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Review

Opportunities in cancer imaging: risk-adapted breast imaging in screening

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In the UK, women between 50–70 years are invited for 3-yearly mammography screening irrespective of their likelihood of developing breast cancer. The only risk adaption is for women with >30% lifetime risk who are offered annual magnetic resonance imaging (MRI) and mammography, and annual mammography for some moderate-risk women. Using questionnaires, breast density, and polygenic risk scores, it is possible to stratify the population into the lowest 20% risk, who will develop <4% of cancers and the top 4%, who will develop 18% of cancers. Mammography is a good screening test but has low sensitivity of 60% in the 9% of women with the highest category of breast density (BIRADS D) who have a 2.5- to fourfold breast cancer risk. There is evidence that adding ultrasound to the screening mammogram can increase the cancer detection rate and reduce advanced stage interval and next round cancers. Similarly, alternative tests such as contrast-enhanced mammography (CESM) or abbreviated MRI (ABB-MRI) are much more effective in detecting cancer in women with dense breasts. Scintimammography has been shown to be a viable alternative for dense breasts or for follow-up in those with a personal history of breast cancer and scarring as result of treatment. For supplemental screening to be worthwhile in these women, new technologies need to reduce the number of stage II cancers and be cost effective when tested in large scale trials. This article reviews the evidence for supplemental imaging and examines whether a risk-stratified approach is feasible.

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Introduction

In the UK women aged 50–70 years are invited for 3-yearly mammography as early detection has been shown to be cost effective in prevention of breast cancer deaths.[1,2] Since the start of screening in the UK in the late eighties improvements have been made with the adoption of double reading, two-view mammography, and the move from analogue mammograms to digital mammography and a world-leading quality-assurance system. This differs to other screening programmes where annual or biennial screening takes place by either double or single reading, with the European Society of Breast Imaging recommending screening women age 50–69 years to be screened every 2 years as well as every 3 years for women age 70–74 and 2–3 years for women age 45–49.[3] In the US the American Cancer Society (ACS) recommends annual screening age 45–54 then biennial screening with only single reading.[4]

The screening programme includes all women, irrespective of their risk of developing breast cancer. For this age-based or "one-size-fits-all" approach to breast screening, the estimated benefit includes an estimated 20% reduction in mortality[5]; however, the risks of overdiagnosis (estimated at 11–19%) and potential effects of overtreatment and on psychological wellbeing, although difficult to quantify, should not be overlooked.[5] A cost-effectiveness study of 364,500 hypothetical women found that targeted screening of women with a higher risk of breast cancer was associated with reduced overdiagnosis and reduced cost of screening while maintaining reduced breast cancer deaths.[6] Risk-stratified approaches to breast screening should aim to improve the benefit-to-harm ratio as well as the cost-effectiveness of screening.

Interval cancers

Interval cancers, defined as "a breast cancer diagnosed in the interval between scheduled screening episodes in women who have been screened and issued with a normal screening result",[7] are a feature of any screening programme and have a worse prognosis.[8,9] One reason for interval cancers or indeed cancers not being diagnosed until the next screening round is the presence of dense parenchymal tissue, which hides the features indicating a cancer, the so-called masking effect. Dense breast parenchymal patterns are known to confer a fivefold risk of interval cancer compared with the lowest breast density.[10] Compared to "average" breast composition, the increase is twofold. Mammographic sensitivity falls to around 60% in the 9% of the screening population with the highest breast density10. Analysis of 365,426 women from the American Breast Cancer Surveillance Consortium demonstrated that advanced stage interval cancer rates were highest in women with the highest category of density and in women with a 5-year risk of >2.5% and BIRADS C density.[11]

The screening interval will affect interval cancer rate, but cancers can also go undetected at screening for a variety of reasons, such as search error, perception error, decision-making error, and image-quality error.[12–14] The cancer may be outside the imaging field of view or it may be mammographically occult, secondary to masking. Categorisation of interval cancers is an important part of quality assurance of the NHS Breast Screening Programme (NHSBSP). Most are classed as satisfactory true interval cancer; no actionable abnormality on the prior screen but in a certain proportion minimal signs or even frankly suspicious imaging signs will be evident on the prior screens (classified as satisfactory with learning points or false negative respectively). Interval cancers are often of higher grade and T stage compared to screen-detected cancers with poorer survival outcomes, chiefly because of the latter, and behave in a similar way to breast cancers diagnosed in women who have not been screened.[8,9,13,15] A large Dutch study found that volumetric breast density was a strong predictor of interval cancer risk (hazard ratio 8.37 for the highest quartile of volumetric density compared with the referent lowest density quartile).[10,16]

