Chapter 3
MRI and Screening

Sabrina Rajan and Barbara J.G. Dall

Abstract Identifying women at higher risk is a combination of assessment of family history, genetic testing and review of clinical history. The management of women at increased risk of breast cancer presents a challenge and includes chemoprevention, risk-reducing surgery and intensified imaging surveillance. Recommendations for imaging surveillance are based on the individual's risk dividing the population into low, moderate, high and very high risk. MRI has a significantly higher sensitivity in comparison to mammography and ultrasound, and this is not affected by age, mutation status or breast density. Additional cancers detected by MRI alone are smaller and less likely to involve lymph nodes than cancers detected by conventional imaging. The majority of invasive cancers demonstrate typical malignant morphology and enhancement kinetics. However, in a small proportion of high-risk women, cancers may present as a morphologically benign mass with smooth borders and this emphasises the importance of considering a wider range of diagnostic features that could represent malignant disease in this group. A consistent and high quality MRI examination is required, complying with recommendations of a robust quality assurance programme with prospective collection and audit of data. In the future, personalised screening based on accurate risk assessment and gene testing in specialised family history clinics will facilitate the development of a tailored screening programme.

Keywords Breast MRI • Screening • Family history

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3.1 Risk Assessment

MRI is an established screening test in women who have a higher than population risk of developing breast cancer. Identifying women at higher risk is a combination of three factors; family history assessment, genetic testing and review of clinical history. Important factors within the family history are young age at onset of disease, bilateral disease, multiple cases on one side of the family, male relatives with breast cancer, other related early onset cancers including ovary, prostate and sarcoma.

The highest risk of breast cancer is among women with an inherited predisposition to breast cancer due to genetic mutations of BRCA1 or BRCA2. Birth prevalence of BRCA1 is 0.07–0.09 % and BRCA2 is 0.14–2.22 % and mutations in these genes account for 5–10 % of all breast cancers [1]. Among these women, the cumulative lifetime risk of breast cancer is 50–85 % [2, 3]. The peak decade for occurrence of breast cancer in these women is 40–50 years [4]. Other genes with a high risk of breast cancer are TP53 (Li-Fraumeni syndrome) and PTEN (Cowden and Bannayan-Riley-Ruvalcaba syndromes); these are much less common but most cases of breast cancer occur between 30 to 40 years and these individuals are at increased risk of multiple cancers. Genetic testing should ideally start with an affected individual which is essentially mutation searching. It can then be offered to adult members of families with a known gene. If a gene has been identified in a family and a family member tests negative, his or her breast cancer risk drops to population risk. However in a high-risk family without a known gene, failure to find a mutation does not reduce an individual's risk [5].

Careful review of the clinical history including a personal history of breast cancer, breast atypia or ovarian cancer must be noted. The greatest risk to women presenting with a breast cancer is recurrence of that breast cancer. They are however also at increased risk of a second breast cancer, as are women presenting with premalignant conditions such as atypical ductal hyperplasia and lobular neoplasia. Supra-diaphragmatic irradiation conveys a risk similar to BRCA1/2 mutation carriers; the risk varies with the estimated dose to the breast, age at treatment, and modifying factors such as dose to ovaries and chemotherapy, which are protective. A number of epidemiological factors convey a modest increased risk and these act multiplicatively. These include parity, age at menopause, hormone use (oral contraceptive and hormone replacement therapy), alcohol consumption, obesity and breast density. These epidemiological factors become increasingly relevant in women who have a family history or a personal history of breast cancer.

3.2 Management Options

The management of women at increased risk of breast cancer presents a challenge. Women who are mutation carriers have cancer risk management options that include chemoprevention and risk-reducing mastectomy and salpingo-oophorectomy.

Prophylactic bilateral mastectomies for such women reduce mortality by more than 90 % [6, 7]. Despite this, the majority of women still opt for intensified imaging surveillance [8]. The effectiveness of a screening test can be demonstrated by showing that it reduces patient mortality, as opposed to simply increasing lead-time. This may be inferred from evidence that the screening test detects additional cases of disease with a reduction in rates of interval cancers and incidence of disease in subsequent screening rounds [9].

