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Breast cancer screening in high risk women

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Abstract

Women who are at a significantly raised risk of developing breast cancer should be assessed by a medical geneticist to confirm their history, counselled as to appropriate management and offered breast screening. Currently mammography with magnetic resonance imaging is considered the optimal method of early detection of breast cancer in these women. While there is no evidence of mortality benefit there is evidence from surrogate markers that this intervention is worthwhile and cost effective. National recommendations have been produced by the National Institute of Clinical Excellence in the UK and also by the American Cancer Society.

Keywords: *High risk; familial breast cancer; breast MRI; screening; mammography; ultrasound; clinical breast examination; guidelines.*

Introduction

A family history of breast cancer can confer an increased risk of the disease on the individual. In order to estimate the likelihood of developing the disease, detailed information is required about the relatives and this is best assessed by a medical geneticist[1]. Gene testing can be undertaken which can help refine the risk estimate. Approximately 5–10% of breast cancer is caused by an inherited mutation. The best known are the tumour suppressor genes *BRCA1* and *BRCA2.*

Women can be grouped into high, medium and low risk. High risk is defined as greater than 8% chance of developing breast cancer over the next 10 years; or a lifetime risk of more than 30%; or a greater than 20% risk of having faulty *BRCA1*, *BRCA2* or *TP53* genes in the family. Medium risk is 3–8% over 10 years; or a lifetime risk of 17–30%. This compares to a population risk of <3% chance of developing breast cancer over the next 10 years when aged 40–49 years. The lifetime risk to the population is under 17%.

Mammographic screening

The US preventive services task force analysis of the seven randomised trials of breast screening has shown that a mortality reduction of 22% can be expected in the over 50 age group and 17% in the 40–49 age group[2]. The reduction in mortality is dependent on the size and lymph node status of tumours that are detected, with a population screening programme expected to achieve an 80% node negative rate. It is thought that the lower mortality reduction in the younger women is due to reduced sensitivity of mammography and due to more aggressive tumours found in this group. The reduced mammographic sensitivity is partly a result of the increased parenchymal tissue found in premenopausal women. The US ACRIN trial comparing digital with film/screen mammography in 150,000 women has shown that digital mammography is superior for the detection of cancer in women under age 50 years and also in those with denser breast tissue[3].

Magnetic resonance imaging screening

Six major prospective cohort studies comparing annual magnetic resonance imaging (MRI) and mammography have been published to date. The results are summarized in Table 1. The Canadian study was a single centre trial of 236 women aged 25–65 who were known gene carriers, of whom 70 had had previous breast cancer[4].

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Table 1 Trials of MRI and mammography undertaken in high risk populations

Author, country	Cancers (DCIS)/no. of women	Mean age (years)	Mammography		Ultrasound		MRI		Clinical breast examination	
			Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Warner *et al.* 2004, Canada[4]	22(6)/236	47	36	100	33	96	77	95	9	99
Kriege *et al.* 2004, Netherlands[5]	50(6)/1909	40	40	95	–	–	71	90	17.8	98
Leach *et al.* 2005, UK[6]	35(6)/649	40	40	93	–	–	77	81	–	–
Kuhl *et al.* 2005, Germany[7]	43(9)/529	42	33	97	40	91	91	97	5	100
Hagen *et al.* 2007, Norway[8]	25(4)/491	41	50	–	–	–	86	–	–	–
Sardanelli *et al.* 2007, Italy[9]	14(4)/278	46	59	–	65	–	94	–	50	–

The Dutch study recruited 1909 unaffected women aged 25–70 years who were estimated to have at least a 15% lifetime risk of developing breast cancer at six centres. Nineteen were known gene carriers[5]. The UK MARIBS trial reported 649 unaffected women aged 35–49 years who were gene carriers or at greater than or equal to 50% risk of having a gene from 22 centres[6]. The German single centre study screened 529 women over 30 years who were at least 20% lifetime risk from their family history or their personal history of a previous breast cancer[7]. The five centre Norwegian study of 445 *BRCA1* and 46 *BRCA2* gene carriers examined the added benefit of MRI to annual mammography. The results reported findings up to January 2006[8]. The nine centre Italian study reported 278 women aged 25 years or older with a risk of greater than 25%[9].

