



### Meagan Brennan

BMed, FRACGP, DFM, FASBP, is a breast physician and Clinical Senior Lecturer, Screening and Test Evaluation Program (STEP), The University of Sydney, New South Wales. [m.brennan@usyd.edu.au](mailto:m.brennan@usyd.edu.au)

### Andrew Spillane

BMBS, MD, FRACS, is Associate Professor of Surgical Oncology, Royal North Shore and Mater Hospitals, North Sydney and The University of Sydney, New South Wales.

### Nehmat Houssami

MBBS(Hons), FASBP, FAFPHM, MPH, PhD, is Associate Professor and Principal Research Fellow, Screening and Test Evaluation Program (STEP), The University of Sydney, New South Wales.

# The role of breast MRI in clinical practice

## Background

The use of magnetic resonance imaging (MRI) for breast screening is increasing. Women may approach their general practitioner for advice on its role in breast screening and diagnosis.

## Objective

This article provides an evidence based update on the role of breast MRI.

## Discussion

There is good evidence to support the use of MRI for cancer screening in younger women at high genetic risk of breast cancer. Its use for assessing the extent of disease in the breast after breast cancer is diagnosed (local staging) is controversial. Certainly MRI is more sensitive than conventional imaging for detecting multifocal/multicentric disease, however, there is evidence that some women have more extensive surgery as a result of MRI without clear evidence of benefit. There is no role for MRI as a substitute for mammography or for screening women at average risk of breast cancer. It also has no routine role as a diagnostic test in women with symptoms.

■ **Over the past 10 years, the use of magnetic resonance imaging (MRI) for screening and diagnosis of breast cancer has been increasing. Uses include screening in women at high genetic risk of breast cancer, evaluating the extent of disease in women with a recent diagnosis of breast cancer, and detecting synchronous contralateral cancer. Magnetic resonance imaging has high overall sensitivity and has at times been promoted as a 'gold standard' in breast imaging. However, its role remains controversial. Importantly, breast MRI has a high false positive rate and evidence of benefit in some clinical situations is lacking. There may be a high level of awareness of MRI among some women presenting to specialist clinics with breast symptoms. It is important that practitioners provide evidence based answers to their questions.**

## Categories of breast cancer risk

One in 11 Australian women will develop breast cancer before the age of 75 years.<sup>1</sup> As the disease is so common, it is not unusual for women to have a relative with breast cancer. However, having a relative with breast cancer, even a first degree relative (mother, sister or daughter) may not necessarily mean the woman herself is at higher than average risk. Women frequently overestimate their personal risk,<sup>2</sup> and it is often the clinician's role to reassure the woman that her risk is not as high as she thought.

When assessing individual risk it is important to consider the age of the affected relative at diagnosis and the rest of the family history (maternal and paternal). The National Breast and Ovarian Cancer Centre (NBOCC) has developed guidelines for assessing risk of breast (and ovarian) cancer based on family history (*Table 1*).<sup>3</sup> The guidelines are available to clinicians in print and online; the online facility includes a web based calculator.

Women in NBOCC 'Category 3' are proven to carry a BRCA-1 or BRCA-2 gene mutation or have a very strong family history as outlined in *Table 1*. These women make up less than 1% of the

general population and are at highest risk. The lifetime risk of breast cancer for this group is one in 4 to one in 2; these women are also at potentially high risk of ovarian cancer with a one in 30 to one in 3 lifetime risk (Table 1).

Women in NBOCC 'Category 3' (potentially high risk) should be assessed by a genetics team at a familial cancer clinic. If it is considered appropriate, there is a living relative affected by cancer, and informed consent is obtained, the family may be offered testing for a BRCA-1 or BRCA-2 gene mutation.

It is important that this testing be done by a specialised clinic as there are many issues for the family to consider in relation to testing. The genetics team can help obtain pathology reports to clarify the family history and offer tailored advice on individual risk and appropriate screening and risk reduction strategies. In some cases women in this group may be offered MRI screening.

