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ARTICLE

Should we use MRI to screen women at high-risk of breast cancer?

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Abstract

Women with a strong family history of breast cancer are at increased risk of developing the disease themselves. Mammographic surveillance is recommended in the over 40 age group but the evidence of benefit from this strategy is limited until the individual reaches age 50 years. There is increasing evidence from the trials of breast magnetic resonance imaging that women at high risk may benefit from this technique as sensitivity is not dependent on breast density. The Dutch and Canadian studies have reported the sensitivity of MRI to be 71% and 77% compared to mammography which was 40% and 36%, respectively, in asymptomatic high risk cohorts.

Keywords: *MRI; mammography; screening; breast cancer; familial.*

What is the risk of breast cancer in high-risk women?

Women who have a family history of breast or ovarian cancer are at a higher risk of developing the disease themselves compared to the general population. The level of risk depends on the number of affected first and second degree relatives and whether they carry one of the breast cancer susceptibility genes. In the UK the current recommendation is that women thought to be at risk should be referred to the medical genetics services where their risk can be assessed, they can be counselled and their management options discussed[1]. Between 5% and 10% of all breast cancer is thought to be due to a genetic predisposition. Two breast cancer genes, BRCA1 and BRCA2, have been identified with the mutations appearing at a variety of sites. While these two genes account for much of the familial cancer found in the population other genes are likely to be identified.

The risk of developing breast cancer in a gene carrier depends on a large number of factors including the penetrance of the mutation, environmental influences, the age of the individual and the age of the youngest relative when they developed breast cancer. Estimated risks have been published in a number of studies but a recent comprehensive formal meta-analysis including 22 studies and 6965 breast cancer cases has shown that 'the average cumulative risk in *BRCA1*-mutation carriers by age 70 years was 65% (95% confidence interval 51%–75%)'. The corresponding estimates for *BRCA2* was 45% (33%–54%)[2]. In BRCA1 carriers, the risk is higher if the index case developed breast cancer under 40 years of age. This compares to a lifetime risk of developing breast cancer of 11% by age 85 in the general population[3,4].

When planning an intervention such as surveillance it is important to examine the relative risk as well as the cancer incidence in different age bands. Using the above meta-analysis, Tables 1 and 2[2] give these figures highlighting the low incidence, 0.02% per annum, at ages 20–24 with the incidence peaking at 4.28% at ages 45–49 and then dropping to a steady 3% per year thereafter. The National Institute for Clinical Excellence (NICE) guidelines uses the lifetime risks of breast cancer to demonstrate the difference between women in 10-year age bands from the general population and a woman who has a mother or a sister with breast cancer diagnosed

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between age 30–39 years. Based on the risk to women in the next 10 years, it is shown that at the age of 30 years there is a 2.2% risk over the next 10 years, at age 40, 4.1% risk over the next 10 years and this remains above 4% for the rest of their life. The NICE guidelines compares this with the risk over the next 10 years to a woman of 50 years or more in the general population who has a 2.8% risk of developing breast cancer[1].

Table 1 Relative risks (RR) of breast cancer in mutation carriers

Age group (years)	RR[a] (95% CI) of cancer for carriers of mutations in BRCA1	BRCA2
20–29	17 (4.2–71)	19 (4.5–81)
30–39	33 (23–49)	16 (9.3–29)
40–49	32 (24–43)	9.9 (6.1–16)
50–59	18 (11–30)	12 (7.4–19)
60–69	14 (6.3–31)	11 (6.3–20)

[a] As compared to incidences for England and Wales in 1973–1977[2].

Table 2 Estimated breast cancer incidence (%) in mutation carriers[2]

Age group (years)	Estimated cancer incidence for carriers of mutations in BRCA1	BRCA2
20–24	0.02	0.02
25–29	0.11	0.12
30–34	0.74	0.36
35–39	1.59	0.78
40–44	2.92	0.91
45–49	4.28	1.34
50–54	2.65	1.76
55–59	3.01	2.00
60–64	2.70	2.17
65–69	2.96	2.38

'Low risk' is defined as being at less that 17% lifetime risk of breast cancer. Women at 'moderate risk' are defined as having a lifetime risk of more than 17% or a more than 2.7% risk over the next 10 years and less than 30% lifetime risk. 'High risk' has been set as lifetime risk more than 30%, or more than 8% risk in the next 10 years or at least 20% risk of being a gene carrier[1].

Mammographic screening

The decision as to what age to commence surveillance depends on the risk of the disease and also the efficacy of the chosen screening test in each age group. The UK National Health Service breast screening programme (NHS BSP) was started in 1988 with women being offered 3 yearly mammography[5].