A second consideration is the imaging modality utilised for screening, taking into consideration that the relative cancer risk in women with predisposing mutations is particularly high at younger ages. Mammography is an effective screening method in the normal population particularly in those over 50 with an overall sensitivity of about 86 % [10]. However, with the early onset of disease in the high-risk population, there is a need to screen at a younger age where the higher proportion of glandular breast tissue can result in high density mammograms which have a reduced sensitivity for malignancy [11, 12]. Although ultrasound is readily available and relatively inexpensive, it has no evidence-based role as a primary screening test although, in the United States, ultrasound may be considered in high-risk women who are unable to tolerate MRI [13]. Contrast-enhanced breast MRI does not use ionising radiation, which is particularly relevant in this younger age group with active glandular breast tissue that is more radiosensitive. In addition, MRI maintains a high sensitivity for cancer detection even in breast with a dense parenchymal pattern [14].

3.3 Efficacy of MRI Screening

The greatest challenge in reviewing the evidence on the effectiveness of MRI screening is the lack of randomised trials. Riedl et al. recently reported on a prospective non-randomised comparison study that offered BRCA mutation carriers and women with a lifetime risk of breast cancer >20 % annual screening with mammography, ultrasound and MRI [15]. Of the 559 women screened, 40 cancers (invasive n = 26, DCIS n = 14) were identified. The sensitivity of MRI (90 %) was significantly higher than that of mammography (38 %) and ultrasound (38 %). Of the 40 cancers, 45 % were detected by MRI alone, 5 % by mammography alone and no cancers were detected by ultrasound alone. The two cases detected by mammography alone were areas of microcalcification representing ductal carcinoma in situ (DCIS) with microinvasion and DCIS with <10 mm invasive component. Importantly, age, mutation status and breast density had no influence on the sensitivity of MRI. Similarly, in the Italian multicentre screening study, Sardanelli prospectively compared clinical breast examination, mammography, ultrasound and MRI in the surveillance of asymptomatic women at high risk of inherited breast cancer [16]. MRI had a significantly higher sensitivity at 91 % in comparison to mammography and ultrasound, with 31 % of all cancers detected by MRI only.

The EVA trial which was a prospective multicentre observational cohort study based in Germany screened 687 asymptomatic women with a lifetime risk ≥20 % [17]. The sensitivity of MRI (93 %) was significantly higher than mammography (33 %) or ultrasound (37 %). Cancer yield by MRI alone was significantly higher and this was not significantly improved by adding mammography and did not change by adding ultrasound. In this study, MRI was not only superior to mammography for diagnosing invasive breast cancer, but also for DCIS with more than half of the cases of DCIS diagnosed by MRI only. Whilst there is concern that the increased detection of DCIS may lead to overdiagnosis, all cases of DCIS identified on MRI were biologically relevant intermediate or high nuclear grade. The is because the detection of cancer on MRI is determined by angiogenic activity that underpins tissue alterations implicated in cancer proliferation, therefore serving as a biomarker for cancer vitality. The only mammographically detected case of DCIS that was occult on MRI had a low nuclear grade.

The UK Magnetic Resonance Imaging in Breast Cancer Screening (MARIBS) trial compared MRI with mammography in a prospective multicentre cohort study including 649 women with a strong family history of breast cancer or a high probability of carrying mutations in BRCA1, BRCA2 or TP53 [18]. MRI was almost twice as sensitive as mammography in this high-risk group and combining both techniques gave an overall sensitivity of 94 % and specificity of 77 %. Despite a high proportion of grade 3 cancers, 52 % were less than 15 mm in size and 81 % of women with invasive cancer were node negative. Similarly, Kuhl et al. reported that in patients with a lifetime risk of breast cancer of at least 20 %, additional cancers detected by MRI alone, were statistically significantly smaller and less likely to involve lymph nodes than cancers detected by mammography and ultrasound [19]. Warner et al. reported on a Canadian prospective observational study that followed 1,275 women with BRCA1 or BRCA2 mutations, of which 445 women underwent annual MRI screening and 830 women in the comparison group were screened with protocols that did not include MRI [20]. This study demonstrated a stage shift with a significant reduction in the incidence of advanced-stage breast cancer (stages II–IV) in BRCA1 and BRCA2 carriers who were in the MRI screening group.

