Title: Attributes, Performance, and Gaps in current & emerging breast cancer screening technologies

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Abstract:

Early detection of breast cancer, combined with effective treatment, can reduce mortality. Millions of women are diagnosed with breast cancer and many die every year globally. Numerous early detection screening tests have been employed. A wide range of current breast cancer screening methods are reviewed based on a series of searchers focused on clinical testing and performance. The key factors evaluated centre around the trade-offs between accuracy (sensitivity and specificity), operator dependence of results, invasiveness, comfort, time required, and cost. All of these factors affect the quality of the screen, access/eligibility, and/or compliance to screening programs by eligible women. This survey article provides an overview of the working principles, benefits, limitations, performance, and cost of current breast cancer detection techniques. It is based on an extensive literature review focusing on published works reporting the main performance, cost, and comfort/compliance metrics considered. Due to limitations and drawbacks of existing breast cancer screening methods there is a need for better screening methods. Emerging, non-invasive methods offer promise to mitigate the issues particularly around comfort/pain and radiation dose, which would improve compliance and enable all ages to be screened regularly. However, these methods must still undergo significant validation testing to prove they can provide realistic screening alternatives to the current accepted standards.

Keywords:

Mammography; Magnetic Resonance Imaging; Ultrasound; Thermography; Microwave Imaging; Elastography
1.0 Introduction

Breast cancer is a leading cause of death among women [1]. In 2012 almost 1.67 million new cases were diagnosed worldwide with approximately 324,000 and 198,000 deaths recorded in less and more developed regions, respectively [2]. Regardless of advances in treatment over the past decades, breast cancer still remains the second leading cause of cancer related death in women [3]. The American Cancer Society estimated the number of new breast cancer cases and at 234,190, with around 40,730 deaths in the United States during 2015 alone [4]. Including of these 10,000 – 12, 000 cases are invasive cancer in women less than 40 years who are not typically screened [5]. With around 3000 deaths in women aged less than 45 [6].

Breast cancer can affect both men and women of any age, but the incidence is much higher in women [7]. Several other factors increase the risk of developing breast cancer, including a family history and radiation exposure [8, 9]. The risk of breast cancer increased for women of all ages in Hiroshima and Nagasaki due to low dose radiation exposure [9]. Nulliparity, early menarche, late menopause also increase women’s risk of developing breast cancer. During women’s reproductive years the ovary produces steroid hormones that directly affect development and function of the breast.[10, 11].

Cancer treatments are expensive. In the United States breast cancer remains one of the most costly cancers [12]. In 2010, the United States spent approximately $16.5 billion on breast cancer treatment [13]. Reducing the cost of treatments and balancing the patients’ needs with available healthcare resources is far from an easy or intuitive task. Using breast cancer related health insurance claims, Ray et al. [14] showed that increased follow up periods for breast cancer patients were associated with reduced mean monthly per patient costs. However, the cumulative costs per patient increased from US$78,882 for a follow up period of <6 months to US$443,062 for a follow up period of >36 months. Early detection of breast cancer screening not only reduces mortality rate, but also decreases overall treatment expenditure [15, 16]. Thus, screening programs for the early detection of breast cancer are key to increasing the chances of successful treatment and reducing costs.
There are several tests and examinations routinely used for the detection of breast cancer [17, 18]. To reduce breast cancer mortality rates, breast screening needs to be successful in producing a desired results [19], low cost, fast, and available without risk to women of all ages. This review provides an overview of current breast cancer detection techniques in light of these requirements. In particular, the novelty of the article is based on around a review of multiple modalities and the use of a range of key features including cost, invasiveness and comfort/compliance metrics, which all play a role in the quality and compliance, and thus efficacy of screening programs.
2.0 Current methods of screening for breast cancer

2.1 Mammography

Over the years, X-ray mammography (XM) has become the primary, non-self-exam screening technique for breast cancer [6, 20]. Mammography forms images of the breast density by passing X-rays through the tissue as shown in Figure 1. However, exposure to this ionising radiation may be harmful and possibly cause cancer itself [21]. Risk is one of the reasons it is not recommended for screening in women under 40 years [22].

Mammography can provide benefit to women aged 40 to 49 years. Mortality rates at these ages can be reduced up to 15% after 14 years of follow up [23]. However, women who started screening every second year at age 50, until 69 years of age, have shown more benefit with less harm [24, 25], and thus this age range and interval are more commonly used in national screening programs. Due to the extensive validation and use, mammography is the most widely used and well-accepted imaging modality for breast screening [26].