Despite the recent vigorous debate over the efficacy of breast screening by mammography in the over 50 age group[6,7] there is still huge support for the conclusions of the Working Group of the International Agency for Research on Cancer who met in 2002[8] and stated that the seven population-based breast screening trials 'have provided sufficient evidence of efficacy of mammography screening between 50 and 69 years'. The combined estimates of death in the 50–69 age screened group was 0.75 (0.67–0.85) and for the 40–49 age group was 0.81 (0.65–1.01). Therefore they concluded there was only 'limited evidence of efficacy in the 40–49 age group.

In the large UK age trial, women age 40–41 were randomised to be screened annually by mammography or followed up only (this trial has closed recruitment and continues to follow up women and will report later this year)[9]. In the 20 year follow-up of the Swedish Two County study it was found that screening the 40–49 age group did produce a significant reduction in mortality[10]. However, it was suggested that part of the reason for the efficacy was the 18 month screening interval compared to the 2 yearly interval in the over 50 age group[10]. The main problem with mammography in the under 50 age group is that the majority of women are premenopausal and have increased breast density. This reduces the sensitivity of mammography to detect breast cancer[11]. It is estimated that approximately 70% of women in the under 50 age group will have dense breasts[12]. Observational studies have been undertaken in the BRCA mutation carriers and those at moderate or high risk from their family history and it has been found that mammographic screening detected only 50% of cancers with the rest presenting as interval cancers[13].

Current recommendations from NICE state that in women at moderate or high risk, annual mammography should be offered from age 40–49. This should meet NHS BSP standards, and wherever possible be part of the NHS Health Technology Assessment programme trial 'Evaluation of mammographic surveillance in women under 50 with a family history of breast cancer'[14] so that data can be collected and efficacy assessed.

There is general agreement that there is no benefit of mammography screening under the age of 40 and that mammography should not be offered under the age of 30. This causes difficulty as a small number of women have increased risk in the under 40 age group and so the guideline states that from the ages 30–39 mammography can be offered if it is part of a research or nationally agreed protocol where data can be analysed to try to assess efficacy. The document does state that should the mammographic surveillance of the under 50 age group prove not to be cost effective, then it should be stopped. Women who are at high risk or known gene carriers should have tailored surveillance but the nature of this is not specified.

Radiation sensitivity in BRCA1/2 mutation cancers

BRCA genes are involved in one of the DNA repair pathways, through homologous recombination[15].

Ionizing radiation typically causes double strand DNA breaks and homologous recombination is responsible for repair of this type of damage. This is similar to the Ataxia telangiectasia (ATM) gene in which women show increased sensitivity to radiation damage[8]. The damage is seen at the large doses used in radiotherapy rather than the small doses (average 3 mGray) administered in mammography. However, in contrast to this is the report of outcomes from conservatively managed early onset breast cancer in 22 BRCA1/2 carriers. After 12 years follow-up the risk of contralateral breast cancer was no greater in women treated with breast conservation followed by radiotherapy compared to those gene carriers who had unilateral mastectomy without radiotherapy[16]. This suggests that gene carriers may not have increased sensitivity to radiation. There does remain a theoretical risk of induction of breast cancer from mammography, which may outweigh the benefit of this form of screening especially in the under 35 year age group[17].

Magnetic resonance imaging screening

Magnetic resonance imaging has demonstrated high sensitivities for the detection of breast cancer irrespective of age of the patient or the density of the breast parenchymal tissue. Studies from 1989 to 1997 reported sensitivities of between 88% and 100% with specificities ranging from 37% to 97%[18–25].

This prompted a number of pilot studies in different countries in women at increased risk of breast cancer to establish if MRI was more sensitive than mammography and ultrasound in screening younger women. Tilanus-Linthorst reported a Dutch cohort of 109 women at more than 25% risk of breast cancer and >50% breast parenchymal density (mean age 42 years). In this group were 12 BRCA1 or 2 gene carriers. MRI detected all three cancers, which were occult on mammography[26]. The pilot study for the German Cancer Aid Society of 192 women at increased risk (35 BRCA1 or 2 gene carriers) compared annual MRI, double read with consensus with annual mammography read independently. MRI detected all six cancers in the prevalent round and three cancers in the incident round, while ultrasound and mammography only detected one-third of these cases. The Canadian pilot of high-risk women comparing annual MRI, mammography, ultrasound and clinical breast examination (CBE) recruited 196 women (96 were BRCA1 or 2 carriers). The six invasive cancers were detected by MRI but the one DCIS case was only found on mammography[27]. Stoutjesdijk reporting a cohort of 179 women in Holland at >15% lifetime risk having annual MRI, mammography and 6 monthly CBE found MRI detected the nine invasive cancers, three DCIS and one non-Hodgkins lymphoma with readers reporting each examination blindly. Mammography did not detect seven of these cancers[28]. An American series of 367 women at increased risk as a result of their personal history of breast cancer, LCIS or atypia or family history found that MRI had 69% sensitivity as 89 MRI cases were reported as M3 on the BIRADS system, i.e. indeterminate requiring a 6 month follow-up. At the repeat MRI examination nine cancers were found[29].