Although there is an association between tumour size and lymph node involvement for most tumour types, this pattern is not invariable. In North America, data from 276 BRCA1-related breast cancers demonstrated that there was no consistent relationship between tumour size and lymph node status [21]. Such cancers grow faster than non-hereditary breast cancer with the propensity to metastasise to distant sites through the bloodstream, independent of local lymphatic spread and this contributes to the poorer prognosis associated with BRCA1-related breast cancers. A national population-based study of Israeli women reported that tumour size had minimal impact on survival among women with BRCA1-related breast cancer [22]. If the size-survival relationship is attenuated, then it is unclear how much can be gained from detecting a cancer when it is small. These findings have important

implications for evaluating the effectiveness of early diagnosis in BRCA1-related breast cancers.

In a Norwegian study, Hagen et al. assessed the sensitivity of MRI in comparison to conventional screening in the diagnosis of BRCA-associated breast cancer [23]. In 491 BRCA mutation carriers (BRCA1 n = 445, BRCA2 n = 46) screened, there were 25 cancers detected, with a MRI sensitivity of 86 % and mammography sensitivity of 50 %. Of note, 20 % of the cancers presented as interval cancers between scheduled screening investigations, with a mean time of 8.4 months since the last examination. This higher rate of interval cancers may reflect the underlying aggressive tumour biology with a shorter doubling time in BRCA1 mutation carriers, which represented 90 % of the study population. Further analysis of the UK MARIBS study [18], the Canadian study [24] and the Dutch MRI study [25, 26] subsequently highlighted subtle differences between BRCA1 and BRCA2-associated breast cancer [27]. In total, 1,275 BRCA1/2 mutation carriers participated in the studies, with a total of 124 cancers detected. BRCA2 mutation carriers were diagnosed with relatively more DCIS and T1a/b tumours and fewer interval cancers in comparison to BRCA1 mutation carriers. The predicted duration of the preclinical detectable phase was longer for BRCA2 than for BRCA1, which means that BRCA2 cancers grow more slowly and therefore have a higher probability of being screen-detected. The differences in the natural history of BRCA1 and BRCA2 mutation carriers suggest the optimal screening regimen may differ in both groups.

At present, there is no convincing evidence that annual breast MRI surveillance reduces breast-cancer specific mortality, especially in women who are BRCA mutation carriers. The Dutch MRI screening study is a non-randomised multicentre prospective cohort study that included 2,157 women with a cumulative lifetime risk of breast cancer of ≥15 %, who were screened every 6 months with a clinical breast examination and annually with mammography and MRI [26]. Within the group, there were 599 carriers of a pathogenic gene mutation in BRCA1 (n = 422), BRCA2 (n = 172) and PTEN/TP53 (n = 5). In the BRCA1/2 mutation carriers who developed invasive cancer, the cumulative distant-metastasis free survival was 84 % and overall survival was 93 % at 6 years. In comparison, in the non-mutation carriers who developed cancer, the cumulative distant-metastasis free survival and overall survival was 100 %.

In Norway, as part of a national initiative, women with a BRCA1 mutation were offered annual screening with breast MRI in addition to mammography [28]. The 5-year breast cancer-specific survival for BRCA1 women with cancer was 75 % and the 10-year survival was 69 %. In addition, the 5-year survival for BRCA1 women with stage 1 breast cancer was 82 % compared to 98 % in the population based on the Norwegian Cancer Registry. In an updated analysis that compared the survival in BRCA1 breast cancer cases detected through annual screening with mammography and MRI with cases detected through annual screening with mammography only, although tumours did appear to be downstaged in the MRI series, the expected survival benefit was not observed [29].