However, mammography has also been criticized for a number of reasons. Thornton and colleagues listed physical, emotional, social, financial, or psychological harm caused by mammograms [27]. Additionally, to get the best possible images of breast tissue must be squeezed between two plates as the image is taken [28]. Many women found this compression painful and uncomfortable [29]. Several women experienced enough pain that it affected their decision to attend another examination [30-34] reducing compliance and the likelihood at early detection.
Fig. 1. (a) Mammogram Equipment (National Cancer Institute by Alan Hoofring, 2003)

Fig. 1. (b) Mammogram showing a small cancerous lesion as well as calcific deposits in veins (National Cancer Institute, March 1991)
Mammographic breast density is a strong predictor of breast cancer [35-38]. However, younger women naturally have denser breast tissue and it can be difficult to detect cancer with mammography [39], which can lead to misdiagnosis and increased false positive/negative rates [40]. Mammography with adjunctive ultrasonography results in higher rate of cancer detection in young or women with dense breast, but also increases the number of false positive results. The Japan Strategic Anti-cancer Randomized Trial (J-START) investigates sensitivity and specificity with 36,000 women in each group (XM and XM+US) and about 180 cancers per group. Sensitivity rises to 90% with added ultrasound but specificity drops to 87%. Thus, positive predictive value is likely poor given low incidence rates [41].

This modality is highly dependent on equipment, operator, radiographer, and as well as breast density. False-negative rates for mammography range from 4% to 34% [42-46]. Table 1 provides a summary of published performance results for mammography. Research has shown that the sensitivity of mammography for detecting multiple malignant foci is often less than 50% [21, 47, 48]. Due to radiation exposure and false positive results, both patients and physicians are concerned about using mammography to screen women below 45 [49]. As a result of these limitations, many unnecessary biopsies have resulted from low specificity of mammography [50].

Finally, mammography has been proven and established in terms of its detection of ductal carcinoma in situ (DCIS) [51]. It is also established in terms of potentially differentiating the micro-calcifications that can occur in breast tissue from cancerous lesions. However, as noted, these difficult cases are also a function of operator and radiologist experience and capability, even though the physics of the modality enables their detection and diagnosis.

The financial costs of breast cancer are high. Several studies show breast cancer screening for women aged 50-70 years is cost-effective and costs range between $13,200 and $28,000 per year of life saved [52-56]. In New Zealand, mammogram costs approximately $180 [57]. However, for women below 45
years the number of false positives and cost for extra examinations, unnecessary biopsies, and other effects [58-60], means it is not cost effective. For all these reasons, continuous efforts have been made by researchers to explore alternative imaging modalities for breast cancer screening and diagnosis.

Mammography usually takes only one picture, across the entire breast, in two directions: top to bottom and side to side. Digital breast tomosynthesis is a technique that creates 3-dimensional picture of the breast to improve breast cancer detection especially with dense breast [61, 62]. Digital breast tomosynthesis has improved on the limitations of traditional digital mammography by increasing cancer detection and decreasing false-positive examinations [63]. Additionally, a digital breast tomosynthesis can reduce the pain and displeasure that occur from compressing breast between two plates while taking mammogram. For these reasons digital breast tomosynthesis can replace traditional mammogram in breast cancer screening [64]. The major disadvantage of digital breast tomosynthesis is prolonged time and more radiation exposure at twice that of standard mammography, although it reduces the need for repeat mammographic images and increased dose from those tests. In addition, it leads to increased recommendations for biopsies, increasing detection, but also cost when cancer is not present [65].

However, overall, it is important to note that mammography is still the only proven and accepted wide scale screening modality.

2.2 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has been progressively integrated into breast imaging and is used to detect lesions [66]. A magnetic field is created to align all the protons in the body in a single direction. Radio waves are sent from a scanner to perturb this alignment. As the protons realign, they emit radio waves which used to determine the molecule type and location. These radio signals are analysed and converted into an image [67]. When applied to soft tissue, MRI can be used to generate highly detailed images of the internal structure of the breast. MRI signal strength, and therefore image contrast, is determined by the density of hydrogen protons within the imaged tissue and their response to rapidly
changing radio waves and magnetic fields. The image contrast of MRI systems can be significantly enhanced using a range of chemicals ingested or injected prior to the scan [68]. As show in Figure 2.

![MRI of individual breast, demonstrating marked enhancement (bright area) which was confirmed to be cancer (National Cancer Institute, February 1994)](image)

**Fig. 2.** (a) MRI of individual breast, demonstrating marked enhancement (bright area) which was confirmed to be cancer (National Cancer Institute, February 1994)

MRI can provide superior imaging results and outcomes compared to mammography and other breast screening techniques for women at high risk of breast cancer [69, 70]. MRI is a sophisticated imaging method without the need for ionizing radiation and cannot induce cancers [71]. Women with dense breasts are also considered high risk and for this cohort annual MRI is recommended first for screening with further validation of the outcome [72].