As Tables 3 and 4[26,28–33] show, in all these small observational studies, MRI detected more cancers than mammography. In general, women were on average <50 years. As can be seen from the studies presented, MRI does appear to have better sensitivity that conventional imaging in this high risk cohort.

This prompted several countries to undertake observational trials in asymptomatic high risk women to compare the sensitivity of MRI with the conventional breast imaging modalities of mammography and ultrasound. Most countries have limited their studies to known gene carriers or to women at more than 25% risk of being a carrier. The relatively low number of women eligible to be recruited in each country made a randomised trial design comparing MRI screening to no intervention or to conventional breast imaging unfeasible.

A number of the groups have published abstracts of numbers recruited to date with some information on sensitivity and specificity of MRI and mammography and again the data so far shows MRI to have superior sensitivity to conventional imaging[34–37].

The UK MARIBS trial limited entry to BRCA1/2 or Li-Fraumeni p53 gene carriers or to individuals who are at least 50% risk of being a carrier who were between age 35 and 50 at entry (Li Fraumeni age 25–50). Women in this trial had annual mammography (except Li Fraumeni), MRI and clinical breast examination[38]. Even the large numbers of women recruited into the UK study means that a meta-analysis will be necessary to decide if MRI is more appropriate than mammography and if screening by this technique is efficacious.

The Dutch study recruited women at more than 15% lifetime risk to be screened annually with MRI and mammography, and by clinical breast examination every 6 months. A total of 1909 women with a mean age of 40 were screened including 358 mutation carriers. Sensitivity of clinical breast examination, mammography and MRI was found to be 17.8%, 40% and 71.1% with specificities of 98.1%, 95% and 89.8%, respectively. There were four interval cancers, all of which were found in BRCA1 carriers. One cancer was found by clinical breast examination alone. MRI was only able to detect 17% of the DCIS cases[32].

The Canadian study recruited BRCA gene carriers who were offered annual MRI, mammography and ultrasound with 6 monthly CBE. A total of 236 women between age 25 and 65 years were screened and 16 invasive cancers and six DCIS cases were detected. The respective sensitivity and specificity was 77% and 95.4% (MRI), 36% and 99.8% (mammography), 33% and 96% (ultrasound) and 9.1% and 99.3% (CBE)[33]. The authors state that combining MRI with mammog-

Table 3 Screening trials of women with familial risk of breast cancer[a]

Author	Country	Entry criteria	No of patients	No of BRCA	Age median (range)	Screening method	Cancers: invasive/ DCIS alone
Kuhl *et al.*[30]	Germany	PBC, FH	192	35	39 (18–65)	MRI, M, US, CBE	7/2
Tilanus-Linthorst *et al.*[26]	Holland	FH	109	12	42 (22–68)	MRI, M, CBE	3/0
Stoutjesdijk *et al.*[28]	Holland	FH	179	15	(21–71)	MRI, M, CBE	9/3
Podo *et al.*[31]	Italy	FH, PBC	105	—	46 (25–77)	MRI, M, US	5/3
Morris *et al.*[29]	USA	PBC, LCIS, atypia, FH	367	19	50 (23–82)	MRI, M	6/8
Kriege *et al.*[32]	Holland	FH, BRCA	1909	358	40 (19–72)	MRI, M, CBE	44/6
Warner *et al.*[33]	Canada	BRCA	236	236	47 (26–65)	MRI, M, US, CBE	16/6

[a]BRCA, BRCA1 or BRCA2 carrier; CBE, clinical breast examination; FH, family history breast cancer >15% risk; LCIS, lobular carcinoma in situ; M, mammography; MRI, magnetic resonance imaging; PBC, previous breast cancer; US, ultrasound.