3.4 Imaging Recommendations

The recommendations below are based on UK National Institute for Health and Care Excellence (NICE) Familial Breast Cancer Guidance [30] with reference to imaging recommendations from the Society of Breast Imaging, American College of Radiology (ACR) [13] and American Cancer Society (ACS) [31]. The European Society of Breast Imaging also has its own recommendations that will not be addressed in detail in this chapter [32]. The UK NICE guidance is a comprehensive document on how to assess an individual's risk, dividing the population into low, moderate, high and very high risk and how to manage that risk. Individuals at low risk are considered to be equivalent to population risk and do not require any specialist surveillance. They should be reassured, educated about breast awareness and encouraged to undergo routine screening surveillance. Individuals at moderate risk and above do benefit from referral to specialist family history clinics. These clinics provide expert advice using risk assessment models and have access to gene testing if considered appropriate.

LOW risk: Breast cancer risk between age 40 and 50 years is <3 %, lifetime risk <17 %

- MRI: NOT recommended for lifetime risk <15 % (UK or ACR) because low incidence means harm of false positives outweighs benefits of true positives.
- Mammography: 3 yearly from 50 years (UK); opportunity to begin annual screening between ages 40 and 44 (ACS) and annually from 40 years (ACR).

MODERATE risk: Breast cancer risk between age 40 and 50 years is 3–8 %, lifetime risk 17–30 %

- MRI: NOT recommended in UK. In the US, MRI may be considered in women with between 15 and 20 % lifetime risk for breast cancer on the basis of personal history of breast or ovarian cancer or biopsy proven lobular neoplasia or atypical ductal hyperplasia (ACR). For US guidelines for women with >20 % lifetime risk of breast cancer, please see HIGH risk section below.
- Mammography: recommended annually 40–60 years and then 3 yearly (UK); annually from 40 years (ACR). For US guidelines for women with >20 % lifetime risk of breast cancer, please see HIGH risk section below.

HIGH risk: Breast cancer risk between age 40 and 50 years is >8 %, lifetime risk >30 %, untested but 20–30 % chance of faulty gene

- MRI: NOT recommended in UK unless there is a personal history of breast cancer where it would be advised annually until 50 years. Annual MRI recommended by ACR for women ≥20 % lifetime risk on the basis of family history starting at 30 but not before age 25, or 10 years before the age of the youngest affected relative, whichever is later.
- Mammography: consider annually 30–40 years, recommended annually 40–60 years and then 3 yearly (UK). Annual mammogram recommended by ACR for women ≥20 % lifetime risk on the basis of family history starting at 30

but not before age 25, or 10 years before the age of the youngest affected relative, whichever is later.

VERY HIGH risk: Lifetime risk 50–85 %, gene positive, untested but >30 % chance of faulty gene (note that guidelines in the US do not make a distinction between HIGH risk and VERY HIGH risk groups)

- TP53: MRI 20–69 years, mammography not recommended at any age.
- >30 % equivalent risk of TP53: as for TP53 but reassess at 60 years, if no personal history of breast cancer then risk of gene is reduced and can be screened as normal population.
- BRCA1/2: MRI and mammography annually 30–49 years; mammography only 50–69 years unless dense breast tissue when MRI should continue (UK). In the US, annual mammogram and annual MRI starting by age 30 but not before age 25 (ACR).
- >30 % equivalent risk of BRCA1/2: as for BRCA1/2 but reassess at 60 years; if no personal history of breast cancer then risk of gene is reduced and can be screened as normal population (UK). In the US, annual mammogram and annual MRI starting by age 30 but not before age 25 (ACR).
- Supra-diaphragmatic irradiation: the risk is delayed and therefore surveillance should not start until a minimum of 8 years following treatment. UK recommends annual MRI from 30 years and annual mammography from 40 years. ACR recommends annual MRI; mammography is not recommended before 25 years.

3.4.1 Higher Risk Screening in Pregnancy

The incidence of breast cancer during pregnancy is estimated to be 1.3–2.4/10,000 live births, which equates to 2–3 % of total breast cancers. MRI may be useful in the first trimester, but there are safety concerns around its effects on the foetus, due to the heating effect, noise and potential toxicity of the gadolinium-based contrast agent. Later in pregnancy, the capacity of MRI scans to detect small tumours will fall due to intense background enhancement. The collective expert opinion from MRI specialists in the UK is that MRI screening during pregnancy and lactation is not recommended but can be resumed 6 weeks after cessation of breast feeding [33].