The sensitivity of MRI was significantly greater than mammography (71–94% and 36–59%, respectively). The specificity for screening MRI was lower than with mammography reflecting the complexity of the examination and lack of experience of the readers. The recall rate for further investigations varied between 8 and 17% with biopsies varying between 3 and 15%. Few centres undertook MRI guided biopsies and many abnormalities were resolved by a second MRI examination, second look ultrasound (US) and additional mammography.

For mammography the sensitivity increased with increasing tumour size and this correlation was shown in the Norwegian study. In this study women with dense breasts had supplementary ultrasound. Ductal carcinoma in situ can prove problematic for MRI particularly where the pixel size of the MR sequence is large. Combining data from the published studies, there were 35 cases of ductal carcinoma in situ (DCIS). This was detected in 57% by MRI and 57% by mammography.

Ultrasound screening

The trials of annual screening in the high risk cohorts that included breast ultrasound showed disappointing results for this technique. The sensitivity ranged from 33 to 40% in the earlier studies[4,7] but improved to 65% in the most recently published Italian study[9]. Ultrasound is generally regarded as the most acceptable technique for women as there is no ionising radiation, there is no contrast injection, it is low cost and the examination is reasonably rapid. However it is operator dependent and is prone to operator error. The improved US technology has resulted in greater sensitivity for cancer detection and performance is not reduced by dense parenchymal tissue found in younger women. Most units do not offer screening US outwith a trial. However it may be that the combination of US with mammography will give results comparable to MRI. In the Norwegian high risk screening study US is used in addition to mammography and MRI in women with dense breasts[8]. Berg reported a large multicentre study of

screening US and mammography in women at increased risk[10]. The average age was 55 years and 2637 women were analysed. Using standardised scanning and interpretive criteria this study showed a diagnostic accuracy for US of 80% compared to mammography of 78% and a combined accuracy of 91% ($p = 0.003$). The number of false positives is considerably higher than with mammography. The authors concede that where screening MRI is performed, US is not necessary except in the workup of abnormalities identified by MRI.

Clinical breast examination

There is little support for using formal breast examination as a screening tool. There is no evidence of benefit in a screening setting. In the four trials of high risk women where clinical breast examination has been reported the sensitivity varied between 5 and 50%[4,5,7,9] with high specificity. The Italian study showed the highest cancer detection although the reason for this is not clear. The Norwegians abandoned clinical breast examination by national consensus between the oncologists, surgeons and geneticists[8].

Efficacy of MRI screening

Although there is good evidence that MRI has greater sensitivity than mammography for detecting cancer and also for a stage shift to a more favourable prognosis, there is no direct evidence that this translates to a mortality benefit. It is highly unlikely that a randomised trial comparing MRI and mammography screening with a mortality endpoint will be undertaken so surrogate markers are used to impute benefit. However this is subject to lead time bias. Data from the trials suggest that 74–94% of tumours are <2 cm in size, 11–27% are DCIS and 76–87% are node negative. The Dutch did a direct comparison with age matched historical controls and showed that the proportion of tumours <1 cm in size was significantly greater in the surveillance study (43.2%) than in either of their control groups (14% and 12.5%) and similarly showed that the node positive rate of 21.4% was significantly better than the controls (52.4% and 56.4%)[5]. However Hagen compared the combined MRI and mammography to the previous mammography only protocol in the *BRCA1* carriers and showed very similar DCIS rates and node negative rates (16%, 8% and 26%, 27% respectively) but fewer pT2 tumours detected by MRI compared to previous mammography alone[8]. These surrogate endpoints suggest that there may be a mortality benefit similar to that achieved by mammography in the population randomised screening trials. However many tumours in this high risk group are of basal phenotype and grade 3 suggesting that a poorer survival should be expected. Important information will be gained from collecting recurrence and survival data from these screened cohorts.

