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Breast cancer imaging - A rapidly evolving discipline

Fredrik Strand [a, b], Sophia Zackrisson [c, *]

[a] Breast Radiology, Karolinska University Hospital, 17176, Stockholm, Sweden
[b] Department of Oncology-Pathology, Karolinska Institute, 17177, Stockholm, Sweden
[c] Department of Translational Medicine, Diagnostic Radiology, Lund University, Skåne University Hospital Malmö, Malmö, 20502, Sweden

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Summary of predictions (Fig. 1)

- Image-based breast cancer screening will spread globally
- Awareness of mammography shortcomings will increase
- Tomosynthesis will become an established screening modality
- Mammographic breast compression will be optimized
- Contrast-enhancement will make mammography an alternative to MRI in limited settings
- The usefulness of automated ultrasound will be determined
- High-resolution diffusion and abbreviated protocols will enable MRI as a screening modality in certain subgroups
- Risk-stratification will be used to guide women to an adequate screening modality
- Artificial intelligence will potentially enhance many aspects of breast imaging
- Radiomics - there will be a continued search for quantitative image features having observable biological correlates
- Minimally invasive image-guided procedures will replace open surgery for smaller lesions
- Precise guidelines for MRI in preoperative mapping will be established
- Neoadjuvant therapy will be continuously guided by image-based functional biomarkers
- Along with improved treatment options, the importance of imaging in the metastatic setting will increase
- Medical disciplines will be more closely integrated for the full benefit of the patient

The introduction of early detection of breast cancer through mammography screening was the most important preventive achievement to reduce breast cancer mortality. Today, breast imaging is the patient's companion through the entire process of detection, diagnosis, prognosis, treatment choice and follow-up. Mammography is the core modality in breast imaging, complemented by ultrasound, magnetic resonance imaging (MRI) and, in certain settings, positron emission tomography (PET). In this preview article we share our personal perspective on possible future developments in the field.

Image-based breast cancer screening will spread globally

Although heavily debated during the last decades, it has been shown that regular invitation to mammography screening reduces breast cancer mortality with up to 23–40% in women aged 50–69 years, the latter number pertaining to women who actually attend [1]. In the position paper on mammography from World Health Organization it is described how screening is cost-effective in upper-middle income countries but not, currently, for lower-middle income countries [2]. We believe this will change due to improving economic resources and due to an increasing breast cancer incidence in low- and middle-income countries. When a country is unable to provide this on a population-wide scale there is an increasing risk that opportunistic screening will gain ground. Even though certain individuals might experience a benefit, we agree with the statement of WHO that “Opportunistic screening or screening that is not well organized run the risk of causing more harm than good and should not be implemented in any setting”.

* Corresponding author.
E-mail address: sophia.zackrisson@med.lu.se (S. Zackrisson).

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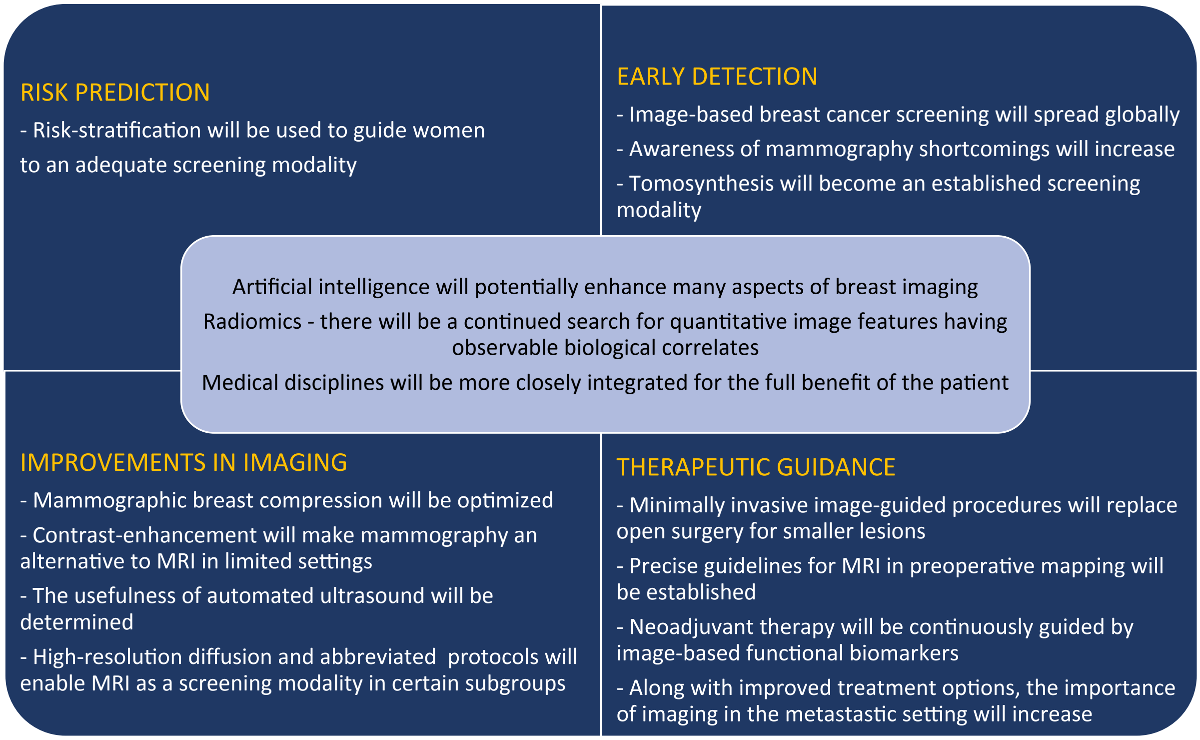