The UK interval cancer rate is reported at approximately 2.9/1,000[8] compared to a cancer detection rate of 8/1,000 in a 3-yearly programme. A study of 306 interval cancers from five NHSBSP screening sites found the average time to diagnosis for interval cancers of 644 days, such that the highest proportions are diagnosed in the second (42%) and third years (36%) after screening, and an estimated average tumour volume doubling time of 167 days.[9] Measures to reduce interval cancers and larger cancers found in incident rounds would be an effective method of improving survival and there is much interest in the role of artificial intelligence (AI)-based computer-aided detection software in this context. AI could potentially work independently or synergistically with readers to detect cancers as well as triage scans for an adapted stratified screen reading workflow.

Risk stratification

Risk prediction models use personal information, such as family history, age, previous breast biopsy, etc., as well as single nucleotide polymorphisms (SNPs) to give the likelihood of developing breast cancer.[17] Breast density is incorporated into these models and gives an additional 7% accuracy although appropriate choice of automated density tool in each model is not yet known.[18–20] Risk prediction models require validation; the Tyrer-Cuzack model (developed in women with a family history of breast cancer)[21] is being refined and tested in a large Manchester normal population risk cohort. The CR-UK CanRisk programme aims to develop and validate breast cancer risk prediction tools that can be used at all levels of healthcare within the NHS.[22] CanRisk includes the BOADICEA model[23,24] that has recently been extended to include all known breast cancer susceptibility SNPs and breast density. In a recent validation study of 10,000 high-risk women participating in screening in the UK BOADICEA has been found to be well calibrated in all deciles of predicted risk. There is an acknowledgement that all stakeholders now need to consider the benefits and harms, costs and acceptability of moving to a risk-stratified

approach in a transparent manner, for example, including a single assessment check point at age 40/50, using a combined model (e.g., Tyrer–Cuzack or BOADICEA) incorperating personal information, SNPs, and breast density. Such targeted screening could alter the age of screening commencement, as well as frequency and modality used. The continuous review of such risk due to changes in risk over time (e.g., breast density involution as well applying and uptake of prevention strategies alongside screening) is required. We must also consider population compliance, with a current screening attendance of 70%. How this targeted screening would alter adherence is uncertain. The potential advantage is that fewer people may need to attend screening in order to achieve the same impact, and that a better balance of benefits and harms may result from using different screening strategies for people at different risks.[25] At present, AI can undoubtedly help with diagnosis and image interpretation; however, it also offers the promise of integrating information on risk from questionnaires including family history, SNPs, and extraction of information from digital radiographs and other imaging to better inform a woman's risk of developing breast cancer. It is hoped that a better integration of this complex information can be translated into an implementable personalised risk score.

Breast density

Mammographic density, or breast density, is the proportion of radiopaque fibroglandular tissue (fibrous connective tissue or stroma and glandular epithelial tissue) compared to radiolucent adipose tissue within the breast.[26,27] It may be regarded as a global measure of breast composition and varies according to age, genetic predisposition, ethnicity, body mass index, hormone exposure, and lifestyle factors.[28,29] As well as affecting mammographic screening performance through masking, density is also an independent risk factor for breast cancer, with women in the higher breast density categories reported to have a 2.9- to sixfold increase in relative risk for developing breast cancer when compared to those in the lowest breast density category.[30,31] The distribution and heterogeneity of density within the breast is also important, as focal density can result in masking.[12,26,32] Additionally, it has been demonstrated in longitudinal studies that localised density predicts future tumour location.[33]