## Breast MRI

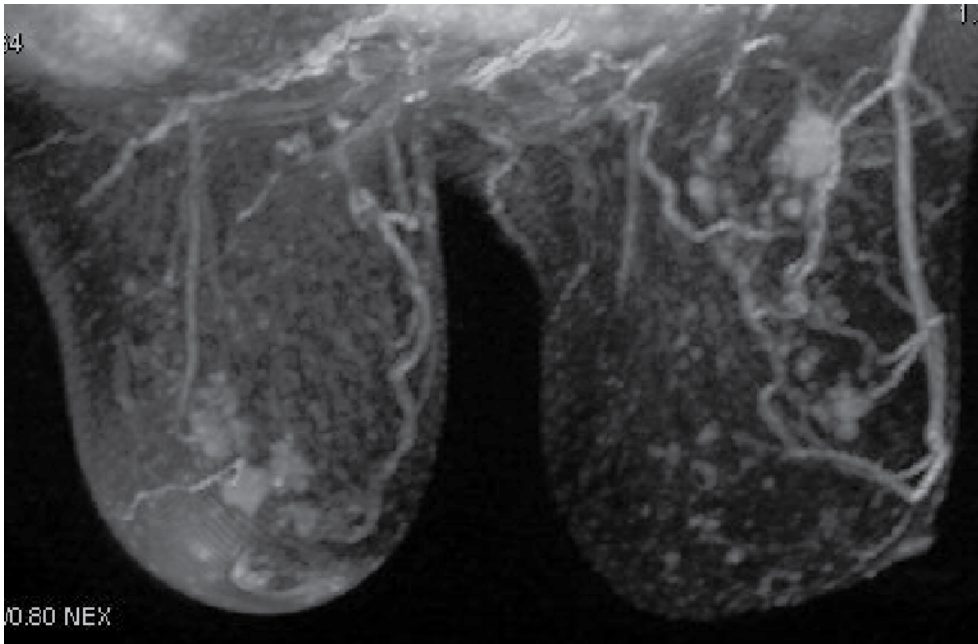
Breast MRI is performed using a standard MRI machine with a special attachment (a 'breast coil'). The patient lies prone for the procedure and images are acquired before and after the rapid injection of the contrast medium gadolinium. Interpretation of breast MRI requires the expertise of a specialised radiologist and involves analysis of the pattern of enhancement and the morphology of lesions, as well as the kinetic features. Kinetic features refer to the pattern and rate of uptake and washout of contrast (Figure 1).

When a suspicious lesion is identified on MRI, a 'second look' ultrasound is frequently performed, and if the lesion is seen, then biopsy is performed under ultrasound guidance. This is a simpler, cheaper and more widely available procedure than MRI guided biopsy or localisation. Lesions may be seen on second look

