MRI for breast cancer screening

M. O. Leach
Cancer Research UK Clinical Magnetic Resonance Research Group, Institute of Cancer Research, Royal Marsden NHS Foundation Trust, Sutton, UK

Introduction

For many years the tendency of some families to exhibit a high incidence of breast cancer has been well known, with such families contributing some 10%, depending on age, to total breast cancer [1]. These families may show a range of other cancers, including ovarian, colon and prostate cancer, a higher incidence of bilateral breast cancer, and the presence of breast cancer at early ages [2]. With the increasing understanding of the genetic changes underlying cancer, a number of genetic mutations that predispose to breast cancer have been identified. These include Li Fraumeni Syndrome (TP53) [3, 4] and the BRCA1 [5, 6] and BRCA2 [7, 8] gene mutations. The characteristics of cancers arising from these mutations are being progressively identified, showing differences in biology that may affect the nature of disease, its appearance and response to treatment [9–11].

In the general population, the incidence of breast cancer is well characterised, being about 0.2% per annum at age 50 and 0.05% per annum at age 35. By comparison, BRCA1 and BRCA2 carriers have an incidence of 3% and 1.5%, respectively, at age 50 and 1% and 0.7% at age 35. The cumulative risk of breast cancer is about 6% by age 70 in the normal population, compared with 45%–65% in BRCA1 and BRCA2 carriers [12]. BRCA1 and BRCA2 carriers are responsible for some 2% of breast cancers. Thus gene mutation carriers have a very high risk of breast cancer at a young age.

There is a limited range of options available to women with a strong family history or carrying a breast cancer predisposing gene mutation. While chemo-prevention approaches are under test, they are not yet routinely available or recommended for women at genetic risk [13]. Some women elect bilateral prophylactic mastectomy [14], although take up of this option varies considerably. High-risk women are commonly offered annual breast mammography [15], although the trade-off of this option varies considerably. High-risk women tend to have mammographically dense breasts, reducing the efficiency of this approach. In the normal population, X-ray mammography misses some 22% of invasive cancers in women below 50, compared with 10% in women over the age of 50 [15]. Breast cancer in younger women is associated with faster growing tumours, with poorer prognosis. The limitations of current techniques, together with the associated radiation dose in young women, which may be of particular concern where mutations have impaired cellular damage recovery mechanisms, has led to interest in alternative methods of screening high-risk women to enable early detection of cancer.

Magnetic resonance imaging of breast cancer

Magnetic resonance imaging (MRI) has shown promise in the evaluation and management of symptomatic breast disease, and in this group has been reported to have a high sensitivity for detecting cancer, although specificity is more variable [16–27]. Examinations use a dedicated bilateral breast coil, which provides improved sensitivity for breast imaging, with the woman lying prone in the scanner. The basic examination is a T1-weighted measurement, using an injection of a paramagnetic contrast agent containing chelated gadolinium, which has the property of reducing the T1 relaxation times of tissues with contrast uptake. Tumours characteristically have a leaky, highly permeable, vasculature and the contrast agent passes from the vasculature into the surrounding extracellular space in most tumours, leading to a bright area on T1 weighted images. In the breast the conspicuity of lesions is reduced due to the large amounts of fatty tissue, which also appears bright. Therefore it is usual to take a set of images (usually a 3D volume) prior to contrast administration and then a further set of images typically at 60–90 s following contrast administration. Subtraction of the pre-contrast images from the post-contrast images then removes the fat signal. Alternatively, many MR systems can produce good quality fat suppressed images, using a feature of the MR scanner to remove signals from fat. Either of these techniques provides images with excellent contrast for enhancing lesions. The examination may include a dynamic series of images through the lesion, to follow the uptake and washout of the contrast agent (DCE-MRI), which can help in discriminating benign from malignant disease, and other types of imaging sequence such as a T2-weighted sequence. One of the challenges of breast MRI is to separate benign from malignant disease. Evaluation of the shape and appearance of the lesion provides valuable information, as does the contrast uptake, distribution pattern and washout [28]. Initially, different groups used one or the other of these two approaches, but increasingly the examination is taking both approaches into account.