Original radiological reporting classifications of breast density date back to the 1970s[34–36] and included an element of texture or parenchymal complexity. The most widely used measure of breast density currently is visual assessment of mammographic percent dense area by a reader, assigning a three-[37] or more usually, a four-point scale (BI-RADS 5th edition).[38] The move from the 4th to the 5th edition of the BI-RADS scale has moved the emphasis from estimation of area-based percent density towards a description of the likelihood of masking. As a consequence, there is a tendency to score more breasts as heterogeneously dense (BI-RADS C). In research settings, marking a 10 cm visual assessment scale (VAS) to give a percent density or generating a score in conjunction with semi-automated thresholding techniques (Cumulus)[39] is more commonly used. Such subjective assessments are not very reproducible, due to inter-reader variability.[40–42] Quantitative software algorithms produced by companies such as Quantra, Volpara, Densitas and DenSeeMammo provide density scores from raw or processed full-field digital mammography (FFDM) images and derive values that vary from each other.[40,43] Tools such as Volpara and Quantra have been shown to be reliable when performing repeated measures.[40,44] The software programmes provide an area/volume score and a BIRADS category. It may be that the need for supplemental imaging should be based on a numerical score as this might more closely give the risk of breast cancer or likelihood of masking. There are many algorithms available for automated density measurement and continued external benchmarking comparison studies using a standardised test sets is needed.[45]

Breast density can be affected by positioning, radiographic factors such as tube voltage and current and the inclusion of additional/non-standard views.[39,44] Algorithms are being constantly developed, using deep learning to achieve good reader agreement ($k = 0.67–0.85$), and techniques such as federated learning to improve generalisability.[46,47] The development of density algorithms requires labelled data and raw mammographic images. Although sites in the USA report breast density, most institutions do not routinely report this and the majority of hospital sites do not store raw images. Although these tools can be used as standalone systems, their incorporation into existing cancer prediction models to improve performance was shown by a recent systematic review to result in a statistically significant increase in area under the receiver operating characteristic (ROC) curve (AUC; 0.03–0.14).[48] Alternative measures to quantify breast density with non-ionising radiation techniques have been proposed using magnetic resonance imaging (MRI) and ultrasound.[26,27]

Legislation passed by the US Congress in 2019 directs the Food and Drug Administration (FDA) to ensure reports are provided for patients and doctors, detailing breast density as part of the US breast screening programme.[49,50] Women classified as having dense breasts are recommended to discuss with their doctor if they should undergo additional imaging, although no unanimous recommendation has been put in place.[50–52] Breast density varies across populations with the greatest proportion of the population reported to be represented in the middle two categories of BI-RADS density and up to 40% of the population are estimated to have dense breast (heterogeneously or extremely dense) from studies carried out on US Breast Cancer Surveillance Consortium (BCSC) populations.[53,54]

Introducing automated tools to provide consistent reliable density measures would fill a gap where density is currently not reported without increasing the reading duties and time.[55] It would also allow for the incorporation of density information into risk-prediction models as well as possibly facilitating a standardised measure from which a threshold can be determined to target supplemental imaging strategies.[56]

Digital breast tomosynthesis

Digital breast tomosynthesis (DBT) has already been adopted by many countries as research indicates that this three-dimensional (3D) technique can result in improved sensitivity as well as reduced recall rates[57]; however, the improved performance may be less marked in women with very high breast density and in those cancers presenting as microcalcification.[58,59] There is also concern that some of the additional cancers being found are slow-growing lesions, which may not be life threatening, potentially over-diagnosis. Several studies have now suggested that there is reduction in interval cancers when DBT is being used,[60] but others have found no such reduction.[61–63] Interval cancer reduction is one of the key outcome measures in the UK large randomised controlled trial comparing two-dimensional (2D) with 2D plus 3D recruiting 100,000 women.[64]

Mindful of the increased radiation dose with DBT trials have been undertaken which demonstrate that the standard 2D mammogram can be replaced by a synthetic 2D mammogram created from the 3D dataset. It is likely that DBT will be a powerful step in the improvement of performance of the screening programme, although it is likely not be useful for those women with the densest category of breast tissue.

Breast ultrasound

Several studies have shown high diagnostic performance of automated whole breast ultrasound (ABUS), similar to screening with hand-held breast ultrasound (HHUS)[65] with an incremental cancer detection rate of 1.9–7.7 cases per 1,000 women compared to mammography alone,[15,66–70] increased sensitivity of between 21.6–41%, but with variable specificity. Recall and biopsy rates were higher while positive predictive value-3 (PPV3) decreased by 4.2–15.8%. The largest ABUS study (SomoInsight Study) detected 1.9 additional breast cancers per 1,000 women,[67] similar to the results of Japan Strategic Anti-cancer Randomized Trial (J-START)[71] but lower than the results of American College of Radiology Imaging Network 6666.[72] The differences in additional cancer-detection rates was probably due to differing inclusion criteria of these studies. In the SomoInsight study, 93.3% of cancers were invasive, with mean size of 12.9 mm and 92.6% node negativity,[67] similar to the results of HHUS screening.[71,72] Overall, ABUS screening was effective in detecting small, invasive, and predominantly node-negative breast cancers.