Table 1. Categories of breast cancer risk based on family history<sup>3</sup>

<b>Category 1: At or slightly above average risk</b>	<b>Category 2: Moderately increased risk</b>	<b>Category 3: Potentially high risk</b>
<p><b>Covers &gt;95% of the female population</b></p> <ul style="list-style-type: none"> <li>• No confirmed family history of breast cancer</li> <li>• One first degree relative diagnosed with breast cancer at age 50 years or more</li> <li>• One second degree relative diagnosed with breast cancer at any age</li> <li>• Two second degree relatives on the same side of the family diagnosed with breast cancer at age 50 years or more</li> <li>• Two first or second degree relatives diagnosed with breast cancer at age 50 years or more but on different sides of the family (ie. one on each side of the family)</li> </ul> <p>As a group, lifetime risk of breast cancer is between one in 11 and one in 8. This risk is no more than 1.5 times the population average</p>	<p><b>Covers &lt;4% of the female population</b></p> <ul style="list-style-type: none"> <li>• One first degree relative diagnosed with breast cancer before the age of 50 years (without the additional features of the potentially high risk group, see Category 3)</li> <li>• Two first degree relatives, on the same side of the family, diagnosed with breast cancer (without the additional features of the potentially high risk group, see Category 3)</li> <li>• Two second degree relatives, on the same side of the family, diagnosed with breast cancer, at least one before the age of 50 years, (without the additional features of the potentially high risk group, see Category 3)</li> </ul> <p>As a group, lifetime risk of breast cancer is between one in 8 and one in 4. This risk is 1.5–3.0 times the population average</p>	<p><b>Covers &lt;1% of the female population</b></p> <ul style="list-style-type: none"> <li>• Women who are at potentially high risk of ovarian cancer</li> <li>• 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: <ul style="list-style-type: none"> <li>– additional relative(s) with breast or ovarian cancer</li> <li>– breast cancer diagnosed before the age of 40 years</li> <li>– bilateral breast cancer</li> <li>– breast and ovarian cancer in the same woman</li> <li>– Ashkenazi Jewish ancestry</li> <li>– breast cancer in a male relative</li> </ul> </li> <li>• One first or second degree relative diagnosed with breast cancer at age 45 years or less plus another first or second degree relative on the same side of the family with sarcoma (bone/soft tissue) at age 45 years or less</li> <li>• Member of a family in which the presence of a high risk breast cancer gene mutation has been established</li> </ul> <p>As a group, lifetime risk of breast cancer is between one in 4 and one in 2. Risk may be more than three times the population average. Individual risk may be higher or lower if genetic test results are known</p>

Figure 1. Ipsilateral (left) and contralateral (right) breast cancer. A woman, 55 years of age, who presented with a clinical mass in the left breast. Histopathology showed a 25 mm invasive cancer; MRI performed to assess the extent of disease showed a lesion in the contralateral breast, an 18 mm area of ductal carcinoma in situ



ultrasound after MRI even when initial pre-MRI ultrasound was reported as normal. Having precise knowledge about the location and approximate size of the lesion often makes it easier to identify on subsequent ultrasound, particularly in women with large breasts and dense parenchyma.

There is now a Medicare Benefits Schedule (MBS) rebate for MRI screening of women less than 50 years of age who are at high genetic risk of breast cancer. These are women assessed as 'Category 3' (potentially high risk) according to the NBOCC guidelines.<sup>3</sup> The rebate only applies when the test is requested by a specialist. For women who do not fit these criteria, the cost ranges from \$350–700 or more.

### Breast MRI versus mammography and ultrasound

Magnetic resonance imaging should be used selectively as an add on test rather than a replacement for conventional imaging. Although the sensitivity of MRI alone is greater than that of mammography alone, there are still some cancers that are seen only on mammography or ultrasound and not on MRI. In addition, the findings on conventional imaging assist in the interpretation of MRI.

Mammography remains the most reliable detection test for DCIS because the associated calcifications are usually seen well on mammography. Mammography is particularly sensitive in women with minimal parenchymal density (fatty replaced) breast tissue. While this pattern of tissue is most frequently found in older women, some younger women also have atrophic breast tissue. Magnetic resonance imaging will not add significantly to the

already high sensitivity of mammography in these women and is not indicated.

### MRI in high risk young women

In young women less than 50 years of age, the sensitivity of screening mammography is lower than in older women, possibly due to a higher breast density and the fact that they may have faster growing cancers. Magnetic resonance imaging has been evaluated as an additional cancer screening test in this group of women. A systematic review showed strong evidence that screening high risk younger women with MRI can detect more cancers than mammography alone (or mammography plus ultrasound).<sup>4</sup> High risk in this context refers to women proven to carry a BRCA-1 or BRCA-2 gene mutation and may also include women in the NBOCC 'Category 3' family history group.<sup>3</sup> The addition of MRI to conventional screening provides sensitivity of 86–100%. In these high risk women, MRI has an incremental sensitivity of 58% above mammography alone, ie. screening with MRI in addition to mammography detects 58% more cancers than mammography alone. This incremental sensitivity of breast MRI is only slightly less (44%) when added to screening with mammography plus ultrasound.<sup>4</sup>

