exploratory** cohort study with good† reference standards; CDR after derivation, or validated only on split-sample§ or databases
2c	n/a
3a	SR (with homogeneity*) of 3b and better studies
3b	Non-consecutive study; or without consistently applied reference standards
4	Case-control study, poor or non-independent reference standard
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

<sup>a</sup> (Phillips et al 2001). SR = systematic review; CDR = clinical decision rule - these are algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category; RCT = randomised controlled trial; n/a = not applicable. \* Homogeneity means a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. Studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level. \*\* Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'. † Good reference standards are independent of the test, and applied blindly or objectively to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study. †† An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis. § Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.

## Sources of Further Information

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A pilot study utilising MRI for the surveillance of women at high-risk of breast cancer is currently being conducted by Professor Christobel Saunders from the School of Surgery and Pathology, University of Western Australian.

## Conclusions

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The current “gold standard” for breast cancer screening in Australia is mammography, which is offered free to all Australian women 40 years and over, by BreastScreen Australia. Mammography involves exposing the patient to radiation, which may represent a risk in women with a genetic pre-disposition to breast cancer. On a mammogram of normal breast tissue, fat will appear as grey and the denser breast tissue as white. Mammography has been demonstrated to be insensitive in the presence of dense breast tissue. Abnormalities are easier to identify in older, post-menopausal women who will have proportionally greater amounts of fat. The participation rate in the Breast Screen Australia program, for the target group of 50-69 year olds, is 57 per cent of eligible Australian women. Australian women have an approximate lifetime risk of one in eleven of developing breast cancer before the age of 75 years.

MR imaging of breast tissue, utilising contrast enhancement agents, has been in use since the mid 1980s. Malignant tissue tends to be highly vascularised when compared to benign or normal tissue. MRI, in conjunction with the injection of contrast dyes, is able to visualise highly vascularised regions, and in so doing may differentiate between benign and malignant tissue. MRI does not use ionising radiation and is not affected by the density of breast tissue.

MRI may be of particular use as a breast screening modality in women considered to be at high-risk of developing breast cancer who tend to develop disease at a significantly younger age and are usually pre-menopausal. These women, due to their age, have high-density breast tissue and therefore are difficult to screen utilising mammography. Women considered to be at high-risk of developing breast cancer include those with a familial or personal history of breast or ovarian cancer, or women with a demonstrated germ-line mutation in a breast-cancer associated gene such as BRCA1, BRCA2 or Tp53. Breast cancers in younger patients tend to be more aggressive, high-grade and receptor negative, making early diagnosis critical. It has been estimated that the number of women considered to be at high-risk of developing breast cancer would be less than one per cent of the total female population of Australia.

The majority of cancers detected in all studies were either high grade or invasive. However, most studies did not report which screening modality detected invasive or DCIS cancers.

Of the studies assessed in this report for the effectiveness of MRI for the screening of breast cancer, six studies presented sensitivity and specificity data. Sensitivity for MRI compared to mammography ranged from 71 to 100 per cent, and 33 to 43 per cent respectively, for both asymptomatic women who did not, or may have had a previous history of breast cancer. Specificity for MRI compared to mammography ranged from 88 to 95 per cent, and 94 to 100 per cent respectively, for the same group of women. Therefore MRI appears to provide improved sensitivity when compared to mammography as a screening modality in asymptomatic high-risk women who have had no, or may have had a previous history of breast cancer.

All studies included in this assessment recruited women at high-risk of developing breast cancer who satisfied eligibility criteria such as a familial history or carrying a mutation of the known breast cancer genes. Age was not stipulated as an eligibility criteria, however the majority of women participating in these trials were young. Seven studies reported the mean age ranged from 39 ( $\pm$  9) to 46 years of age. In addition, four studies reported the median age of participants ranged from 41 to 50 years of age. The poor sensitivity of mammography in these populations may be related to the young age of the women and the density of their breast tissue. One study characterised the density of breast tissue in women participating in the trial. Of the six invasive breast cancers detected in this study, four of the women were characterised as having high-density breast tissue and two as having low density. Only those women with low-density breast tissue had breast cancer detected by mammography, whereas MRI detected all six cases.