Recall and biopsy rates tend to increase with ABUS, with an additional value of 2.5 per 1,000 screens and PPV3 of 8.3% for the biopsies overall.[73] These values have improved in time though, due to increased reader experience and software improvement with the latest ABUS systems,[73,74] and fall in incident rounds. ABUS has a learning curve, so adequate training in order to perform state-of-the art examinations, as well as awareness of technical pitfalls and artefacts, will improve correct interpretation and reduce false-positive studies.

ABUS interpretation time tends to vary significantly in published studies (2.9–9 min), due to differences in reader experience as well as complexity of cases.[67,68,75,76] To reduce reading time, a computer-aided detection (CAD) software for 3D ABUS (QVCAD, QView Medical) has been developed recently and granted FDA approval.[77] Recent reader studies have shown that the use of concurrent-read CAD systems for interpretation of screening 3D ABUS may significantly decrease interpretation time up to 35%, as well as reduce unnecessary recalls, resulting in improved diagnostic accuracy.[78–80] Computer-aided detection systems might be a valuable tool to improve workflow in large-volume screening centres.[81]

In terms of diagnostic performance, several studies have evaluated the interobserver reliability in BI-RADS assessment so far, but with heterogeneous results and a considerable variation in kappa values according to a recent systematic review.[82] In a recent retrospective study of 1,886 women, a very high (99.8%; kappa = 0.994, $p<0.0001$) interobserver agreement in BI-RADS classification was found between 3D ABUS and HHUS.[75]

A unique feature of ABUS is the use of coronal reformatted images, contributing to improved detection rates by enabling lesion identification in three orthogonal planes.[83,84] Vourtsis and Katchulis found that ABUS outperformed HHUS in the detection of architectural distortion in the coronal plane and could supplement mammography in the detection of non-calcified carcinomas in women with dense breasts.[75] Furthermore, ABUS demonstrated significant higher accuracy for volumetric measurements, compared to HHUS.

Future perspectives include ongoing research in the field of deep learning such as radiomics-derived 3D ABUS signatures, as well as combinations of 3D ABUS and tomosynthesis in one device in order to improve workflow in breast imaging.[85,86]

The US task force concluded that mammography with supplemental US finds additional breast cancers in dense breasts but increases false-positive results.[87] All supplemental US studies in dense breasts found additional cancers but with variable and sometimes high recall rates.[67,71,88] Berg concluded that supplemental US should be offered to all women with dense breasts.[89] Recent EUSOBI guidelines suggest the usage of HHUS or 3D ABUS as a supplemental screening modality following a negative mammogram in women of average or intermediate risk with dense breasts.[90] Another possible indication for screening ABUS is as alternative to MRI in high-risk women.[91]

Contrast-enhanced mammography

Contrast-enhanced mammography (CESM) combines iodinated contrast medium with standard mammography to improve lesion conspicuity, particularly in women with dense background parenchymal patterns. Abnormal blood flow related to neovascularity associated with a carcinoma is imaged in a similar fashion to contrast-enhanced breast MRI. Two minutes after the injection of the contrast agent

standard craniocaudal and mediolateral oblique views are acquired of both breasts. The CESM is a dual-energy technique generating two sets of images in the same breast compression, a low energy image, which is equivalent to a standard 2D digital mammogram and a recombined image, which demonstrates the contrast medium uptake.[92] Consequently, when a CESM study is performed, standard 2D digital mammography can be safely omitted. The radiation dose of CESM is between 1.2 and 1.8 times that of a standard 2D digital mammogram, but is well within QA guidelines for mammography.[93,94]

Retrospective reading studies comparing CESM with standard 2D digital mammography have shown a significant improvement in the sensitivity and specificity of CESM for detecting breast cancer (Table 1). The patient populations in all these studies are either symptomatic patients or patients recalled to assessment after an abnormal screening mammogram. CESM compares favourably with MRI for the local staging of breast cancer (Table 2). Studies have shown equal sensitivity between CESM and MRI for detecting the index cancer, but with the positive predictive value of additional biopsies significantly higher with CESM compared to MRI due to a reduction in false-positive interpretations of additional lesions away from the index tumour site.[95–97] Sumkin *et al.* found that MRI depicted twice as many additional suspicious lesions compared to CESM, without diagnosing more additional malignancies. The PPV of additional biopsies for MRI was 28% (13 malignancies diagnosed from 46 additional biospies) compared to CESM were the PPV was 52% (14 of 27 additional biopsies being malignant).[95]