The false positive rate of MRI in the context of screening high risk women is uncertain as many studies assessing screening MRI did not report the false positive rate. A meta-analysis estimated the rate of recall for additional tests that subsequently excluded cancer was 3–5 times higher when MRI was added to conventional screening tests (71–74 additional false positive recalls per 1000

Table 2. Clinical use for breast MRI

**Screening for breast cancer in young high risk women**

Magnetic resonance imaging is indicated for screening women less than 50 years of age who carry BRCA-1 or BRCA-2 gene mutations or have a very strong family history of breast cancer (NBOCC Category 3)<sup>3</sup>

**Assessment in women with a new breast cancer diagnosis for:**

- Assessment of extent of disease (local staging) in women with a recent breast cancer diagnosis
- The role of MRI in this situation is controversial. It can estimate tumour size and diagnose unsuspected multifocality/multicentricity with a high sensitivity, however, it may lead to more extensive surgery without definite evidence of benefit<sup>9</sup>
- Screening the contralateral breast for cancer in women with a recent (ipsilateral) breast cancer diagnosis. The role of MRI in this scenario is also uncertain<sup>11</sup>

**Other uses**

- Assessing the integrity of breast prosthesis – where there is concern about rupture of breast prostheses following augmentation, MRI is a useful test to assess the integrity of implants. MRI has not been evaluated as a screening test for breast cancer in women with implants
- Assessment of the breast in occult primary breast cancer – rarely, breast cancer presents with malignant lymph nodes in the axilla (with positive staining for oestrogen receptors, suggesting metastases from a primary breast cancer) but without evidence of disease in the breast. When conventional assessment with clinical examination, mammography and ultrasound does not reveal a primary, MRI, may add information to guide management options
- Monitoring response to neo-adjuvant chemotherapy in women with breast cancer – a more recent use for MRI is monitoring response to chemotherapy in women with locally advanced breast cancer who are being treated with chemotherapy before or instead of surgery. MRI is still being evaluated in this clinical scenario

screening rounds).<sup>4</sup> This is not insignificant, and women should be warned of this; recall for further assessment generates anxiety, particularly in women known to be at high risk of cancer. The recall rate tends to decrease with subsequent screening rounds and may be lower in units with higher levels of expertise. As with many areas of medicine, the best available results in the literature are not necessarily those achieved in community practice.

It is not known whether the additional cancers detected by MRI in this setting translate to a reduction in breast cancer related deaths. There are several reasons why additional detection of cancer may or may not achieve mortality reduction in this context:<sup>5</sup>

- there is inconsistent evidence on whether MRI detected cancers are earlier stage than cancers detected with mammography
- the expectation that MRI detection will lead to reduced mortality in women undergoing screening MRI is based on early trials of screening mammography that showed early mammographic detection of cancer leads to reduced mortality. Whether high risk younger women receive the same benefits from early detection and treatment of MRI detected cancers has not yet been established
- women with gene mutations may have different cancer biology; this has been suggested by gene expression profiling research. These cancers may have different metastatic potential.

**MRI for local staging of breast cancer**

Magnetic resonance imaging can be used for preoperative assessment of extent of disease within the breast in women with

a new diagnosis of breast cancer (local staging). It may also be used postoperatively after an initial excision finds more extensive disease than expected based on conventional assessment. In these women, MRI may provide more information about the size of the index tumour than conventional clinical and imaging assessment and detect additional foci of disease, diagnosing the tumour as multifocal (multiple foci in the same quadrant) or multicentric (multiple foci in different quadrants).