Fig. 1. Graphical abstract with summary of predictions.

Awareness of mammography shortcomings will increase

Before mammography screening was introduced during the 1990's there was no prevention for breast cancer. There is now a strive to challenge and try to improve the one-size-fits-all model for breast cancer screening with mammography, given the shortcomings when it comes to for instance high breast density and reduced sensitivity. From the scientific community perspective there are numerous ongoing trials on personalized or risk stratified screening involving stratification based on breast density, family history, genetics etc. From the women's perspective, a more widespread awareness of the higher breast cancer risk associated with higher breast density in synergy with the knowledge of the limitations with 2D mammography has encouraged lobby groups to establish. In the US, this has eventually stimulated the density legislation in a majority of states mandating notification of risks associated with breast density directly to women undergoing mammography [3].

Tomosynthesis will become an established screening modality

It is a well-known fact that 2D mammography has limitations when it comes to sensitivity of breast cancer detection in screening, especially in women with dense breasts where normal structures in the breast may hide a tumor [4]. 3D mammography, or digital breast tomosynthesis, is a development of the mammography method which partly may overcome the overlapping tissue effect inherent in 2D mammography and the results from several prospective screening trials show improvement in cancer detection with at least 30% [5]. Whether 3D mammography will (complement or) replace 2D mammography in screening is still an open question, since evidence of the effects on breast cancer mortality is challenging to prove. 3D mammography screening trials with breast cancer mortality as endpoint will not take place, although meta-analyses with surrogate measures such as reduction in interval cancer rates and analysis of tumor biology may orient us in a near future.

Mammographic breast compression will be optimized

Another focus for recent optimization in mammography is better breast compression. Guidelines for correct breast compression remain very vague [6]. Justified breast compression is an important issue both from an attendance (comfort) point-of-view as well as from the image quality and diagnostic perspective in order to ensure compression of the relevant parts of the breast for tissue separation. Two large studies with up to 200.000 screening mammograms showed that the sensitivity was lower in the highest compression group, after adjustments for breast volume and density [7,8]. When it comes to 3D mammography it has been shown that less compression may be used, still with a superior screening performance, as compared to 2D mammography [9]. It is worth noticing that the mentioned studies were all performed in countries where quite high pressures in general are applied and more studies are needed to further elucidate the effects of compression in different settings. Many manufacturers are working on better solutions for compression with flexible paddles etc to optimise comfort and image quality. We foresee that coming generations of women will put higher demands on comfort during mammography and further optimization is to be seen.

Contrast-enhancement will make mammography an alternative to MRI in limited settings

A major advantage of breast MRI is the use of an intravenous contrast agent which visualizes the vascularity of various lesions. However, contrast agents can also be used with mammography and the first studies are from early 2000s [10]. Malignant lesions are prone to show up after contrast injection due to their increased arterial and venous blood flow and highly permeable capillaries.

The downside with contrast agent injection is that it involves an invasive procedure placing a needle into a vein in the arm, takes more time, makes it less easy to schedule patients due to large variability in the time it takes to place a needle, and it may cause oversensitivity reactions. The information from a contrast-enhanced mammography does not fully replace the contrast enhanced series from MRI [11]. First, there is the physiological problem of the compression pressure in regular mammography being higher than the venous pressure. In addition, with MRI you can visualize the contrast-enhancement between the left and right breast at the same time points, and you can assess the dynamics over time thanks to repeated examinations over a few minutes. Considering the time-requirements we do not believe this will become a standard screening modality for all women. Due to the disadvantages compared to MRI, including the potentially harmful use of ionization radiation among young women with BRCA mutations, we do not believe that it will replace MRI. However, in certain settings where MRI is not possible or too expensive, contrast-enhanced mammography could be a reasonable compromise [12].