Screening for breast cancer using MRI

While there is a large body of work describing the use of MRI in the management of symptomatic cancer, there have been relatively few publications describing its use for screening, where the challenges are greater. A screening test must have a high sensitivity for detecting potentially abnormal lesions.
A screening test may be followed by further tests to diagnose and manage the findings. While it is desirable for the screening test to be as specific as possible, this must not be at the cost of missing a significant proportion of real cancers. The requirement for specificity in the screening test depends on the cost and impact of follow-up investigations. In designing and evaluating a screening test, it is important therefore to balance sensitivity in detecting the maximum number of cancers, against the need for and impact of follow-up investigations.

Several large studies of MRI for screening women at high risk of breast cancer have recently reported their findings [29–31]. Each of these studies differs in some aspects, but there is remarkable concordance in their main findings. A number of previous papers have reported some results on high-risk women, interim results or related work [32–43]. These are less comprehensive and so are not discussed in detail here. Aspects of the design, background considerations and findings of the MARIBS trial [31], which involved the largest number of centres and thereby may be closest in structure to a practical screening service, will be discussed below, followed by comparison with the other major trials and discussion of the overall findings and their implications for surveillance of women at a high risk of breast cancer.

**comparisons with other techniques**

In designing a study to test a new screening method, it is necessary to demonstrate whether it improves on current practice, which is annual X-ray mammography [44, 45]. Although clinical examination is also often employed, it does not form part of routine screening for breast cancer in the UK and so was not included as a part of the trial. Ultrasound is widely used as a secondary detection method and can identify lesions not seen on X-ray mammography. However, there was little evidence to support its use in a screening role. In addition, it is highly operator-dependent and does not document the entire breast in a way that permits retrospective or prospective comparison. To ensure that comparisons accorded with best practice and to take account of the fact that MRI for breast cancer screening would be a new technique for many radiologists, X-ray mammography was performed using two views for each breast, to UK NHS Breast Screening Programme standards, training was provided for MR radiologists and both modalities were double read blinded to all other readers [46].

**target population for screening**

Selecting a population for screening is an important aspect of trials and of any subsequent service. However the requirements and criteria differ for these two situations. In designing a trial, it is essential to power the trial sufficiently to provide a clear result, and to ensure that the study is as informative as possible. This means that the trial must accumulate enough ‘events’ to allow significant comparisons to be made. In designing the MARIBS trial a number of potential designs were considered, based on the information then available on individuals tested for BRCA1 and BRCA2 and TP53 mutations; families with documented histories of breast cancer, the willingness of centres to collaborate in a trial, and their potential access to MRI equipment that could be used in a trial [44, 45]. Because of the availability of an effective national X-ray mammographic screening service for women over the age of 50 in the UK, with the expectation that mammographic density would pose less of a problem in this age group, age in the trial was restricted to 35–49 (or 25–49 in TP53 carriers, who have earlier onset). This was a pragmatic decision on the basis of study power, as cancer incidence reduces rapidly with age, and diluting the study with a large number of younger women who were unlikely to develop cancer whilst in the study would reduce the study power and increase cost. Other studies have used different criteria and a population screening service would also need to consider the larger number of screens per cancer detected and the expected morbidity and worry involved in follow-up assessments that did not result in confirming malignant disease if less stringent entry criteria were employed.

Based on assumptions of MRI and X-ray mammography sensitivity in the target group, derived from a literature review, and that gene mutation carriers had a 3% per annum risk of cancer, it was determined that a total of 84 cancers would be required in a comparative trial, leading to a requirement for 2800 screens of gene carriers in the study, which would require recruitment of 250 gene carriers per year for 3 years and measurement for up to 5 years. This exceeded the anticipated number of tested individuals available, and so the design was broadened to include women at 50% prior risk of being gene carriers based on family history, leading to a requirement to recruit 100 tested carriers and 400 women from high-risk families per year. A comparative trial does not directly allow the evaluation of the effect of the new intervention on mortality to be assessed. A fully randomised trial would have required about five times as many women to be recruited, which was clearly unattainable. For the same reason, the other studies have also used a comparative design. The high genetic risk requirements selected for the study (mutation carriers or a one in two risk of carrying a mutation) were required to provide as high an event rate as possible, avoiding the cost of screening many women at lower risk.

Other trials have explored different risk groups and it is important to question to what extent the findings in a high-risk group can be applied to individuals at lower risk, or with risk arising from different risk factors. In a service context different criteria may be applied, but they would need to take account of economic issues and morbidity arising from false-positive screens.