False positive rates for MRI and mammography were similar, ranging from 5 to 9 per cent and 0.5 to 7 per cent respectively. However, one study, which compared MRI only to biopsy, reported a false positive rate for MRI of 19 per cent. False negative rates were significantly higher for mammography, ranging from 57 to 67 per cent, compared to a range of 0 to 4 per cent for MRI. False positive findings may result in patients undergoing unnecessary biopsies or surgery. False negative results may give false reassurance to patients that they are disease free and therefore may have serious consequences in terms of their future treatment. In addition, one study reported higher recall rates for MRI (10%) compared to mammography (4%). These patients may experience high levels of stress and anxiety while awaiting further investigation.

Currently the use of MRI as a screening modality in Australia would be limited to the availability of scanning time on available MRI scanners in public or private hospitals. MRI scanners in Australia are currently working at capacity and the introduction of a MR breast-screening program may require the purchase of additional MRIs. The UK National Health Service estimates the cost of targeted MRI screening as £350 (A\$860) per patient, per annum, and a cost per cancer detected of approximately £13,700 (A\$ 34,000). This compares with the current cost of population mammographic screening of between £5-8,000 (A\$12-20,000) per cancer detected. Other studies indicate that the estimated cost per cancer detected using MRI as €uro13,930 (A\$ 23,000) compared to €uro9,000 (A\$ 15,000) for conventional mammography.

In summary, MRI appears to be of benefit in the diagnosis of women at high-risk of developing breast cancer. 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, the majority of studies included in this assessment have presented preliminary results of ongoing screening trials. The number of rounds of screening are low for the women included in the studies and longer follow-up is required to be able to make firm conclusions. In addition, the number of breast cancers detected were small ranging from 1.6 to 17 per cent of all women enrolled. Most of the studies were conducted on relatively small numbers of women, the largest number of participants being 1,848.

The grade of a breast cancer is considered to be a guide to how aggressive the tumour is and how likely it is to spread:

- A 'low' grade (Grade I) is where the breast cancer cells look very like normal breast cells, with only slightly abnormal changes.
- An 'intermediate' grade (Grade II) is somewhere between the high and low grades.
- A 'high' grade (Grade III) is where the cells look very abnormal and show little or no resemblance to normal breast tissue (Breast Cancer Source 2004).

## Appendix B

Profiles of the studies included for assessment for the safety and effectiveness of MRI screening for breast cancer in *asymptomatic*, genetically high-risk women.

Diagnostic level of evidence	Study	Location	Study design	Study population	Outcome assessed	Length of follow-up
3b	Hartman, A-R. Daniel, B.L. Kurian, A.W. Mills, M.A. Nowels, K.W. Dirbas, F.M. Kingham, K.E. Chun, N.M. Herfkens, R.J. Ford, J.M. Plevritis, S.K. (2004)	California, United States	Cross-classification of patients on MRI, CBE and mammography, compared to core-needle and/or excisional biopsy	41 asymptomatic women at high-risk of developing breast cancer 24/41 (58.5%) with known BRCA1 or BRCA2 mutation 12/41 (29.3%) with a previous history of breast cancer Median age 42.5 years, range 27-72 years	Detection of breast cancer	Not stated Biannual screenings
3b <sup>a</sup>	Kuhl, C.K. Schmutzler, R.K. Leutner, C.C. Kempe, A. Wardelmann, E. Hocke, A. Maringa, M. Pfeifer, U. Krebs, D. Schild, H.H. (2000)	Bonn, Germany	Cross-classification of patients on MRI, US and mammography, compared to core-needle and/or excisional biopsy	192 asymptomatic women with a personal or family history of breast cancer, or a confirmed BRCA1 or BRCA2 mutation Mean age 39 ± 9 years, median 38 years, range 18-65 years Validation of screening was only available in 105 women.	Detection of breast cancer	Preliminary results, ongoing study Follow-up at least 1 year