There are many unresolved issues in using MRI for breast cancer screening, including lack of standardised techniques and interpretation criteria [73]. In 2013, Sutcliffe Iii and his colleague published an article which reiterated the issues with MRI and noted that the different levels of training and experience of the radiologist result in significant variation in MRI findings of benign and malignant tumours [74]. Other limitations mentioned in past studies have also suggested that MRI is less reliable in the detection of ductal carcinoma in situ (DCIS) because it is unable to image calcifications, tiny calcium deposits that can indicate breast cancer [10].
The U.S. Food and Drug Administration (FDA) approved MRI in 1991 to help diagnose breast cancer. However, because of its high sensitivity and lower specificity which can lead to false positives, the American Cancer Society does not recommend MRI for all women [75, 76]. The range of specificity varies from 37% to 100% [77-81] and this low specificity leads to more false positives and unnecessary biopsies [82]. These outcomes are summarised in Table 1.

To improve specificity, recommendations for breast MRI state that the dynamic contrast-enhanced (DCE) acquisition should be obtained [83]. The most widely used form of DCE-MRI analysis is the assessment of the type of time-signal intensity curve. The shape of the time-signal intensity curve is an important criterion in differentiating benign and malignant enhancing lesions [84]. To further improve lesion classification, a high-resolution T2 sequence and diffusion-weighted sequences have been added to the state-of-art MRI protocol [83, 85, 86]. However, this makes breast MRI time-consuming, with report investigation times between 20 and 40 min [87].

In addition, the cost of MRI is approximately ten times the cost of mammography [22]. Since the current cost of mammography is one factor leading to limited mammogram prescription and use, this added cost is not sustainable for widescale screening. MRI cost with screening and treatment is estimated at $123 672 per detected breast cancer [88], which is ten times higher than mammography. In addition to the high cost, results take more time to produce [89, 90], and there is a lack of standardization in terms of technique, as well as interpretation guidelines [91].

2.3 Ultrasound

Ultrasound sends high frequency sound energy into the tissue from a hand-held transducer. This sound is reflected by boundaries between tissue where the acoustic impedance changes. Reflected sound is received by the transducer and the depth of reflection can be determined by ‘time of flight’. Depth and detection information is combined into an image of cancerous tissue, as it has different density to surroundings tissue.
Ultrasound is currently used to differentiate breast masses [92], and guide aspirations and biopsies [93]. Studies report ultrasound as a useful adjunct to mammography [94-96], and that in this role it yields improved cancer detection. However, it is not recommended as a screening tool, in part because it is more specifically useful for assessing whether a lump is fluid filled or solid [97].

Current technological advances in ultrasound equipment include very high-frequency 15MHz and multiarray transducers, as well as matrix broadband transducers. These transducers provide high levels of spatial and contrast resolution that allow detection of breast carcinomas as small as a few millimetres. To yield the highest spatial resolution, all modern transducers should be operated at the highest clinically appropriate frequency. However, high resolution ultrasound equipment can be more expensive than traditional machines. In addition, there is a limitation that no high frequency probe can image deeper than 4 cm and this limitation should be kept in mind when evaluating large breasts or lesions, as the operator may have to switch to a lower-frequency probe to achieve better penetration and a wider field of view [98].

Similar to Mammography and MRI, ultrasound also has limitations. It too requires a well-trained, skilled operator and a follow up team that includes radiologists, breast surgeons, pathologists, and expert physician input to interpret images [99]. Screening takes 15 min or longer for each breast and it takes additional time for radiologists or physicians to review the images manually, which introduces subjectivity and error based on experience.

Costs for ultrasound screening include review by radiologists, technician time, and communicating results to the doctors. The average cost per patient has been estimated at €127 [100], but may vary by country. Hence, it is almost similar to mammography.