**imaging approach**

In the MARIBS study, it was necessary to perform the trial on a range of equipment. An MR imaging protocol [46] was developed for this research study that combined acquisition of dynamic 3D data sets with good spatial resolution and with a 90-s time resolution. The 90-s time resolution is required to capture the rapid uptake of contrast that can occur in lesions, which can also wash out rapidly, and allows discrimination of lesions from the more slowly enhancing normal parenchymal tissue. Spatial resolution is required to identify small lesions and to assess the appearance of lesions. With new equipment, it is possible to improve spatial resolution and reduce the time...
between acquisitions. In the MARIBS study, additional high spatial resolution 3D measurements were acquired before and after the dynamic contrast enhanced series, to aid morphological evaluation. Further research measurements were included in the measurement protocol. These sequences were all implemented on a wide variety of platforms. In addition to defining an acquisition protocol, considerable thought was given to how best to evaluate the images, and to assess which aspects of this evaluation contributed to accuracy of detection and diagnosis. To aid this process a formal prospective scoring scheme was devised that scored a range of features including morphology and uptake characteristics [46]. Combining the scores for individual classes of feature provided an overall score that assigned the lesion to cancer, suspicious of malignancy or benign. This scoring scheme has recently been evaluated [47] and shown to provide good sensitivity and specificity. For double reading the sensitivity was 91% [95% confidence interval (CI) 83% to 96%] and specificity was 81% (CI 79% to 83%), with single readers having a specificity of 88% (CI 86% to 90%).

MRI measurements were performed on days 6–16 of the menstrual cycle, to minimise the risk of small hormone-dependent intermittent enhancements appearing and being followed-up. Positive results were either scored as malignant and referred to further investigation, suspicious, when they might be recalled or a repeat measurement in the alternate phase of the menstrual cycle could be performed, and/or the individual could be recalled for a further evaluation at 3 months. Each centre had a clinical lead, who took account of the results from all investigations in recommending follow-up actions.

### sensitivity and specificity of MRI compared with X-ray mammography (XRM)

From a total of 1881 screening visits receiving both MRI and XRM, 35 cancers were detected, of which two were interval cancers. The number identified by each modality is shown in Table 1. Table 2 shows the sensitivity and specificity of MRI and XRM alone, and in combination, together with the values if patients with ductal carcinoma in situ (DCIS) are excluded [31].

From Table 2 it can be seen that MRI is almost twice as sensitive as XRM in detecting cancer in this high-risk group. The sensitivity for XRM is lower than that expected from the literature, although there are few studies of the sensitivity of XRM in this young age group, and most reports evaluate efficiency in terms of cancer detection rates. It should be noted that the sensitivity for XRM may be reduced compared with literature reports due to the comparative nature of the evaluation. A lesion detected in year 1 by MRI but not by XRM may have become evident on XRM by year 2. However, in this period the local extent and stage of disease might progress, particularly in tumours resulting from BRCA1/2 mutations. The sensitivity advantage of MRI is further increased if cases of DCIS, which may not require such urgent action, are excluded. It will be seen that while MRI detects most cancers, neither modality detects all cancers and there is, therefore, an advantage in combining MRI and XRM, providing an overall sensitivity of 94%, which compares well with other population screening methods.

### sensitivity and specificity grouped by mutation status

Table 3 provides a breakdown of sensitivities and specificities for women who tested positive for either BRCA1 or BRCA2 mutations, or who had an uninformative test, allowing the contribution of MRI and XRM to be assessed for these different groups. From this Table it can be seen that for BRCA1 carriers, XRM adds little to the assessment (particularly if the one case of DCIS is excluded). With the BRCA1 mutation, MRI is four times as sensitive as XRM. In BRCA2 carriers there is only a small difference in sensitivity between MRI and XRM, but the two techniques pick up some different cancers. If the three cases of DCIS are excluded, the relative sensitivity of MRI is twice that of XRM. In women with a family history of breast and ovarian cancer who do not test positive for BRCA1 or BRCA2, MRI is more sensitive than XRM and again the two techniques detect sone different tumours. In all groups the sensitivity of a combined test ranges from 92% to 100%, providing satisfactory sensitivity for both those who test positive for a known mutation, as well as those with a family history but an uninformative mutation test. Differences in sensitivity for MRI and XRM in the groups with different genetic characteristics reflect probable biological differences between these groups. In the MARIBS study, BRCA1 mutation carriers had predominantly grade 3 tumours, which were mostly node-negative, oestrogen and progesterone receptor-negative. BRCA2 mutation carriers also were predominantly grade 3, but had a higher incidence of DCIS, had more nodal involvement and were mostly oestrogen and progesterone receptor-positive. Women who did not have an informative test had a higher proportion of lower grade tumours, less nodal involvement and mixed receptor status.

