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Focus On

MRI in familial breast cancer

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Abstract Five to ten per cent of all breast cancers are associated with a proven genetic predisposition for the disease or a strong family history of breast cancer in which yet unknown genetic predisposition is suspected. Carriers of germline mutations in genes breast cancer 1 or 2 (BRCA1/2) have up to 85% chance of developing breast cancer during their lifetime. The majority of these women develop the disease before the age of 50 years. Consequently, breast-cancer screening programmes aimed at reducing mortality in this population may only be effective if they start at much younger age than the general breast-cancer screening programmes. Unfortunately, the efficacy of conventional X-ray mammography in premenopausal women is often limited by dense fibroglandular tissue that obscures suspicious lesions. As a result, more advanced breast-imaging techniques have been considered, such as contrast-enhanced (CE) magnetic resonance imaging (MRI). In symptomatic patients, the sensitivity of CE MRI to detect invasive breast cancer is known to be high, regardless of the density of the fibroglandular tissue. Conversely, the specificity of CE MRI to discriminate between benign and malignant lesions is variable, and depends on the indication of the examination. Low specificity could result in many recalls on benign lesions, thus negatively affecting the cost–benefit ratio of CE MRI as a screening technique. Several single- and multi-institutional studies have been performed to investigate the efficacy of CE MRI as a screening tool exclusively for asymptomatic women at increased lifetime risk of breast cancer. Mounting evidence suggests that the addition of CE MRI results in cost-effective detection of tumours at earlier stage in BRCA1/2 mutation carriers. The value of CE MRI in other populations at risk is currently uncertain, and it is unlikely that CE MRI will be cost efficient in the general screening population of women who are not at increased lifetime risk.

Keywords: Familial breast cancer; Germline mutation; BRCA1/2; CE MRI; Fibroglandular tissue; Breast-cancer screening

Introduction

Breast cancer is a major cause of mortality among women in western countries. In the Netherlands, approximately 10 000 new cases of breast cancer are diagnosed each year and 3500 die of the disease [1].

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Breast cancer constitutes nearly one-third of all cancers in women. In 5–10% of the cases the cancer is associated with a proven genetic predisposition [2–4], or a strong family history of breast cancer [5]. Germline mutations in two genes, breast cancer 1 and 2 (BRCA1 and BRCA2, respectively), account for approximately 50% of the genetically induced breast cancers [3,4]. The remaining cancers are suspected to be caused by other, yet unidentified, gene mutations. Women with mutations in BRCA1/2 have up to 85% risk of developing breast cancer sometime during their lifetime [6]. Moreover, genetically induced cancers typically develop at considerably younger age than sporadic breast cancers, and are typically more aggressive. At the age of 50 years, more than half the population of women who carry mutations in the BRCA1/2 genes are diagnosed with high-grade, rapidly growing breast cancers with pushing borders and negative hormone receptors [7–10]. As these factors are associated with poor prognosis of disease-free survival, several strategies are pursued to reduce mortality: prophylactic surgery (mastectomy, oophorectomy), chemoprevention, and surveillance.

Although prophylactic surgery and chemoprevention considerably reduce the risk of breast cancer (by 90% and 49%, respectively) [11,12], a significant proportion of BRCA1/2 mutation carriers are more inclined towards surveillance as a first option [13]. Surveillance typically constitutes semi-annual physical examination and annual mammography from age 25 years onwards [14]. The efficacy of mammography screening to reduce mortality in premenopausal women at increased lifetime risk of breast cancer – as opposed to reducing mortality caused by sporadic cancers in postmenopausal women – is, however, largely unproven and subject of debate. This overview discusses the limitations of conventional breast imaging to screen women at increased lifetime risk of breast cancer, as well as the complementary value, pitfalls, and current consensus on the use of contrast-enhanced (CE) magnetic resonance imaging (MRI) for this purpose.