The use of CESM as a screening tool for higher risk women is a logical step, given the equivalent sensitivity to MRI for detecting malignancy. Several studies have compared the performance of CESM to standard 2D digital mammography in higher risk screening populations. Sorin *et al.*, assessed performance in a population of 611 women of intermediate risk, where 48% had a personal or family history of breast cancer and 93% had a breast density classified as BIRADS C or D. CESM had a sensitivity of 90.5% for detecting malignancy, which was significantly higher than standard digital mammography with a sensitivity of 52.4% (an incremental cancer detection rate increase of 13.1 per 1,000 women).[98] In a series of 904 women with an increased breast cancer risk, Sung *et al.* found the entire CESM study had a significantly higher sensitivity of 87.5% compared to 50% for the low energy image alone (equivalent to a standard 2D mammography), with cancer detection rates of 15.5 and 8.8 per 1,000 women screened respectively.[99] In this study, 77.4% of the screening cohort had a dense parenchymal background pattern (BIRADS C or D), 40.2% had a personal history of breast cancer and 48.6% had a family history of breast cancer with 9.1% of the population being BRCA mutation carriers.[99] Jochelson *et al.* compared the performance of CESM and MRI in 307 women at an increased risk of breast cancer; 56.4% had a family history of breast cancer including BRCA gene carriers and 33.6% had a personal history of breast cancer. Of the cohort, 93.8% of the women had a negative CESM exam compared to 92.8% who had a negative MRI study. There were 13 lesions that underwent a biopsy following CESM with two cancers diagnosed (PPV of biopsy 15.4%) and 21 lesions underwent biopsy following MRI yielding a diagnosis of three breast cancers (PPV of biopsy of 14.3%). Specificity rates of CESM and MRI were 94.7% and 94.1%, respectively.[100] All three studies demonstrate that CESM is a promising technique for screening women at increased risk of breast cancer.

There are other issues to take into account when considering CESM as a screening tool. Physiological/benign background parenchymal enhancement can be seen with CESM in a similar manner to that observed in breast MRI. As with MRI, it is significantly associated with menopausal status, radiation therapy, hormonal treatment, and breast density.[101] No clear pattern in variation of parenchymal background enhancement across the menstrual cycle has been demonstrated for CESM, so it is unclear whether menstrual cycle timing would need to be taken into consideration when scheduling CESM studies in a screening setting.[101]

CESM has some advantages over MRI as a screening tool, being potentially cheaper and better tolerated by women.[102] There are the disadvantages too, around radiation dose and the use of an iodinated contrast agent. The use of any contrast agent is not entirely without risk. Concerns have been raised about the long-term use of gadolinium-based contrast agents in MRI. The iodinated contrast agent used in CESM carries a very small risk of allergic reaction, typically around 1%, with the vast majority of these mild and self-limiting. In one study of 839 women, five allergic reactions were reported (0.6%) with one women requiring corticosteroid administration to treat urticaria and shortness of breath.[103] Sung *et al.* reported contrast agent reaction in 15 of 904 women (1.7%), with two women requiring the administration of an anti-histamine.[99]

CESM is a potentially useful screening tool for women at increased breast cancer risk. Clinical trials are currently underway to establish its role in a risk-adapted, personalised approach to breast cancer screening.[56] It has clear benefits for women not currently well-served by conventional mammography, providing the increased sensitivity achievable from a vascular-based breast cancer screening test.

Table 1
Comparison between standard two-dimensional digital mammography and contrast-enhanced mammography (CESM) for breast cancer detection.

Ref.	n	Mammography		CESM	
		Sensitivity %	Specificity %	Sensitivity %	Specificity %
Dromain (2011)[93]	120	80	50	93	56
Jochelson (2013)[86]	52	81	-	96	-
Fallenberg (2014)[82]	107	77.9	-	94.7	-
Cheung (2014)[94]	89	71.5	51.8	92.7	67.9
Lobbes (2014)[95]	113	96.9	42	100	87.7
Lalji (2016)[96]	199	93	35.9	96.9	69.7

Table 2
Comparison between breast magnetic resonance imaging MRI and contrast-enhanced mammography (CESM) for the local staging of breast cancer.