### acceptability, recall rates and comparison with the UK NHS Breast Screening Programme (NHSBSP)

In a new screening approach, acceptability is an important criterion for a successful service. In the MARIBS study, the number of patients withdrawing due to MR specific concerns was low. Less than 2% of patients in this study withdrew due to claustrophobia or discomfort, 0.3% withdrew due to the size restrictions of the scanners, none failed their metal checks. The MARIBS study detected a similar proportion of invasive cancers in women between 35 and 49 as the NHSBSP did in...
women over 50 (82.9% and 79.5%, respectively). The proportion of cancers detected with sizes below 15 mm was also similar (42.9% and 42.5%, respectively), suggesting that the combined MRI and XRM screening method was providing early detection in younger women in a way similar to existing population screening methods in older women.

In the MARIBS study there were more recalls per cancer detected resulting from the MRI scans than from the XRM scans, 7.48 versus 5.29 respectively. Given that MRI is a new technique, that many of the study radiologists had limited experience in this context, and that radiologists were encouraged to recall MRI abnormalities for a further MRI, if they were not convinced that the lesion was malignant, rather than move directly to invasive investigation, these recall rates are reasonable, particularly in the context of the high risk of cancer in the study group. The reasons behind advising an MR follow-up investigation in lesions that did not seem immediately to be malignant were that hormonally dependent transient enhancement is well known in younger women, that it can be difficult to distinguish small areas of enhancement from blood vessels, and that at the time of the study, availability of MR-guided biopsy was limited and lesions could be difficult to detect by other modalities. Research performed as part of this study has demonstrated a fall in the number of suspicious lesions identified and investigated with the number of cases studied, providing clear evidence of a learning curve and of a need for training and quality assurance of radiological reading. In the MARIBS study the overall recall rate per cancer detected was 7.8 compared with 8.5 for the NHSBSP (the latter in women over 50). The benign surgical biopsy rates per cancer detected were 0.19 compared with 0.21 for the NHSBSP. These figures are very encouraging, particularly for a new technique where experience is limited and in a high-risk population.

### Table 2. Sensitivity and specificity in women with at least a 50% chance of a breast cancer mutation (with 95% confidence intervals)

<table>
<thead>
<tr>
<th>Result</th>
<th>Cancers</th>
<th>Non-cancers</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
<th>Sensitivity excl. 6 DCIS % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI+</td>
<td>27</td>
<td>344</td>
<td>77 (60–90)</td>
<td>81 (80–83)</td>
<td>86 (68–96)</td>
</tr>
<tr>
<td>XRM+</td>
<td>14</td>
<td>121</td>
<td>40 (24–58)</td>
<td>93 (92–95)</td>
<td>31 (15–51)</td>
</tr>
<tr>
<td>P value for MRI versus XRM</td>
<td></td>
<td></td>
<td>0.01</td>
<td>&lt;0.0001</td>
<td>0.0009</td>
</tr>
<tr>
<td>Either MRI or XRM +</td>
<td>33</td>
<td>428</td>
<td>94 (81–99)</td>
<td>77 (75–79)</td>
<td>97 (82–100)</td>
</tr>
</tbody>
</table>

CI, confidence interval; DCIS, ductal carcinoma in situ; MRI, magnetic resonance imaging; XRM, X-ray mammography.

### Table 3. Sensitivity and specificity in women testing positive for BRCA1/2 mutations, or having a non-informative test result (with 95% confidence intervals)

#### BRCA1 positive

<table>
<thead>
<tr>
<th>Result</th>
<th>Cancers</th>
<th>Non-cancers</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
<th>Sensitivity excl. 1 DCIS % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI+</td>
<td>12</td>
<td>76</td>
<td>92 (64–100)</td>
<td>79 (75–83)</td>
<td>100 (74–100)</td>
</tr>
<tr>
<td>XRM +</td>
<td>3</td>
<td>30</td>
<td>23 (5–54)</td>
<td>92 (88–94)</td>
<td>25 (5.5–57)</td>
</tr>
<tr>
<td>P value for MRI versus XRM</td>
<td></td>
<td></td>
<td>0.004</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Either MRI or XRM +</td>
<td>12</td>
<td>95</td>
<td>92 (64–100)</td>
<td>74 (69–78)</td>
<td></td>
</tr>
</tbody>
</table>