Finally, ultrasound has low spatial resolution, low specificity [101], and is unable to image micro calcifications [99], especially when they are inside fibroglandular breast tissues [102-104]. These factors all increase the rate of false positive results [105, 106]. Table 1 summarizes the reported performance of ultrasound in breast cancer screening. The performance, particularly the percentages
range of FPR and FNR are higher than for other modalities, limiting its efficacy in widespread screening or pre-screening.
2.4 Microwave Imaging

Microwave imaging (MI) is based on the dielectric properties of tissues. This imaging technique is applicable to breast cancer detection, due to the differences in dielectric properties between normal and malignant breast tissues [107-110]. There are three types of microwave: passive, hybrid, and active. Passive microwave relies on tumour temperature and detects regions of increased temperature in the breast [111-113]. The key concept of passive microwave is similar to thermography with different range of spectrum [114]. Hybrid methods heat tumours with microwaves and forms images using an ultrasound transducer to detect pressure waves generated by the expansion of heated tissues [115]. Active microwave techniques are classified as radar or tomographic methods. In both approaches, scattered microwave signals are measured after transmitting low-power microwave signals into the breast using an array of 16 antennas are attached in a circular fashion. Each antenna in turn transmits electromagnetic wave in the microwave spectrum and the remaining 15 collect measured data [110, 116].

In the tomographic approach, narrowband signals are used to record a set of scattering parameters of the breast. An inversion algorithm is used to reconstruct a complete map of the dielectric properties of the breast [117, 118]. In contrast, radar methods use wideband or ultra-wide band (UWB) signals to create images that indicate the presence and location of significantly scattering objects [119].

Active microwave imaging techniques are totally dependent on the dielectric properties: permittivity and conductivity. It is reported that dielectric properties for cancerous tissues are three or more times greater than healthy tissues [120]. Radar-based approaches have only involved testing with phantoms [121, 122] and early-stage clinical investigations [123]. There are thus few reports on clinical trials that reflect the significant technical challenges involved in sensor design and implementation, measurement hardware, and the development of patient interfaces [119].
Unlike mammography, this technique is free from ionizing radiation, non-invasive, requires no breast compression, and is less expensive than MRI [124]. The major hurdles limiting patient use are both at the hardware level (challenges in collecting accurate and no corrupted data) and software level (often plagued by unrealistic reconstruction times in the tens of hours). Resolution of the image is also limited to 0.5cm and 1.0 cm in healthy and denser breast, respectively, which limits overall and early detection [110].
2.5 Elastography

Elastography (E) is a medical imaging technique to examine elastic properties of breast tissues, and this technique may be useful to distinguish malignant and benign masses [125]. In elastography, static and dynamic are two methods to examine mechanical properties [126, 127]. Based on viscoelastic behaviour of breast tissues, echo signals are obtained before and after compression from tissues and then converted to displacement distribution images. From measured displacement, elastography is able to provide tissue stiffness information [128].

Elastography is currently most widely method used in clinic. In various organs such as, breast, prostate, and thyroid elastography has proven highly accurate in the evaluation of cancerous tissues [157-159]. Ultrasonography (US) elastography was introduced to overcome limitations of ultrasound and mammography with combine US technology and basic principles of elastography [129, 130]. Unlike mammography, it is non-invasive [160].

The combination of ultrasound elastography and sonography had the best results in detecting cancer with an average 89.7% sensitivity and 95.7% specificity. Due to the lowest false-negative rates elastography is a promising technique and has the potential to reduce unnecessary breast biopsies [131].

The performance of elastography reported by several authors is summarised in Table 1.

Elastography compare to MRI has the lowest cost [132]. Some lesions may contain benign and malignant, elastography can be helpful working with complicated breast lesions. Additionally, elastography reduces unnecessary biopsies costs [133]
The fundamental concept of DIET (digital image elastography) is based on elastography and was first published in 2004 [134]. DIET is non-invasive, portable, inexpensive, comfortable breast cancer screening technique that measures the stiffness of tissue within the breast [135, 136]. The DIET system captures low amplitude surface oscillations in the range 10 – 100 Hz generated by mechanical actuation applied to the breast [136]. Several images are captured during one cycle of a typical frequency, all at different phase angles relative to the input motion. Instead of digital imaging sensors, lasers or other non-contact displacement measurement methods could also be used to detect the actuated surface motion.

The main features are non-invasive, low cost, and fast. Phantom studies have shown the method is capable of detecting stiff inclusions that mimic cancer. Therefore, it could prove suitable for screening at any age. In addition, it is portable and requires no specialist user, reducing variability.
2.6 Summary

Tables 1 and 2 and Fig. 4 provide an overview of all modalities concerning advantages and disadvantages, such as economic, speed, accuracy, operator independency, risk, and comfort. In particular, the diagram of Fig. 4 provides an overview of how each modality interacts in terms of the key features considered. The results summarised here, particularly in Table 1 and Table 2, clearly show the advantages of the current standard, mammography, in performance, but also its disadvantages in regards to its invasive nature, as well as its wide variability in diagnostic performance. Equally, the results show the potential of emerging modalities, such as ultrasound and elastography, assuming they can overcome some specific limitations they face in performance and/or lack of significant clinical data and testing.