Ref.	n	CESM			MRI			
		Sensitivity %	Specificity %	ROC (AUC)	Sensitivity %	Specificity %	ROC (AUC)	
Jochelson (2013)[86]	52	96	95	-	96	94	-	NS
Chou (2015)[97]	185	-	-	0.878	-	-	0.897	NS
Fallenberg (2017)[98]	604	-	-	0.84	-	-	0.85	NS
Lee-Felker (2017)[85]	120	94			99			NS
Kim (2018)[99]	84	93	-	-	95	-	-	NS
Sumkin (2019)[84]	110	91			93			NS

ROC, receiver operating characteristic; AUC, area under the ROC curve; NS, non-significant.

ABB-MRI

Currently, MRI screening is only recommended for high-risk women (especially those with a history of prior mantle radiotherapy and strong familial risk of breast cancer, especially BRCA1/2 carriers) who are invited for annual examination. Although there is considerable evidence for the high sensitivity for MRI, it is only cost effective in high-risk women.[104,105] The use of ABB-MRI protocols for the detection of breast cancer has gained increasing attention as these acquire a shortened version of the standard full diagnostic protocol (FDP-MRI) in a third of the time with reduced reading times, reducing the cost of the examination considerably.[106]

An abbreviated protocol generally includes an unenhanced T1-weighted (T1W) sequence with at least one contrast-enhanced T1W examination from which subtraction and 3D maximum-intensity projection (MIP) images can be generated. Kuhl *et al.* reported the first prospective reader study evaluating ABB-MRI as a screening technique in a cohort of asymptomatic women with mild to moderate risk of breast cancer, finding a sensitivity of 91% and negative predictive value of 99% using only MIP images with an average reading time of just 3 seconds.[106] These both increased to 100% with the addition of the T1W contrast-enhanced images in a reading time of ~30 seconds. A large number of studies have since investigated ABB-MRI, although the protocols used vary between institutions and the introduction of standardisation would be very valuable.

A meta-analysis of five studies (including 2,588 patients with 62 cancers) comparing ABB-MRI and FDP-MRI in a screening setting found a comparable diagnostic performance (AUCs of 0.94 and 0.97, respectively) and no statistically significant differences in sensitivity and specificity between the two protocols (p=0.18 and 0.27).[107] Pooling eight studies using enriched cohorts (1,432 patients with 540 cancers), ABB-MRI and FDP-MRI were shown to be diagnostically equivalent (AUCs 0.94 and 0.95, respectively). Although this appears promising, combined cohorts enriched with problem-solving, preoperative staging, and selected cases do not reflect the clinical setting of interest and outcome measures should be interpreted as such. To date, there have been few prospective studies evaluating ABB-MRI in a purely screening setting.

For women at high risk of breast cancer, ABB-MRI has been shown to be as effective as full FDP-MRI with a high sensitivity (82–91.4%)[108,109] and significantly reduced interpretation times.[110] As abbreviated MRI aims to reduce the cost, examination times, and interpretation times of MRI, this may enable the more widespread use of MRI as a screening tool for low-to intermediate-risk women for whom MRI screening is currently not cost effective. Given the lack of consensus on current risk-based screening recommendations, many women incorrectly classified as low-risk may benefit from MRI screening. A prospective study of mild-to moderate risk women found a cancer detection rate using abbreviated MRI similar to that of a routine screening MRI protocol in high-risk women (18.2 versus 17–22.1 per 1,000).[106,111,112]

The sensitivity of MRI is not limited by breast density, making it an ideal technique for the screening of women with dense breasts. The multicentre EA1141 trial (Comparison of ABB-MRI and DBT in Breast Cancer Screening in Women with Dense Breasts) evaluated an abbreviated protocol in a screening cohort of 1,444 women with dense breasts, finding a higher rate of invasive cancer detection using ABB-MRI compared to DBT.[113] A study by Weinstein *et al.* found a cancer detection rate of 24.7 per 1,000 using ABB-MRI in a cohort of 475 women with dense breasts with negative/benign DBT findings.[114] In the Dutch DENSE trial women at population risk with extremely dense breasts were randomised to DM alone or supplemental screening MRI.[115] The interval cancer rate, the main outcome measure, was only 0.8/1,000 in those women who actually underwent MRI screening, for a cancer detection rate of 16.5/1,000, whereas in the DM only group, the interval cancer rate was 2.5/1,000 screened.