3.5 MRI Technique

A consistent and high quality MRI examination is required. In the UK, very high risk screening has been incorporated into the National Health Service Breast Screening Programme (NHSBSP) and complies with the recommendations of the Quality Assurance programme [34]. This ensures that all examinations are performed and reported to the same high standard and there is prospective collection and audit of

data. In the US and in continental Europe, there are similarly stringent requirements for MRI quality control, reporting and documentation [32, 35].

3.5.1 Equipment and Protocols

MRI scanners have high-level maintenance contracts that apply manufacturer's thresholds. In addition, weekly quality control tests of signal to noise ratio and suppression effectiveness should be carried out. Training of staff, adherence to protocol and recording of data are all monitored. A 1.5 T MRI machine is required with a dedicated breast coil to ensure patient movement is minimised and there is uniform signal homogeneity across the coils. The scanning parameters should be set up to image both breasts. High spatial resolution is required to assess lesion morphology i.e. a slice thickness of ≤2 mm and in plane resolution of <1 mm. To assess lesion kinetics, high temporal resolution is required with a scan time of ≤60 s and the scan should be repeated out to 7 min following the administration of a gadolinium-based contrast agent (pump injection of at least 0.1 mmol/kg is recommended with a 3 cc/sec flow rate and a 20 ml bolus of saline). Standard sequences should be set up and should include the following:

- T2-weighted fast spin echo
- T1-weighted spoiled gradient echo
- T1-weighted spoiled gradient echo with fat suppression post-contrast

Attention to the timing of the breast MRI study with respect to the menstrual cycle is important. There is a higher prevalence of contrast-enhancing lesions during week 1 and 4 of the menstrual cycle [36]. Therefore, the examination should be carried out in the first half of the menstrual cycle, ideally day 6–16 (in the US, day 7–14), when the background physiological enhancement is less marked [34, 37]. This helps to improve specificity with a reduction in the number of unnecessary recommendations for biopsy of benign lesions and improve sensitivity by minimising the likelihood of a subtle lesion being obscured by marked background physiological glandular enhancement.

Data storage is necessary to store the basic examination in a way that ensures that it can be reprocessed if required in the future. A reporting workstation is required that allows post-processing of images with creation of dynamic enhancement curves, interrogation of subtracted images and maximum intensity projections.

3.5.2 Reporting and Image Interpretation

Reporters embarking on MRI screening should be experienced and the UK NHSBSP and the US ACR requires that each reader should report a minimum of 100 breast MRI examinations per year with double reporting as the gold

standard in the UK [34, 38]. The MRI is reported in conjunction with the screening mammogram and review of the previous MRI examinations. The images should be reported in line with the updated BI-RADS system and conclude with an MRI score of 1–5 to indicate the level of concern (1 indicating normal and 5 indicating malignant) [39] and in the US in accordance with BI-RADS assessment (ACR) [35].

Schrading and Kuhl have reviewed the MRI features of invasive cancer and DCIS in women at familial risk and reported the imaging phenotypes of cancers differ among risk categories [40]. The most frequent finding in women with invasive cancers was an enhancing mass that exhibited typical malignant features in terms of morphology (ill-defined margins, irregular or spiculate shape), enhancement pattern (heterogeneous or rim-enhancement) and the enhancement kinetics (rapid uptake followed by a plateau or washout of contrast). However, the study also reported that 23 % of invasive cancers appeared as a benign enhancing mass with smooth borders, a round or oval configuration, homogenous internal enhancement but suspicious enhancement kinetics. Of these cases, 80 % occurred in women at high risk and documented BRCA1 mutation carriers.

It is increasingly recognised that the imaging features of tumours arising in BRCA1 mutation carriers differs from the characteristics of sporadic tumours. Differing tumour biology in BRCA1 carriers with a high grade and high mitotic activity is associated with rapid growth and reflected in prominent pushing margins around the tumours [41]. The imaging features of such aggressive lesions have a more rounded configuration with sharp, smooth margins, which are morphological characteristics that are more commonly attributed to benign lesions [42]. In contrast, low grade tumours are more likely to incite a desmoplastic reaction within the surrounding tissue, giving rise to the classical appearance of a malignant mass with spiculated margins [43]. However, MRI provides additional functional information with the enhancement pattern and kinetics that allows the level of suspicion to be raised despite the reassuring benign morphology.