The usefulness of automated ultrasound will be determined

Ultrasound relies on a different mechanism than x-rays to obtain the image of the breast tissue. Therefore, certain tumors that are not visible on mammography may be visualized on ultrasound. Ultrasound contrast agent, microbubbles, is not likely to be useful in screening settings due to the long time it takes to acquire images for the entire breast compared to the short time the microbubbles are visible. Since ultrasound is often acquired by the radiologist, it is a modality that requires large amount of radiologist time per examination taking 25–30 min compared to 5 min or less for screening mammography [13]. Automated ultrasound mitigates the need for the radiologist to be present for image acquisition. A technologist then handles the device which involves automated movement of the transducer across the breast acquiring an image volume that can later be assessed by a radiologist. We believe that the use of hand-held ultrasound may increase in middle-low income countries. In high-income countries, where handheld ultrasound is used at all breast centers, the jury is still out on automated ultrasound - will it prove cost-effective or will it be made obsolete by a combination of tomosynthesis and abbreviated MRI? In combination with mammography, MRI has a much higher sensitivity than ultrasound. Across four studies of high-risk women the sensitivity was more than 90% for MRI with mammography and around 50% for ultrasound with mammography [13]. In the therapeutic setting, there is an opportunity for hand-held ultrasound to target the delivery of pharmacological agents contained in microbubbles [14].

High-resolution diffusion and abbreviated protocols will enable MRI as a screening modality in certain subgroups

MRI is a technique which exposes the human body to strong magnetic fields and forms images based on weak radiofrequency signals emitted by hydrogen atoms which are abundant in the body. MRI is without doubt the most sensitive imaging method to detect breast cancer. In a screening study of high-risk women, the sensitivity was 18%, 33% and 80% for clinical examination, mammography and MRI respectively [15]. The corresponding specificity was 98%, 95% and 90% respectively. The proportion of women that had metastatic spread to axillary lymph nodes was 52–56% in the mammography groups compared to 21% in the MRI group. However, MRI does require expensive equipment and the specificity is somewhat lower than mammography leading to more biopsy procedures - most of which can be performed through second-look ultrasound. To address the economics, abbreviated protocols have been developed and shown to be as effective as full protocols in screening [16]. Current protocols for breast cancer detection and evaluation require the use of an intravenous contrast agent. As for contrast-enhanced mammography there are disadvantages with the need to administer contrast agents intravenously. In addition, there are worries that certain, linear, gadolinium chelates might remain in the brain for a very long time, even though that does not seem to be the case with the cyclical compounds that are used today. Similar disadvantages as those listed above in the section on contrast-enhanced mammography as well as an additional worry that linear MRI contrast agents remain in the brain for a very long time, has sparked development of techniques that do not require contrast agent use. Diffusion MRI assess the rate of free movement of water molecules [17]. Malignant tumors are usually more disorganized compared to normal tissue, has less extracellular space and cells of more varying sizes, which translates into decreased diffusion of water molecules. The main issues that must be overcome are to increase the spatial resolution and to make the technique as well as the interpretation standardized across centers. Given current developments we may see diffusion protocols taking center stage in the next 5–10 years. By use of risk stratification to identify the women who are most likely to benefit, we believe that MRI screening, with or without contrast agents, will be incorporated into future population-based screening programs for specific subgroups.

Risk-stratification will be used to guide women to an adequate screening modality

The modality developments described above could increase the proportion of cancers that are detected at an early, curable, stage. However, they also increase the time and cost of screening. Therefore, it is possible that their use might be limited to women at elevated risk of breast cancer and at elevated risk of non-detection at mammography. In the classic screening study by Rose two approaches to prevention and screening are described: focus on high-risk individuals and screening an entire population [18]. Both approaches have advantages and disadvantages. The main disadvantage with a focus on high-risk individuals is the inherent difficulty in predicting if and when a woman will have cancer. It has been estimated that only a third of all cancers are due to environmental or genetic risk factors, and the remainder are due to random events correlated with the number of stem cell divisions [19]. Nevertheless, we believe that risk stratification algorithms will be used, and we believe that they will combine a measure of breast cancer risk with a measure of the risk of mammographic non-detection for that particular woman. The cost-effectiveness perspective of risk stratified screening should be an integrated part of future studies in the area. Communicating risk to individual women puts a high demand on robust risk models, communication strategies and counseling-areas that currently are explored and will need attention before setting the full sails for risk-based screening.