Mammography

Owing to its widely accepted cost–benefit ratio and general availability, X-ray mammography still is the primary method to detect breast cancers. An updated overview of the Swedish randomized trials confirmed that breast-cancer screening with mammography in women between 50 and 70 years results in a significant reduction (21%) of breast-cancer mortality [15]. Nonetheless, there are concerns as to whether mammography retains its efficacy in the screening of premenopausal women at increased lifetime risk of breast cancer. Approximately 40–50% of the mammograms of premenopausal women may not provide sufficient information to exclude presence of cancer because it is obscured by dense fibroglandular tissue [16–18]. The sensitivity of mammography in this age group may be as low as 25% [19–23]. Atypical manifestation of genetically induced cancers (round, well-circumscribed masses) may further attribute to misinterpretation of cancers as benign lesions [10,23,24]. In addition to the limited sensitivity to detect breast cancers in premenopausal women, concern exists about radiation exposure to women carrying BRCA1/2 germline mutations, especially starting at a young age [25]. This concern led to recommendations on a lower limit to the screening interval, thus weighing the risk of (rapidly growing) interval cancers against the risk of radiation-induced cancers at a later age. Nonetheless, concerns about mammography-induced cancers currently have neither been validated nor refuted in studies concerning actual screening populations of premenopausal women. Despite these pitfalls, mammography currently still is the most sensitive examination for the detection of ductal carcinoma *in situ* (DCIS) [26], thus allowing identification of cancers before they potentially reach an invasive stage.

Ultrasonography

Ultrasonography is typically employed as an adjunct to mammography to follow up on suspicious lesions. It has proven effective in the differentiation between cystic and solid masses, and in guidance to biopsy. Major limitations are, however, the dependence of the technique on the experience of the operator, the inability to detect most pre-invasive cancers and a significant percentage of small (<1 cm) non-palpable invasive cancers [27]. Despite these limitations, ultrasonography has proven to be useful in the visualization of suspected cancers within mammographically dense tissue. Consequently, the technique is also evaluated as a screening tool for premenopausal women at increased lifetime risk of breast cancer. So far, these studies have reported moderate to low sensitivity: Warner *et al.* [28] detected 7 of 22 cancers and Podo *et al.* [29] detected 1 of 8 cancers.

CE MRI of symptomatic women

CE MRI employs magnetic and radio frequency fields to visualize the uptake of an MRI-specific contrast agent (gadolinium-DTPA) [30]. Applied intravenously, this agent results in enhancement of areas in the breast that correspond to increased blood flow, capillary permeability, and extracellular volume [31,32]. As these factors are associated with angiogenesis in breast tumours, CE MRI thus visualizes functional processes rather than tissue density. Without the use of contrast agent, MRI is of very little value to detect breast cancers. Currently, CE MRI of the breast is known to be the most sensitive modality to detect invasive breast cancer, yielding sensitivities approaching 100% [33–36]. Sensitivity is not impaired by dense parenchyma. Moreover, the technique is known to detect breast cancers that are undetected at mammography even when the breast tissue is not dense [37,38]. In addition, MRI does not employ ionizing radiation. These virtues could make MRI particularly suitable for the examination of premenopausal women at increased lifetime risk.

At present, CE MRI does, however, present a number of drawbacks. First, its sensitivity to detect DCIS is inferior compared to that of mammography, and can be as low as 45% [39,40]. Secondly, the specificity of CE MRI to discriminate between benign and malignant lesions varies between 37% and 90% depending on the indication [33,36]. Particularly in young premenopausal women, benign findings such as fibroadenomas, adenosis, or hormone-induced enhancement of normal parenchyma are far more common than carcinomas (e.g. Ref. [23]). The CE MRI characteristics of these benign findings are often similar to those of malignant lesions, and the lack of standardized interpretation guidelines in the past have led to inter-reader variations that further contributed to varying specificity. Current consensus dictates that morphological characteristics of contrast uptake (e.g. shape, margins) as well as temporal characteristics (e.g. speed of uptake, presence of washout) must be considered in the interpretation of CE MRI data [41]. Nonetheless, contrary to the standardized mammography examination, CE MRI of the breast uses various imaging protocols that differ between hospitals. Some techniques emphasize on morphological characteristics, other on temporal, yet other aim at a balance.