3b <sup>a</sup>	Kuhl, C.K. (2002)	Bonn, Germany	Cross- classification of patients on MRI, US and mammography, compared to core-needle and/or excisional biopsy	192 asymptomatic women with a personal or family history of breast cancer, or a confirmed BRCA1 or BRCA2 mutation  Mean age 39 ± 9 years, median 38 years, range 18-65 years	Detection of breast cancer	Preliminary results, ongoing study  192 women have undergone first screening round and 98 women the second (or more) round
3b <sup>b</sup>	Leach, M.O. UK MRI breast screening study (MARIBS) (2002)	Multi- centre, United Kingdom	Cross- classification of patients on MRI and mammography	415 asymptomatic women at >50% familial risk of developing breast cancer and no previous history of breast cancer  Median age 41 years, range 35-49 years	Detection of breast cancer	Preliminary results, study ongoing  Incidence screens  Study consisted of the first 1,236 examinations of 415 women
3b <sup>c</sup>	Liberman, L. Morris, E.A. Benton, C.L. Abramson, A.F. Dershaw, D.D. (2003)	New York, USA	Cross- classification of patients on MRI and mammography, compared to core-needle and/or excisional biopsy	367 asymptomatic women with previous breast cancer, biopsy proven lobular carcinoma in situ or family history of breast carcinoma, at high- risk of developing breast cancer  Median age 50 years, range 23-82 years  355/367 (95%) women had a mammogram performed within 6 months of MRI	Detection of breast cancer	Incidence screens

3b <sup>c</sup>	Morris, E.A. Lieberman, L. Ballon, D.J. Robson, M. Abramson, A.F. Heerd, A. Dershaw, D.D. (2003)	New York, USA	Cross- classification of patients on MRI and mammography, compared to core-needle and/or excisional biopsy	367 asymptomatic women with previous breast cancer, biopsy proven lobular carcinoma in situ or family history of breast carcinoma, at high- risk of developing breast cancer  Median age 50 years, range 23-82 years  355/367 (95%) women had a mammogram performed within 6 months of MRI	Detection of breast cancer	Incidence screens
3b	Podo, F. Sardanelli, F. Canese, R. et al (2002)	Multi- centre, Italy	Cross- classification of patients on MRI, US and mammography, compared to core-needle and/or excisional biopsy	105 asymptomatic women with a personal or family history of breast cancer, or a confirmed BRCA1 or BRCA2 mutation, at high-risk of developing breast cancer (40/105 (38%) had previous breast cancer) or family history  Mean age 46 years, median age 51 years, range 25-77 years	Detection of breast cancer	Incidence screens, study ongoing  105 women have undergone first screening round and 14 women the second round

3b	Stoutjesdijk, M.J. Boetes, C. Jager, G.J. Beex, L. Bult, P. Hendriks, J.H.C.L. van Die, L.E. Wobbes, T. Barentsz, J.O. (2001)	Nijmegen, The Netherlands	Cross-classification of patients on MRI and mammography, compared to core-needle and/or excisional biopsy	75 asymptomatic women with family history of breast or ovarian cancer, BRCA1 or BRCA2 mutation and no personal history of breast cancer, at high-risk of developing breast cancer  Age range 21-71 years of age MRI and mammogram conducted within 4 months of each other	Detection of breast cancer	Incidence screens
1b	Tilanus-Linthorst, M.M.A. Bartels, C.C.M. Obdeijn, A.I.M. Oudkerk, M. (2000)	Rotterdam, The Netherlands	MRI compared to fine needle aspiration cytology	109 high-risk, asymptomatic consecutive women with a family history of breast cancer or 50% density of breast tissue at mammography Mean age 42 years, range 22-68 years	Detection of breast cancer	1 year
3b	Trecate, G. Vernaghi, D. Bergonzi, S. De Simone, T. Costa, C. Spatti, G.B. Pasini, B. Musumeci, R. (2002)	Milan, Italy	Cross-classification of patients on MRI, US and mammography, compared to histology	23 asymptomatic women with a proven or suspected mutation in BRCA1 or BRCA2 Age range 30-61 years 5/23 (21.7%) had previous breast cancer 2/23 (8.7%) had previous ovarian cancer 1/23 (4.3%) had previous breast and ovarian cancer	Detection of breast cancer	Incidence screens