In addition, Schrading and Kuhl reported that non-mass like enhancement was the dominant imaging feature of 20 % of invasive cancers and 92 % of DCIS cases. These lesions do not exhibit a correlate on T1 or T2 weighted MRI sequences, do not cause distortion of the normal fibroglandular architecture and do not exhibit space-occupying effects. It is conceivable that this represents another reason for the lower sensitivity of unenhanced imaging modalities such as mammography and ultrasound in the detection of familial breast cancer. This emphasises the importance of considering a wider range of diagnostic features that could represent malignant disease in this high-risk group (Figs. 3.1 and 3.2).

The MRI report should include a management plan. This should indicate if a MR-directed ultrasound +/− biopsy is required and whether an MRI biopsy would be feasible if the ultrasound is normal. The lesions that do raise concern are a new mass lesion ≥5 mm or new isolated area of enhancement ≥10 mm in breasts which otherwise demonstrate minimal enhancement [39]. Careful directed ultrasound will

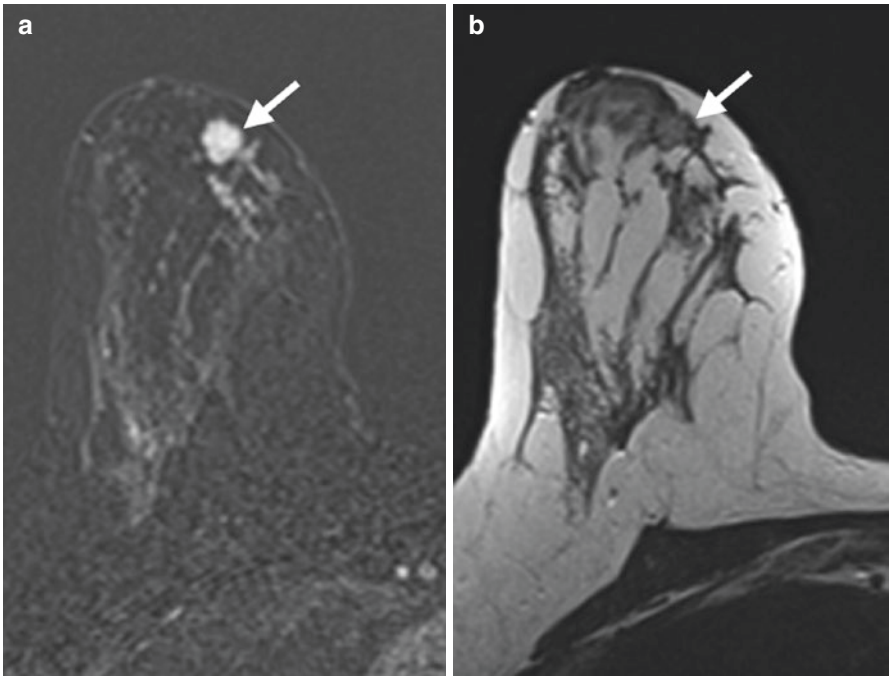

Fig. 3.1 High risk family history patient with normal mammograms. A suspicious 10 mm well-circumscribed rounded enhancing mass in the right upper inner quadrant on post-contrast subtraction images (*white arrow*) (**a**) with a morphological correlate on T2 (*white arrow*) (**b**). Histology confirms grade 2 invasive ductal carcinoma

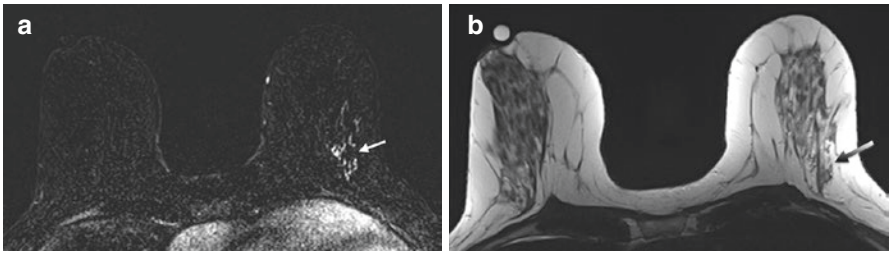

Fig. 3.2 BRCA1 positive patient with normal mammograms. An indeterminate area of segmental stippled enhancement in the lateral aspect of the left breast on post-contrast subtraction images (*white arrow*) (**a**) with no morphological correlate on T2 (*gray arrow*) (**b**). Histology confirms high-grade DCIS