Obtaining histopathological proof of suspicious lesions that are only visible at CE MRI can be a daunting task. If the lesion cannot be localized using targeted second-look ultrasonography, an MRI-compatible biopsy device may be an option. However, although these devices are currently out on the market, only a small number of institutions have experience with them, and they often turn out to be ineffective for small (<1 cm) lesions. Excisional biopsies may cause scarring and architectural distortions that interfere with future screening efforts. Moreover, frequent biopsies on benign lesions are not desirable in a screening setting. Evidence from mammography screening suggests that further workup on lesions that turn out to be benign causes significant psychological distress that may persist months after the final diagnosis has been given [42]. Especially in a population of women who are quite aware of their high risk, biopsies on benign lesions are greatly undesirable. An often applied compromise is short-term follow-up by CE MRI of equivocal and possibly benign lesions. Although this approach resolves the diagnosis of many benign lesions that are caused by hormone-related enhancement, it increases the risk of delaying cancer diagnosis, which is particularly undesirable for the (rapidly growing) genetically induced breast cancers. In light of these limitations, computer programs are being developed to assist radiologists in identifying benign lesions with high certainty, yielding promising initial results [43,44]. Other drawbacks of CE MRI are the restrictions to perform the examination during the second week of the cycle in order to minimize hormone-induced enhancement, the usual contraindications (such as pace makers, aneurysm clips, claustrophobia), and most notably, its relatively high cost.

Despite its limitations, the unmatched sensitivity of CE MRI for invasive breast cancer has warranted its use for a number of selected indications: suspicion of multifocal tumour, detection of unknown primary tumour with positive lymph nodes, and suspicion of recurrence after breast-conserving surgery.

CE MRI of asymptomatic women at increased lifetime risk

In the past decade, single-institutional studies as well as multi-institutional trials in the UK, USA, Canada, Italy, Germany and the Netherlands focused on the complementary value of CE MRI to mammography to detect breast cancer in women at increased lifetime risk. First results demonstrate the ability of CE MRI to increase the sensitivity to detect tumours in BRCA1/2 mutation carriers, and to detect malignancies at earlier stage. Typically, detected tumours were <1 cm in size and had not yet spread to the axillary nodes. Kriege *et al*. [45] reported the results of the Dutch multi-institutional study in which nearly 2000 women participated with a median follow-up of 2.9 years (Table 1). The fraction of invasive tumours that were ≤10 mm in size was significantly greater in the screening group (43%) than in two matched control groups (14% and 13%, respectively). In addition, the combined incidence of tumour-positive lymph nodes (micrometastases and macrometastases) in invasive breast cancer was significantly smaller in the screening group (21% vs. 52% and 56%).

Although all studies agree that screening by CE MRI may be of particular benefit to women at high lifetime risk of breast cancer, that is, women with proven BRCA1/2 mutation carriers, a number of issues require further investigation before definite guidelines can be formulated concerning which women at risk should be screened, and how the information from the various screening modalities should be combined [46,47]. These issues include the sensitivity of CE MRI for DCIS, specificity for invasive as well as for *in situ* cancer, cost–benefit, and impact on mortality.

An accurate assessment of the complementary value of CE MRI to mammography for the detection of DCIS in premenopausal women at risk can currently not be made owing to the small number of DCIS cases included in these studies so far. Evidence suggests, however, that CE MRI cannot replace

Table 1. Prospective studies comparing the efficacy of conventional breast imaging (mammography, ultrasonography) with the efficacy of contrast-enhanced MRI in the screening of women at increased lifetime risk of breast cancer.

Study	Sensitivity	Specificity	Number of women	Number of validated screens[a]	Fraction DCIS[b]	Inclusion[c]
Kuhl *et al*. [23]			192	105	2/9 (33%)	AW + SW + PH + MC + FH
Mammography	0/3 (0%)	89/96 (93%)				
Ultrasonography	3/9 (33%)	77/96 (80%)				
CE MRI	9/9 (100%)	91/96 (95%)				
Tilanus-Linthorst *et al*. [22]			109	109	0/3 (0%)	AW + MC + FH
Mammography	0/3 (0%)	–				
Ultrasonography	–	–				
CE MRI	3/3 (100%)	100/106 (94%)				
Warner *et al*. [28]			236	479	6/22 (27%)	AW + MC + PH + DM
Mammography	8/22 (36%)	456/457 (100%)				
Ultrasonography	7/22 (32%)	433/450 (96%)				
CE MRI	17/22 (77%)	437/457 (96%)				
Podo *et al.* [29]			105	105	3/8 (38%)	AW + MC + FH + PH
Mammography	1/8 (13%)	97/97 (100%)				
Ultrasonography	1/8 (13%)	97/97 (100%)				
CE MRI	8/8 (100%)	96/97 (99%)				
Kriege *et al.* [45][d]			1909	4169	6/51 (12%)	AW + MC + FH
Mammography	18/45 (40%)	3917/4124 (95%)				
Ultrasonography	–	–				
CE MRI	32/45 (71%)	3704/4124 (90%)				