Table 4 Sensitivity and specificity of annual MRI, mammography, ultrasound and 6 monthly CBE in high risk women

Author	Mammography		Ultrasound		MRI		CBE	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Kuhl *et al.*[30]	33	98	33	80	100	95	NS[a]	NS
Tilanus-Linthorst *et al.*[26]	0	100	—	—	100	95	NS	NS
Stoutjesdijk *et al.*[28]	42	96	—	—	100	89	NS	NS
Podo *et al.*[31]	13	100	13	100	100	99	—	—
Morris *et al.*[29]	NS	NS	—	—	69	77	—	—
Kriege *et al.*[32]	40	95	—	—	71	90	18	98
Warner *et al.*[33]	36	100	33	96	77	95	9	99

[a]NS, not stated.

raphy or ultrasound results in improved sensitivity and specificity.

Meta-analysis of screening and diagnostic tests poses many problems. Good guidance on the best approach to assimilating evidence on diagnostic tests comes from Deeks[39]. Different criteria are required to assess the quality of the studies and potential for bias compared to assessing incidence of disease as was discussed earlier. The meta-analysis is reporting a pair of related results—the sensitivity and specificity—compared to a single result in a therapy or incidence review such as the incidence of disease[2].

Defining the quality of the studies included in the meta-analysis is crucial and normally includes study design, recruitment strategy, description of the test and how it was implemented and the reference standard ('gold standard') used. The definition of an appropriate reference standard is critical but often proves problematic. Ideally a histological gold standard should be used but cytology will suffice. A 2-year follow-up period is accepted practice in reporting breast MRI results in order to calculate specificity[28].

Specific exclusion criteria should be listed, the population studied should be defined and in undertaking an analysis of high risk women the level of risk should be appropriately defined together with expected number of cancers in the cohort. Otherwise it is difficult to judge the quality of the examination. In general, studies with less than 10 cancer cases should be excluded, as it is not possible to calculate sensitivity and specificity accurately. For this reason it is inappropriate to undertake a meta-analysis on the data published to date. Once the other high risk cohorts report in detail then a formal meta-analysis can be undertaken.

The effectiveness of MRI screening in this group is central to the justification of introducing this technique as a surveillance strategy. Using surrogate markers of small cancer size and node negative status, the Dutch results appear promising when they compared MRI and mammography screening to their population results and results from another familial cohort[32]. Investigators reporting national familial trials could try to assess efficacy of screening in this fashion.

Can MRI detect ductal carcinoma in situ?

In population screening, ductal carcinoma in situ (DCIS) is found in up to 20% of patients[40]. There is debate as to whether it is clinically useful to detect DCIS as arguably only high grade DCIS will become invasive disease within the next 20 years. High grade DCIS is more likely to become high grade invasive disease and similarly low grade DCIS will become low grade cancer[41–43]. If disease is widespread then current optimum treatment is a

mastectomy and some surgeons argue that this mutilating surgery is inappropriate in a condition that will not prove to be life threatening. The problem at present is that we cannot predict which DCIS will become potentially life threatening although this is likely to change with additional information from molecular markers. It would seem important to detect high grade DCIS particularly as two-thirds of invasive cancers are grade 3 disease. If we accept that it is important to detect early disease and DCIS is the earliest marker then can MRI fulfil this role?

In most of the published series DCIS was found incidentally as part of a larger cohort and few studies have been specifically set up to answer the question 'can MRI detect DCIS?' Many of the series are retrospective and in almost all, the MRI examination has been read with the knowledge and availability of the mammograms with few series reporting the MRI examinations blind[44–51]. Mammographically detected calcification is sometimes used as the entry criteria and MRI is used to differentiate between benign and malignant disease or between invasive and non-invasive disease. MRI is able to detect approximately 67%–100% of DCIS[52]. However, the sensitivity is lower than for invasive disease.

MRI is more likely to detect grade 3 DCIS compared to grade 1 disease. In a retrospective evaluation of 39 consecutive cases of pure DCIS, grade 2 and 3 cancers were identified at a significantly higher rate (92%) compared to grade 1 (53%) ($p < 0.005$)[53]. Typically DCIS is represented as a linear, branching, clumped or regional pattern of enhancement but more commonly an ill defined diffuse segment of enhancement is seen which can be confused with benign fibrocystic change[52]. However, in the Neubauer series, unilateral segmental enhancement with a granular dotted morphology was the hallmark of DCIS[53].

A high index of suspicion is required in identifying DCIS and the MRI screening studies will produce valuable information giving a much more accurate estimate of the ability of MRI to detect in situ disease. In the high risk screening cohorts reported so far, both DCIS cases were found by MR in the Kuhl paper, all three DCIS cases in the Podo series, only one out of six DCIS cases detected by MR in the Kriege report and four out of six DCIS detected by MR in the Canadian series[30–33].