#### BRCA2 positive

<table>
<thead>
<tr>
<th>Result</th>
<th>Cancers</th>
<th>Non-cancers</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
<th>Sensitivity excl. 3 DCIS % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI+</td>
<td>7</td>
<td>41</td>
<td>58 (28–84)</td>
<td>82 (77–87)</td>
<td>67 (30–93)</td>
</tr>
<tr>
<td>XRM +</td>
<td>6</td>
<td>13</td>
<td>50 (21–79)</td>
<td>94 (91–97)</td>
<td>33 (7.5–70)</td>
</tr>
<tr>
<td>P value for MRI versus XRM</td>
<td></td>
<td></td>
<td>1.0</td>
<td>&lt;0.0001</td>
<td>0.45</td>
</tr>
<tr>
<td>Either MRI or XRM +</td>
<td>11</td>
<td>51</td>
<td>92 (62–100)</td>
<td>78 (72–83)</td>
<td></td>
</tr>
</tbody>
</table>

#### Mutation test uninformative

<table>
<thead>
<tr>
<th>Result</th>
<th>Cancers</th>
<th>Non-cancers</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI+</td>
<td>8</td>
<td>1022</td>
<td>80 (44–97)</td>
<td>82 (80–84)</td>
</tr>
<tr>
<td>XRM +</td>
<td>5</td>
<td>1171</td>
<td>50 (19–81)</td>
<td>94 (92–95)</td>
</tr>
<tr>
<td>P value for MRI versus XRM</td>
<td></td>
<td></td>
<td>0.45</td>
<td>0.0001</td>
</tr>
<tr>
<td>Either MRI or XRM +</td>
<td>10</td>
<td>967</td>
<td>100</td>
<td>77 (75–80)</td>
</tr>
</tbody>
</table>

CI, confidence interval; DCIS, ductal carcinoma in situ; MRI, magnetic resonance imaging; XRM, X-ray mammography.

### Table 4. Comparison with other studies of MRI screening in women at high risk of breast cancer

Table 4 compares the three major studies that have reported recently. The Dutch study [29] was performed at six university centres, all using similar equipment. The study included a range of risk categories and a wider age distribution than the MARIBS study. Like the MARIBS study, it excluded women with a prior history of breast cancer. The Canadian study [30] was a single-centre study of proven mutation carriers only, which included women with a prior history of breast cancer and also had a wider age range. These different risk categories are reflected in
the number of cancers detected per screen ranging from 1% for the Dutch study, 1.8% for the MARIBS study, to 4.8% for the Canadian study. Despite these differences and some differences in criteria for recall, the MRI and XRM sensitivities of the three studies are remarkably similar, ranging from 71% to 77% for MRI, 36% to 40% for XRM and 86% to 94% for combining MRI and XRM. The differing specificities to some extent reflect the different natures of the studies. A single-centre study would be expected to have higher specificity (and probably sensitivity) due to the greater standardisation and experience of a single expert centre. The greater the number of centres, the more divergence is likely and the MARIBS study, with 22 centres, reflects the closest parallel amongst these studies to a true population screening service, albeit without the degree of experience with all radiologists that would be consistent with a mature service. Commentaries on each of the three studies have also been published, providing discussion of relevant issues [48–50].

Two other studies have been reported recently. Lehman et al. reported a study with 367 women receiving one screen [51]. The women had an age greater or equal to 25 and a lifetime risk of breast cancer greater than 25%. Four cancers were detected, but the study included no follow-up to detect missed cancers. Kuhl et al. reported the results of studying 529 women, aged 27 to 59 with 1542 screening rounds, at a single centre [52]. The women had a lifetime risk of breast cancer of at least 20% and 139 has a previous history of breast cancer. The subcategories risk presented appear to mix women with prior history of breast cancer and those without. Looking at the entire cohort without prior risk, the mean breast cancer rate for women with a 20% lifetime risk is 2.45%, surprisingly high for this level of risk. The sensitivity of MRI is given as 100%, the sensitivity of XRM is 32.3% and the combined sensitivity of MRI and XRM is 100%. Unfortunately, no confidence intervals are provided for these sensitivity calculations. The paper also reports the sensitivity of ultrasound in this group as 51.6%, which can be compared with the range of 0%–57% reported for the Canadian study, where ultrasound detected two cancers not seen by MRI or XRM. In the report by Kuhl et al., two of 43 cancers were detected by clinical examination, but they were also visible on MRI and ultrasound. In the Canadian study, two of 22 cancers were detected by clinical examination, they were both also visible on MRI but not by XRM or ultrasound.