The preoperative diagnosis of unsuspected multifocality/multicentricity may be advantageous as it may allow surgical treatment to be changed to maximise the chances of the surgeon obtaining clear margins without the need for re-operation. If MRI detects more extensive disease than suspected on conventional clinical and imaging assessment, the surgeon has the option of recommending a wider excision than planned for a woman undergoing breast conservation surgery or recommending mastectomy instead of wide local excision. The preoperative diagnosis of more extensive disease may also change management of the axilla; when breast cancer is >3 cm in diameter or is multicentric some surgeons recommend up front axillary dissection rather than sentinel node based management.

Numerous studies show that MRI detects the presence of multifocal and/or multicentric disease with greater accuracy than conventional imaging. A meta-analysis shows that MRI will detect additional disease in the ipsilateral breast in 16% of women with cancer. How to use this additional information is the subject of current debate. An estimated 8–33% of women having

preoperative MRI for local staging have more extensive surgery than women who do not have preoperative MRI.<sup>6</sup> However, this more extensive surgery has not been shown to reduce the rate of re-excision surgery<sup>7</sup> and has not been shown to reduce the risk of local recurrence.<sup>8</sup> It has been argued that perhaps the additional foci of disease that MRI detects are not of clinical significance as nearly all women having conservation surgery will undergo postoperative radiotherapy and this may effectively treat any small foci of residual disease.<sup>6,9</sup> It is of concern that women may be undergoing wider excision or mastectomy due to additional MRI detected foci which are of uncertain significance.<sup>6</sup>

The high false positive rate of MRI is an important limitation in this setting. In the meta-analysis, MRI had a positive predictive value of 66% and a true positive to false positive ratio of 1.9, ie. around one-third of suspicious MRI lesions are not cancer.<sup>6</sup> It is therefore essential that these lesions are investigated with biopsy before decisions are made about surgical management. False positive test results may lead to a delay before surgery of up to 2–3 weeks if there is not a streamlined process for investigating these additional lesions. While there is no evidence that this delay alters the oncological outcome, it may be very stressful for the patient.

### MRI screening of the contralateral breast

As breast MRI is usually a bilateral test, the contralateral breast is effectively undergoing screening when MRI is performed as an ipsilateral staging procedure in a women with a new breast cancer diagnosis. In this setting it detects suspicious lesions in 9–10% of cases and has an incremental cancer detection rate of 4.8% over conventional imaging (mammography with or without ultrasound), ie. additional cancers are detected in 4.8% of cases.

In the contralateral breast, a meta-analysis showed MRI to have a positive predictive value of only 48% and a true positive to false positive ratio of 0.92, ie. more than half of suspicious lesions are false positives. In fact, initial data from the only randomised control trial evaluating preoperative MRI suggests that the positive predictive value for screening the contralateral breast may be even lower than the estimated 48%.<sup>10</sup> The majority of the MRI detected contralateral cancers are early stage in situ or node negative invasive cancers.<sup>11</sup>

The detection of suspicious contralateral MRI lesions may also lead to a change in surgical management. In some studies, some women underwent bilateral mastectomy without biopsy and with subsequent benign contralateral histopathology.<sup>11</sup> Biopsy is therefore necessary in order for the patient and her surgeon to have an informed discussion about management options.

### MRI for screening and diagnosis in women at average age risk

Women at average risk are beginning to request MRI rather than mammography for screening. Some women see it as a pain free

alternative to mammography. It must be explained that there is no evidence for MRI as a stand alone screening test and there is no evidence of benefit in a population other than younger women at extremely high risk.

Magnetic resonance imaging is not recommended as a diagnostic test in women at average age risk. Women with symptoms and/or image detected lesions must be assessed with the traditional triple test approach of clinical examination, imaging (mammography and/or ultrasound) and percutaneous biopsy. In experienced hands, triple testing is proven to have a sensitivity of 99.6%.<sup>12</sup>

There is no role for MRI as a work up test for women with breast symptoms, except in very specific and uncommon clinical scenarios. In these situations MRI may be indicated after review in a specialised breast service. These include assessment of integrity of breast prostheses (implants) to exclude rupture, and work up of women presenting with axillary lymph node metastases suggesting occult primary breast cancer (*Table 2*).