Can ultrasound be used as an alternative screening technique?

In the observational studies of high risk women, ultrasound has similar sensitivity and specificity to mammography and has much lower sensitivity than MRI (Table 4). Ultrasound is not able to detect DCIS and is therefore unlikely to be useful as a screening tool in this group of women. More work on ultrasound is required as this technology continues to improve. The NICE guidance states that ultrasound alone should not be used as a screening tool[1]. However, it has been reported in one study that in younger women with dense breasts ultrasound is more sensitive than mammography[54].

Should clinical breast examination be used in surveillance?

Based on the results of the randomised controlled trials of population screening that included clinical breast examination (CBE), the IARC concluded that 'clinical breast examination was not effective'[8]. The two MRI high risk trials including CBE as part of the screening strategy showed that the sensitivity and specificity of CBE was 18% and 98% in the Dutch study and 9% and 99% in the Canadian trial[32,33]. Clearly there is no place for CBE alone and Warner further stated that CBE added no further benefit to combined screening with MRI, mammography and ultrasound[33].

Is surveillance required following prophylactic mastectomy?

Prophylactic mastectomy has been shown in various observational studies to be effective in reducing risk by about 90%. Post-operative surveillance is recommended by the Rotterdam group[55]. In a comparative study of 139 women from the Rotterdam Family History clinic, women chose either surveillance or prophylactic mastectomy; eight cancers occurred in the 2:9+1.4 years follow-up in the surveillance group but no cancers were found in the prophylactic mastectomy group[56]. If BRCA1/2 carriers opt for breast conservation with radiotherapy then intensive surveillance remains necessary as they have significantly higher rates of ipsilateral (49% vs. 21%, $p = 0.007$) and contralateral events (42% vs. 9%, $p = 0.001$) than women with sporadic breast cancer[16]. The best operation appears to be complete mastectomy where the nipple areolar complex is removed. However, following surgery, some breast tissue can remain and the question of whether imaging surveillance should be continued is difficult. Several retrospective series have shown that breast cancers can continue to occur[57]. Hartman *et al.* in a retrospective study of 639 women at moderate or high risk had prophylactic mastectomy. After a median follow-up period of 14 years, four cancers occurred instead of the 37 cancers predicted to occur. Mammography is not an option when a mastectomy has been performed leaving clinical examination as the main follow-up option. If a nipple sparing operation has been performed and there is still more than a 10% risk of breast cancer should imaging surveillance still be offered? Arguably, yes but similar surveillance to the general population would be acceptable with mammography being offered in the over 50 year age group if a reconstruction has been performed.

Are mutation carrier cancers the same as sporadic cases?

BRCA1 tumours are mainly high grade ductal carcinomas, oestrogen receptor negative and have a high proliferative index[58]. Medullary or atypical medullary carcinoma is found more often and there is relatively less DCIS in BRCA1 carriers compared to sporadic cases[59]. However, BRCA2 cancers tend to be more akin to sporadic cases. Does this have implications for imaging? BRCA1 cancers tend to have round, smooth or lobulated borders and have homogeneous enhancement, i.e. a 'benign' morphological appearance on MRI but have suspicious or malignant 'washout' kinetics[30]. Although DCIS is less common in BRCA1 carriers, the carrier status is not often known in those women with a familial history. It would seem sensible that both MRI and mammography is offered with MRI alone being confined to the p53 families.

Conclusions

The current NICE guidelines on familial breast cancer suggest that MRI should not be used in routine screening[1]. This recommendation seems sensible meantime but when the MARIBS and other trials report, a formal meta-analysis of the European and North American studies should be undertaken. An assessment of the efficacy of MRI screening is required using surrogate markers and comparison with comparable high risk groups as performed in the Dutch study. In the UK, as a result of the MARIBS trial, expertise in breast MRI has increased, there is more availability of dedicated breast coils and MRI guided biopsy has been developed. In the under 50 age group it is likely that annual breast MRI with mammography will be recommended for women at moderate and high risk from their family history especially where there is more than 50% breast density on their mammogram. Given the poor sensitivity for mammography it is imperative that data is collected on a national basis from centres offering annual mammography in the 40–49 age group in order to try and establish efficacy and ideally this will be through the HTA funded study. Information on surveillance strategies with outcomes from women under 40 years and in the gene carriers is essential in order to inform future guidance. Consideration should be given to comparing 18 monthly with 3 yearly mammography for women in the over 50 age group who remain at moderate or high risk.

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