Cost-benefit of mammography and MRI screening

The cost benefit of MRI screening in high risk women has been examined in the UK: one study based on the Magnetic Resonance Imaging for Breast Screening (MARIBS) trial[11] and one undertaken on behalf of the National Institute for Health and Clinical Excellence (NICE) guideline group[12]. Both included in the costs the estimated radiation burden from annual mammography, the financial costs of additional MRI examinations and additional tests from false positive examinations and estimated the incidence of the disease in different 10 year age bands. Using a Quality Adjusted Life Year (QALY) to measure the cost of an additional year of life potentially gained, they concluded that with the higher incidence found in *BRCA1* carriers mammography screening would cost £5200 and additional MRI £13,486 per QALY for women in the 30–39 age group and £2913 and £7781 respectively in the 40–49 age group[12]. A high rate of risk reducing oophorectomy might lower the cancer incidence and so increase the cost of the QALY. In the Norwegian study 50.3% of the women had had an oophorectomy thus reducing their risk of developing breast cancer. However the prevalence was still 2.7% and an annual incidence rate of 2.3%[8]. In the UK the current threshold cost/QALY is £20,000 for introduction of new technology.

Guidelines for screening high risk women

The UK NICE guidelines on familial breast cancer recommend annual MRI offered with mammography to all gene carriers and those at 50% risk of being a gene carrier from age 30 years. This should be done in conjunction with mammography unless the woman is a p53 carrier where there is concern of increased sensitivity to radiation damage. The guidelines are listed in Table 2. The MRI screening programme will be run under the auspices of the National Health Breast Screening programme and will be quality controlled through this organisation. Guidelines on the MRI protocols and reporting standards will be issued by the breast screening programme and will follow recommendations from the Royal College of Radiologists Breast group.

The American Cancer Society breast cancer advisory group has issued guidelines for breast screening with MRI as an adjunct to mammography[13]. Women with more than a 20–25% lifetime risk of developing breast cancer as a result of their family history or previous mantle radiotherapy between age 10–30 years for Hodgkin's disease should be offered annual MRI. Women at less than 15% risk should not be offered screening. It is suggested that screening begin at age 30 years although this is not evidence based.

Table 2 NICE guidelines on screening high risk women[1]

All women aged 40–49 years satisfying referral criteria to secondary or specialist care (at raised risk or greater) should be offered annual mammographic surveillance	
Surveillance should only be undertaken after provision of information about its potential advantages and disadvantages for the early detection of breast cancer, and where offered, this should be of high quality (equivalent to NHS Breast Screening Programme standard) and audited	
New women who are known to have a genetic mutation should be offered annual MRI surveillance if they are:	– *BRCA1* and *BRCA2* mutation carriers aged 30–49 years – *TP53* mutation carriers aged 20 years or older
New MRI surveillance should be offered annually when indicated:	
From 30–39 years:	– to women at a 10-year risk of greater than 8%
From 40–49 years:	– to women at a 10-year risk of greater than 20%, or – to women at a 10-year risk of greater than 12% where mammography has shown a dense breast pattern.
Genetic testing is appropriate only for a small proportion of women who are from high-risk families	
Risk-reducing surgery (mastectomy and/or oophorectomy) is appropriate only for a small proportion of women who are from high-risk families and should be managed by a multidisciplinary team	

Conclusion

There is now considerable evidence that the addition of MRI to mammography screening in high risk women will improve stage of cancer detection. Further information is required to ascertain whether this is conferring a mortality benefit for these women. National guidelines should be followed, the quality of the service audited to ensure highest standards of MRI are adopted and follow up information on cancer detection and survival gathered.

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