Table 1 Summary of performance results of every modality

<table>
<thead>
<tr>
<th>Techniques</th>
<th>Authors</th>
<th>TPR (%)</th>
<th>FNR (%)</th>
<th>TNR (%)</th>
<th>FPR (%)</th>
<th>Patients (#Pos / #Neg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammography</td>
<td>Kuhl et al. [137]</td>
<td>33.0</td>
<td>67.0</td>
<td>93.0</td>
<td>7.0</td>
<td>(9 / 96)</td>
</tr>
<tr>
<td></td>
<td>Dodd [138]</td>
<td>87.2</td>
<td>12.8</td>
<td>85.1</td>
<td>14.9</td>
<td>(3661 / 4051)</td>
</tr>
<tr>
<td></td>
<td>Kolb et al. [139]</td>
<td>77.6</td>
<td>22.4</td>
<td>98.8</td>
<td>1.2</td>
<td>(246 / 27579)</td>
</tr>
<tr>
<td></td>
<td>Manoliu and Ooms [140]</td>
<td>86.6</td>
<td>13.4</td>
<td>80.7</td>
<td>19.3</td>
<td>(279 / 376)</td>
</tr>
<tr>
<td></td>
<td>Ohlinger et al. [141]</td>
<td>100.0</td>
<td>0.0</td>
<td>72.7</td>
<td>27.3</td>
<td>(3 / 11)</td>
</tr>
<tr>
<td></td>
<td>Habib et al. [142]</td>
<td>72.2</td>
<td>27.8</td>
<td>75.0</td>
<td>25.0</td>
<td>(18 / 8)</td>
</tr>
<tr>
<td>Standertskjöld-Nordenstam and Svinhufvud [143]</td>
<td>Luczyńska et al. [144]</td>
<td>91.8</td>
<td>8.2</td>
<td>95.6</td>
<td>4.4</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Burman et al. [145]</td>
<td>97.8</td>
<td>2.2</td>
<td>83.9</td>
<td>16.1</td>
<td>(47 / 5059)</td>
</tr>
<tr>
<td></td>
<td>Egan and Egan [146]</td>
<td>77.4</td>
<td>22.6</td>
<td>67.4</td>
<td>32.6</td>
<td>(31 / 46)</td>
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### Table 2: All modalities in terms of main aspects

<table>
<thead>
<tr>
<th>Techniques</th>
<th>Economic</th>
<th>Fast</th>
<th>Accurate</th>
<th>Operator Independent</th>
<th>Ionizing Radiation</th>
<th>Comfort</th>
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<tbody>
<tr>
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<td>✓</td>
<td>×</td>
<td>✓</td>
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<tr>
<td>X-ray</td>
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<td>×</td>
<td>✓</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>Mammography</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>×</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>MRI</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>Ultrasound</td>
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<td>✓</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>Microwave Imaging</td>
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<td>×</td>
<td>✓</td>
<td>×</td>
<td>×</td>
<td>✓</td>
</tr>
</tbody>
</table>
Fig. 4 All modalities in terms of main aspects, where blue (Fast, Operator Independent and Accurate) and green (Economic) are desirable aspects, and red (Invasive) is undesirable. The diagram shows the relative location of all major modalities considered where the goal is to be in all blue and green circles and avoiding the red. The diagram is also captured in Table 2.
3.0 Conclusions

Outside of breast self-exam, mammography is the most widely used and well-accepted technique to detect breast cancer, and is thus an effective gold standard in the field. However, its limitations in exposure to ionizing radiation and comfort due to breast compression, both of which can affect compliance to screening, create a significant need for other less invasive approaches. In addition, its variability in diagnosis based on radiologist experience may be a further limitation to be improved by automated methods, within mammography or via another modality. However, it is important to note that mammography is still the only proven and accepted wide scale screening modality.

In contrast, current and emerging methods using ultrasound, MRI, and Microwave imaging all are non-invasive, but their reported results to date are too variable at this time for use in regular screening. Newer emerging technologies, like DIET and advanced ultrasound systems, can offer non-invasive, all age screening that is low cost. However, these latter emerging technologies still face a long validation process to prove their efficacy in relation to accepted standards before they are accepted as realistic screening alternatives.

Overall, this review thus tries to concisely summarise the overall strengths, weaknesses, and thus gaps in the field, with a strong focus on how newer, emerging technologies can offer novel solutions to broader cohorts.
References