[a] Pathology proven or at least 1 year follow-up.
[b] Fraction of DCIS among the total number of cancers found.
[c] AW: asymptomatic women; SW: symptomatic women; PH: personal history of breast/ovarian cancer; MC: mutation carriers; FH: family history; DM: dense mammograms.
[d] Diagnostic indices reflect accuracy at BI-RADS cutoff score 3 (probably benign).

mammography for the detection of DCIS. In the largest study published to date, Kriege *et al.* report that CE MRI failed to visualize 5 of 6 DCIS cases that were visible at mammography [45].

The reported specificity of CE MRI to differentiate between benign and malignant findings in the high-risk screening population ranges between 90% and 99%. These specificities are consistently high, and are in contrast with those reported in symptomatic patients. The discrepancy is mostly caused by the fact that the majority of examinations of asymptomatic women do not show any suspicious enhancement at all. These 'normal' findings are generally grouped in the category 'benign'. It will obviously be more challenging, however, to differentiate between benign and malignant enhancement than to differentiate between 'no enhancement' and malignant enhancement. The positive-predictive value (the percentage of malignant tumours in the total set of abnormal scans that prompted further workup) more accurately reflects the ability to differentiate between benign and malignant areas of enhancement, and does show considerable variation between studies (Table 2). Several explanations exist for this variation. First, differences in opinion regarding which types of workup should be counted in the calculation. Some studies consider only biopsies, while other consider any workup relevant (including short-term follow-up by CE MRI). Groups supporting the former strategy (e.g. Refs [23,29]) typically report higher positive-predictive values than groups supporting the latter strategy (e.g. Ref. [45]). Other reasons for variations between studies are the small numbers of included tumours (especially in the single-institutional studies), differences in age and risk level of included women, relatively short follow-up periods, and differences in interpretation guidelines for CE MRI. Recent guidelines for CE MRI according to the Breast Imaging Reporting and Data System Atlas (BI-RADS) classification [41] were not available at the time that the reported studies started. Although some employed scoring systems equivalent to the mammography BI-RADS scoring system [23,28,45], other systems have been used as well [29]. It should also be kept in mind that CE MRI techniques have not been standardized across studies.

Only few groups have attempted to provide cost estimates of adding CE MRI to the surveillance programme of asymptomatic women at increased risk. Tilanus-Linthorst *et al.* report an additional cost of

Table 2. Positive-predictive value of contrast-enhanced MRI in prospective studies.

Study	Positive-predictive value	
Kuhl *et al*. [23]	9/14	(64%)
Tilanus-Linthorst *et al.* [22]	3/9	(33%)
Warner *et al*. [28]	17/37	(46%)
Podo *et al*. [29]	8/9	(89%)
Kriege *et al*. [45]	32/452	(7%)

€13.930 per detected cancer, which is approximately 1.5 times the cost of detecting a breast cancer in the Dutch general screening programme [22]. Podo *et al.* [29] reports only €6.000 per MRI-detected cancer, constituting two-thirds of the cost to detect a breast cancer in the general screening programme. The small number of cases studied so far, and the differences in inclusion criteria underlie these discrepancies in assessment of cost. Obviously, the larger the risk to detect breast cancer, the more cost-effective CE MRI will become. Future studies must identify subgroups of women at risk who benefit most from screening by CE MRI in terms of reduced mortality as well as in terms of reduced morbidity.

Conclusions

The endpoint of any screening programme is reduction of mortality. Only a prospective randomized trial can assess this endpoint, and no evidence currently exists that the addition of CE MRI to the surveillance programme of women at high risk reduces mortality. Nonetheless, mounting evidence exists that the addition of CE MRI results in cost-effective detection of tumours at earlier stage in BRCA1/2 mutation carriers. The value of CE MRI in other populations at risk is currently uncertain. Moreover, it is unlikely that CE MRI will be cost efficient in the general screening population of women who are not at increased lifetime risk.

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