The benefits and risks of screening MRI for average risk women must be considered with respect to the repeated administration of gadolinium-based contrast agents (GBCAs) over long-term screening periods. GBCAs can cause allergic or physiological reactions (such as nausea or headaches) in a small percentage of patients[116] and are contraindicated in patients with impaired renal function. Recently, studies have also reported the presence of gadolinium deposits in the brain and body with cumulative dose, although no clinical adverse side effects have yet been reported.[117] This is of interest for high-risk healthy women who undergo routine annual MRI screening with contrast

medium who have up to 40 doses of GBCAs during their lifetime. As such, there is growing interest in unenhanced screening MRI techniques. Diffusion-weighted imaging (DWI), an unenhanced MRI technique, has demonstrated sensitivity and specificity comparable to contrast-enhanced MRI[118] and shows promise as a supplemental imaging method to exclude malignancy in women with suspicious mammograms.[119]

Radionuclide imaging

Scintimammography (SM) has been advocated to complement DM in women with dense breast tissue or in those women with structural changes or scars related to previous surgery or radiotherapy. There has been longstanding worldwide debate as to the utility and accuracy of this method[120] and there are several ongoing studies evaluating its positioning in the diagnostic work-up. Most of the debate centres on its role when mammography is indeterminate, compared to the use of MRI and ultrasound[121,122]; however, SM is far from achieving widespread recognition.

The method is very simple and relies on planar or tomographic acquisitions of the breast, generally in the prone position, 5–10 minutes after administration of a tumour-seeking radiotracer such as ^{99m}Tc-sesta-methoxyisobutylisontrile (^{99m}Tc-Sestamibi). Breast malignancies have been shown to have high uptake of ^{99m}Tc-Sestamibi compared to normal breast background as well as regional lymph nodes.[123,124] The technique has been evaluated since the early 1990s and has been more widely accepted in North America where it received FDA approval in 1997.

Advances in dedicated acquisition hardware have refocused attention on the potential of this technique. Compact dual-head gamma cameras specifically designed and optimised for breast imaging have been developed that allow detection of smaller lesions. In a large case series from the Mayo clinic, the use of SM with this dedicated hardware has been shown to significantly increase detection of node-negative breast cancer in patients with mammographically dense breasts.[125] Commercially available dedicated systems resembling traditional mammography units have been developed allowing intrinsic resolution of 1.6 mm, markedly improving sensitivity for the detection of small breast tumours and those located in the upper inner quadrant. The reduced effective dose comparable to that of annual mammographic screening allows widespread applicability.[126,127] Hruska *et al.* analysed the additional diagnostic work-up and costs of a single supplemental molecular breast imaging test in women with dense breasts and concluded that despite an increase in the additional cost and benign biopsy rate, the higher cancer detection rate resulted in a lower overall cost per cancer detected than with screening mammography alone.[126]

Conclusion

Advances in breast cancer imaging have already had an impact on early detection. The more reliable robust automated methods of measurement of breast density mean that these can be used in a reproducible manner to determine the need for supplemental imaging particularly if these are combined with risk. There is strong evidence that MRI is an effective screening tool in women with dense breasts and that ABB-MRI can be also be considered although both have higher false-positive rates compared to mammography. Whole-breast ultrasound is now being used as a supplemental tool, although recall rates may be as high as with MRI. There is some published data on CESM as a screening tool but more evidence is required. The opportunity to reduce false-negative examinations offered by these supplemental techniques is important and outweighs the slightly higher false-positive results. As in the general population where there are acknowledged costs, harms, and benefits of screening, the same will be true of a personalised approach. It is hoped that through risk-adaptive screening, costs would be made more effective, harms would be minimised, and benefits to women would be maximised. Policymakers and healthcare providers now need to consider adjusting their breast screening programmes to a more appropriate offering for their clients rather than justify a “one-size-fits-all” approach.

Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: F.J.G. is a consultant for Alphabet Inc and Kheiron. FJG receives grant support from GE Healthcare, Hologic and Bayer. She has research agreements with Lunit, Transpara, Volpara, Merantix. The remaining authors declare no competing interests.

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