### Summary of important points

- There is clear evidence that for screening women at high genetic risk of breast cancer, MRI detects additional cancers not seen on mammography or mammography plus ultrasound. A MBS item number has been introduced for screening MRI for high risk women (NBOCC Category 3) less than 50 years of age.
- There is no evidence for MRI as a stand alone screening test for women at average risk of breast cancer.
- MRI is used to assess extent of disease in women with a recent diagnosis of breast cancer and for the detection of contralateral disease occult to conventional imaging. The benefits of MRI in this setting are unclear as the relatively high false positive rate can lead to additional investigations and detect multifocal and multicentric disease of uncertain clinical significance, leading to more extensive surgery in some cases.
- Women presenting with breast symptoms must be investigated with the conventional triple test (clinical examination, imaging with mammography and/or ultrasound and percutaneous needle biopsy).
- At present, MRI has limited availability as it requires specialised equipment and expertise to perform and interpret the test.

Conflict of interest: none declared.

### Acknowledgment

The authors thank Dr Ruth Warren, Department of Radiology, Addenbrooke's Hospital, Cambridge, United Kingdom who provided the image of breast MRI.

### References

1. Australian Institute of Health and Welfare & Australasian Association of Cancer Registries (AACR). Cancer in Australia: An overview, 2006 Canberra: AIHW 2007.
2. Black WC, Nease RF, Tosteson AN. Perceptions of breast cancer risk and

- screening effectiveness in women younger than 50 years of age. *J Natl Cancer Inst* 1995;17:720–1.
3. National Breast and Ovarian Cancer Centre. Advice about familial aspects of breast cancer and epithelial ovarian cancer: a guide for health professionals. Camperdown: National Breast and Ovarian Cancer Centre, 2006.
  4. Lord SJ, Lei W, Craft P, et al. A systematic review of the effectiveness of magnetic resonance imaging (MRI) as an addition to mammography and ultrasound in screening young women at high risk of breast cancer. *Eur J Cancer* 2007;43:1905–17.
  5. Houssami N, Lord SJ, Ciatto S. Early detection of breast cancer: Emerging role of new imaging as adjunct to mammography in breast screening. *Med J Aust* 2009; in press.
  6. Houssami N, Ciatto S, Macaskill P, et al. Accuracy and surgical impact of MRI in breast cancer staging: Systematic review and meta-analysis in detection of multifocal and multicentric cancer. *J Clin Oncol* 2008;26:3248–58.
  7. Turnbull L. Magnetic resonance imaging in breast cancer: Results of the COMICE trial. *Breast Cancer Res* 2008;10:10.
  8. Solin LJ, Orel SG, Hwang W-T, Harris EE, Schnall MD. Relationship of breast magnetic resonance imaging to outcome after breast-conservation treatment with radiation for women with early-stage invasive breast carcinoma or ductal carcinoma in situ. *J Clin Oncol* 2008;26:386–91.
  9. Morrow M, Freedman G. A clinical oncology perspective on the use of breast MR. *Magn Reson Imaging Clin N Am* 2006;14:363–78.
  10. Drew PJ, Harvey I, Hanby A, et al. The UK NIHR multicentre randomised COMICE trial of MRI planning for breast conserving treatment for breast cancer (Abstract 51). San Antonio Breast Cancer Symposium San Antonio, USA; 2008.
  11. Brennan ME, Houssami N, Macaskill P, et al. MRI screening of the contralateral breast in women with newly diagnosed breast cancer: systematic review and meta-analysis of incremental cancer detection and impact on surgical management. *J Clin Oncol* 2009; in press.
  12. Irwig L, Macaskill P, Houssami N. Evidence relevant to the investigation of breast symptoms: the triple test. *Breast* 2002;11:215–20.