Artificial intelligence will potentially enhance many aspects of breast imaging

Artificial intelligence (AI) is a recent buzz word which is used for computer software that performs functions that people would normally associate with an intelligent human mind. The commercial advantage of claiming that products “contain AI” has made the abbreviation close to meaningless. In the following we use AI in a narrow sense meaning computer software that has been trained on numerous real-world examples rather than being controlled by human-specified rules. The rapid development of AI was enabled by massive processing power having rapid access to vast amounts of digital data. Mammography is one of the key application areas for AI developers in radiology due to its large volumes of training cases and the large market size. At the last RSNA annual meeting in November 2018, one could visit more than eight companies offering AI applications to help with tumor detection and decision-making in screening mammography. AI systems can potentially act as an assistant to the radiologist, as one of two independent readers, or as the only reader. Many vendors and academic groups show promising results in their own datasets [20]. A recent study showed similar levels of performance of AI as that of radiologists [21]. The published research has so far been based on datasets enriched with cancer cases and not representative of a true screening population. We are still waiting for neutral performance evaluations in common external datasets representative of a normal screening population. Most AI applications in the area of breast imaging are focused on traditional radiologist tasks, such as tumor detection and differential diagnosis. However, there is also work on-going to assist technologists with instant feedback on positioning of the breast and other image acquisition parameters as well as workflow optimization including automated triage for screening MRI [22]. Other research groups are investigating the use of AI in breast cancer risk prediction to optimize the selection of women to whom MRI-based screening should be offered [23,24]. Currently, we perceive AI applications in the field to be in early phases and we expect that it will take another 3–5 years for the field to mature. Regulatory agencies involved in the traditional medical technology field may have to establish new approval processes. There is also a need to rethink how to distribute the medical responsibility, and failure analyses, between health professionals and medical AI companies. It might be necessary for the NIH and its counterparts in other regions to establish a number of officially validated test databases in which companies are required to run their algorithms before applying for certification for use in screening. A decisive factor for AI adoption will be how it is perceived by the women attending screening. Unpublished results from a large screening participant survey from Sweden indicates that many women, once human-level performance has been proven, would be willing to receive computerized assessments of their mammograms for tumor detection and for breast cancer risk assessment. It is important for breast radiologists to put themselves in the driving seat to best direct the possibilities offered by AI.

Radiomics - there will be a continued search for quantitative image features having observable biological correlates

Radiomics is a recent buzzword for the extraction and application of a large number of quantitative image features. Radiomics can potentially be used to improve diagnosis, characterization and prognostication of breast cancer [25]. It has mainly been employed in the more information-rich modality of MRI, and to certain extent PET imaging. Radiomics was inspired by the other omics, e.g., genomics, proteomics, but there is an important difference. Many of the features in the other omics stem from identifiable biological entities, such as the DNA or the proteins in the body. The radiomics features are however more abstract statistical and mathematical features of images of the body, tissues and cells. We believe that to differentiate itself from AI and deep learning, radiomics research will focus on identifying image features robustly associated with observable biological entities [26].

Minimally invasive image-guided procedures will replace open surgery for smaller lesions

Early detection of breast cancer means a shift towards smaller tumor sizes at diagnosis which put a demand on minimal surgical intervention to keep surgery-related morbidity as low as possible. Alongside, technical development has produced several minimally invasive imaging and interventional candidate techniques such as ablation based on cryotherapy, laser, microwaves, high intensity focused ultrasound (HIFU) and radiofrequency. Most of them require a minimally invasive needle insertion although HIFU may be performed non-invasively. A minimally invasive technique can move the surgical procedure from the operating room to an “office setting”, be performed under local anesthesia and thus minimize the need for perioperative resources. A correct tumor visualization and delineation (roadmap) and image guidance during the procedure is crucial. In addition to traditional imaging such as mammography and ultrasound, MRI may be required to select the appropriate patient group and ultrasound (perhaps contrast-enhanced) may be the best way to monitor the invasive procedure in real time. Minimally invasive intervention is of interest both for benign and high-risk lesions, but also for small, malignant lesions foremost in elderly patients or patients with comorbidities where traditional surgery is not an option. The challenge of accepting the fact that the evidence (the tumor) is vanished and not available for pathological investigation with the majority of these techniques after treatment poses high demands on selecting the proper patient group for these procedures. Still, minimal invasive interventions are of great interest as we move towards detection of smaller tumors with more sensitive diagnostic techniques.