Conclusions

Overall the results of all these studies suggest that MRI is the most sensitive means of detecting breast cancer in high-risk women. In general, the best overall sensitivity is provided by combining MRI with XRM. Ultrasound may detect a few additional cancers, but its sensitivity is low compared with MRI, and it suffers from a high degree of operator dependence and the lack of recorded reference images documenting the entire breast, for retrospective comparison. Clinical examination detects very few cancers and these are also visible by other methods. Currently the recall rate for MRI is higher than for XRM, but this can be expected to fall as radiologists gain experience and techniques improve. MRI is still a relatively new technique for breast cancer screening and it is likely to improve in sensitivity and specificity. It is likely that dedicated equipment may improve performance, provide easier access and incorporate easy to use biopsy facilities. In time this may further increase its sensitivity compared with XRM, although digital X-ray mammography may also lead to greater sensitivity in high-risk women.

In determining how to apply MRI as a screening service, it is important to bear in mind the need for standards regarding instrumentation, radiological interpretation, and effective recall and repeat invitation. MRI is a complex examination and requires advanced equipment. The trials reported were performed at field strengths between 1.0 T and 1.5 T, using dedicated breast coils and well defined imaging protocols. It is unlikely that the interests of high-risk women would be best served by anything other than a high quality, regulated service, and this is an important area for health authorities, professional bodies, regulators and insurers to review. Several national bodies are currently preparing guidelines and policy regarding the surveillance of high-risk women and no doubt the studies discussed here will provide a helpful evidence base for this process. While the studies discussed have been very informative, they have not been able to address all the questions. As they are not randomised, they cannot directly measure the contribution screening with MRI would make to cancer mortality and quality of life. However, with growing experience of the outcome of breast cancer in mutation carriers and other risk groups, based on the stage and grade of disease at a given age, it should be possible to model mortality. Certainly the similarities between tumour size detected and that in the NHSBSP, and the relatively low incidence of lymph node involvement is encouraging. However, the high grade and aggressive nature of many of these tumours remains a cause for concern.

The risk levels appropriate for this relatively expensive screening regimen need to be further defined. Studies with
a wide range of risks report a similar poor sensitivity for XRM, and high sensitivity for MRI, although where analysis includes a wide risk group, it may be weighted towards the higher risk groups where there will be a higher incidence of cancer. This suggests that the advantage holds possibly down to the 15%–29% risk group (moderate group in the Dutch study). More work is required to define these limits, which may largely depend on the low sensitivity of XRM in this group. The appropriate age group for screening has also to be determined. A number of the studies have encompassed wide age groups, but maintained the low sensitivity of XRM seen in the MARIBS study. However, in the Canadian and Dutch studies, the numbers of women and tumours detected over the age of 50 are a small proportion of the total and the overall result will therefore be dominated by the women at lower ages. At younger age groups, the decision as to whether MRI will be appropriate will not depend on questions regarding the increased sensitivity of MRI compared with XRM, as the findings of the overall studies will remain relevant at younger ages and could become greater, but on considerations about the risk of the individual, the low event rate and attached morbidity, and concerns regarding exposure of young women to repeated XRM. As mentioned earlier, a part of the lower sensitivity of XRM in these comparative studies may be due to earlier detection by MRI of lesions that would be detected eventually on XRM. However, given the rapid progression of many of these cancers in younger women, delayed detection by XRM is unlikely to be helpful. All of the current studies performed the primary examination annually. Given the rapid progression of some cancers in this high-risk population, there may be some argument for more frequent screening, or alternating the contributing components (XRM and MRI) of the examination at half yearly intervals. However, there is no experimental evidence to support this and it would reduce the ability to compare images at the time of examination. Furthermore, it is the most sensitive component that needs to be performed most frequently.

references