identify about 60 % of these lesions, particularly if there is a mass. Lesions not seen on ultrasound should have an MRI biopsy with clip placement. Facilities that perform MRI should be able to perform MRI biopsy or have an established pattern of referral to a site that can perform these procedures.

3.6 Limitations of MRI Screening

MRI is more expensive and less readily available in comparison to mammography and ultrasound. It also requires the use of an intravenous gadolinium-based contrast agent that may not be suitable for patients with renal disease. MRI may not be feasible for certain women such as those with pacemakers, aneurysm clips or claustrophobia [44]. It is important that patients are appropriately counselled and aware of the methods and frequency of screening investigations, benefits and risks including the possibility of false-positive and false-negative studies with the development of interval cancers.

The increased sensitivity of screening with MRI should be considered with evidence suggesting a 3–5 fold higher risk of patient recall for investigation of false-positive results [45]. Biopsies that do not yield malignancy are considered false-positive results and a disadvantage of MRI screening as this generates unnecessary patient anxiety and has its associated costs in time and money. In the UK MARIBS study, the recall rate was 3.9 % for mammography and 10.7 % for MRI with an overall recall rate of 12.7 % combining both techniques. Overall, there were 8.5 recalls and 0.21 benign surgical biopsies per cancer detected. Therefore, although the absolute recall rate is high, taking into account the high annual risk of cancer in this group at high familial risk, the recall and intervention rate per cancer detected are similar to that found in screening the normal population [46].

In the United States, a multicentre study prospectively evaluated the biopsy rates, positive predictive value and cancer yield of screening mammography, ultrasound and MRI in asymptomatic women who were identified as genetically at high risk including BRCA1/2 carriers or women with at least a 20 % probability of carrying the gene [47]. Findings on MRI prompted biopsy in 8.2 %, while mammography and ultrasound prompted biopsy in 2.3 % of patients. The positive predictive value of biopsies performed as a result of MRI was 43 % with a diagnostic yield of 3.5 % in comparison to 1.2 % for mammography and 0.6 % for ultrasound. This study demonstrated that although screening MRI had a higher biopsy rate, it did help to detect more cancers than either mammography or ultrasound. This suggests that MRI is potentially cost-effective for screening younger women at very high risk of breast cancer, but less cost-effective for screening populations with a wider risk or wider age distribution.

False-negative results can occur when the MRI is reported as normal and fails to diagnose a cancer that is already present. This may be due to a suboptimal study causing difficulties in interpretation due to inadequate contrast agent administration, poor fat suppression or movement artefact. Lesion size and location can also affect accuracy of interpretation with difficulties arising when the abnormality is small (<5 mm) or if the lesion is located close to the boundary of the field of view [48]. In some cases, the lesion may be missed or misinterpreted by the reader [49].

3.7 Conclusion

Standardised high quality MRI examinations achieving a high sensitivity, in addition to available evidence of the efficacy of MRI screening, have allowed expert opinion to support MRI as a screening test in higher risk women who have been appropriately assessed in a specialist clinic. It is different from mammographic screening where the stronger evidence allows it to be applied to a whole population. Women who are choosing between risk-reducing mastectomy and screening should be counselled that although the sensitivity of MRI in combination with mammography is excellent, it will always be less than 100 %. In addition, some very small tumours will already be incurable at the time of detection. Women who opt for screening should be willing to accept the risk of a false negative result as well as the extra investigations generated by a false positive examination. Ideally in the future, personalised screening based on accurate risk assessment and the increased availability and speed of gene testing in specialised family history clinics will facilitate the development of a tailored screening programme. This may require more intensive screening strategies in some younger women, although the cost benefit of this in terms of increased surveillance, recalls for further work-up and economics would have to be considered.

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