Precise guidelines for MRI in preoperative mapping will be established

The goal of breast cancer surgery is to remove the malignant tissue in a tailored manner. The proportion of women receiving breast-conserving surgery is high. When there are positive or minimal margins the patient must suffer a second surgery. In a recent randomized study including all recently diagnosed women below 56 years of age, it was shown that MRI changed the treatment plan in 18% of the patients whilst the re-excision rate after breast conserving surgery was 22% without MRI and 5% with MRI [27]. The use of MRI leads to an increased number of biopsies. One study found that around 50% of additional findings on MRI could subsequently be located by second look ultra-sound and an additional 25% by tomosynthesis. Of the remaining additional findings which would require an MRI biopsy procedure to confirm, 4 out of 5 corresponded to malignant lesions. Long-term follow-up of 470 patients showed that the in-breast recurrence rate was 4.2% without MRI and 1.6% with MRI [28]. At the same time, an individual-level meta-analysis showed no difference in local recurrence comparing MRI with no MRI [29]. We are still waiting for final results on the impact on mortality [30]. When examining radiotherapy, it has been shown that a 5-year difference in local recurrence rates translated into differences in 15-year mortality [31]. In the decision for which women to offer preoperative MRI, both the absolute risk of future recurrence and the increased accuracy of MRI should be balanced. We believe that the use of pre-surgical MRI will become standard procedure, especially for younger women, for lobular cancers and in cases of mammography-ultrasound discrepancy in accordance with current guidelines from EUSOMA [32].

Neoadjuvant therapy will be continuously guided by image-based functional biomarkers

There are advantages with neoadjuvant therapy: the algorithmic choice of therapy can be evaluated in terms how it affects the actual tumor, and increase post-surgical compliance with adjuvant treatment. The tumor response can be complete (no tumor remains), partial, stable or progressive. To optimize treatment, it is helpful to be able to predict the final response at an early stage. MRI has been shown to be a powerful tool for response prediction [33,34]. If the final response is predicted to be poor the patient could be offered a change to a different treatment regimen. If a complete response is predicted, the planned surgery could be expedited. We believe that we will see new adaptive algorithms in the next years that makes use of biomarkers from several domains: imaging, pathology and genetics. Cross-discipline AI software might be applied to combine biomarkers from these various fields in ways that human specialists are unable to do. The use of MRI in the neoadjuvant setting is expected to increase.

Along with improved treatment options, the importance of imaging in the metastatic setting will increase

Survival from primary breast cancer has steadily increased. Still, many women have distant metastases already at the time of diagnosis and quite a few women are diagnosed with a disease that has spread 5 years after diagnosis. The most common metastatic sites are bone, lymph nodes, liver, lung, pleura and brain. Sometimes there is a heterogeneity in tumor characteristics between the primary tumor and the metastases or a shift occurs after treatment. The most common imaging method for monitoring metastatic disease is contrast enhanced computed tomography (CT) for thoracic and abdominal metastases and bone metastases in these regions. Nuclear imaging methods such as bone scintigrams are used to further diagnose and map the extent of e.g. bone metastases. The current treatment options for metastatic disease includes both cytotoxic and targeted therapies which act differently in the tissues and hence may result in various types of tissue changes. Monitoring treatment response in the metastatic situation challenges the traditional, structural imaging methods such as CT and calls for more functional imaging to enable visualization of for example decreased metabolism rather than decrease in tumor size. In PET, positron-emission- tomography where a radioactive tracer coupled to a metabolite that is consumed preferably by tumor cells is used, combined with whole-body CT (or MRI) for anatomical correlation, is a strong candidate. The tracers need to be specific enough for breast cancer and initiatives such as HER2-targeted PET have shown promising initial results [35]. We foresee a stronger focus on patients in the metastatic situation and new treatment strategies coming up, leading to more women living longer with their breast cancer. The high costs of using newly developed drugs will drive the exploration of well-working structural and functional imaging methods for monitoring treatment response in order to select the right patient for treatment.

Medical disciplines will be closer integrated for the full benefit of the patient

In addition to the numerous opportunities that we foresee within the field of breast imaging, we also believe that there will be an increased integration between all involved medical disciplines. First, the diagnostic disciplines radiology and pathology are likely to merge to provide a joint foundation on which to base treatment decisions. Second, the diagnostic disciplines will be integrated with the treatment disciplines to improve the continuous evaluation and optimization of treatment. Third, we may see a more important role for preventive disciplines using knowledge acquired from epidemiological studies of incident breast cancer diagnoses.

Conflicts of interest

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