3b	Warner, E. Plewes, D.B. Shumak, R.S. Catzavelos, G.C. Di Prospero, L.S. Yaffe, M.J. Ramsay, G.E. Chart, P.L. Cole, D.E.C. Taylor, G.A. Cutrara, M. Samuels, T.H. Murphy, J.P. Murphy, J.M. Narod, S.A. (2001)	Toronto, Canada	Cross-classification of patients on MRI, US, CBE and mammography, compared to biopsy	196 asymptomatic women with a proven or suspected mutation in BRCA1 or BRCA2, or family history of breast cancer.  55/196 (28%) women had a previous history of breast cancer and 34/55 (62%) had a known BRCA1 or BRCA2 mutation  Mean age 43 years, range 26-59 years	Detection of breast cancer	Incidence screens
3b <sup>b</sup>	Warren, R.M.L. Pointon, L. Caines, R. Hayes, C. Thompson, D. Leach, M.O. UK MRI breast screening study (MARIBS) (2002)	Multi-centre, United Kingdom	Cross-classification of patients on MRI and mammography	415 asymptomatic women at >50% familial risk of developing breast cancer and no previous history of breast cancer  Median age 41 years, range 35-49 years	Recall rate after abnormal finding	Preliminary results, study ongoing  Incidence screens  Study consisted of the first 726 examinations of 415 women
3b Abstract	Kriege, M. Brekelmans, C.T. Boetes, C. Rutgers, E.J.T. Oosterwijk, J.C. Tollenaar, R.A. Manoliu, R.A. Holland, R. de Koning, H.J. Klijn, J.G. (Dutch National Screening Study, MRISC) (2003)	Multi-centre, The Netherlands	Cross-classification of patients on MRI and mammography, compared to histology	1,848 asymptomatic woman at high-risk of developing breast cancer (>15% risk of breast cancer due to familial or genetic disposition and no previous history of breast cancer)  294/1848 (16%) with known BRCA1 or BRCA2 mutation  Mean age 41 years, range 19-70 years	Detection of breast cancer	Preliminary results, ongoing study  Biannual CBE, annual mammography and MRI

3b <sup>a</sup> Abstract	Kuhl, C.K. Schrading, S. Leutner, C.C. Morakkabati, N. Trog, D. Schmutzler, R.K. Schild, H.H. (2003)	Bonn, Germany	Cross- classification of patients on MRI, US and mammography, compared to core-needle and/or excisional biopsy	462 asymptomatic women with a personal or family history of breast cancer, or a confirmed BRCA1 or BRCA2 mutation  Mean age 39 ± 9 years, median 38 years, range 18-65 years  Validation of screening was only available in 105 women.	Detection of breast cancer	Follow-up 5 years
3b Abstract	Robson, M.E. Morris, E. Kauff, N. Scheuer, L. Borgen, P.I. Hudis, C. Norton, L. Offit, K. (2003)	New York, United States	MRI compared to biopsy	53 asymptomatic women at high- risk of developing breast cancer, with a confirmed BRCA1 or BRCA2 mutation	Detection of breast cancer	53 women who underwent 115 examinations

MRI = magnetic resonance imaging, US = ultrasound, CBE = clinical breast examination

<sup>a</sup> the three papers by Kuhl (2000, 2002, 2003) are from the same study reported at different time points, <sup>b</sup> Leach and Warren reported on different aspect of the same study, <sup>c</sup> Liberman et al (2003) and Morris et al (2003) reported the same study

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