Screening for Breast Cancer with Mammography: Current Status and An Overview

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Abstract This article reviews the current status of Mammographic screening in early detection of Breast cancer. A brief introduction on the global breast cancer burden is followed by an overview of the data proving the benefits of screening mammography in those countries where screening programs are in place. The screening recommendations, the benchmarks of a successful mammographic screening program and an overview of the guidelines that have been implemented for ensuring quality assurance in the USA and Europe are presented. The pertinent aspects of mammographic interpretation and the role of non mammographic screening methods are also discussed.

Keywords Breast cancer · Screening · Mammography

Introduction & Background

Breast cancer is the most prevalent cancer in women worldwide and a leading cause of cancer related deaths in women [1, 2]. Historically low and middle resource countries have reported significantly lower incidence of Breast cancer compared to the Americas and Europe. However in the past two to three decades there has been increasing incidence and mortality from Breast cancer in low and middle resource countries [3]. Of the over million

new cases of breast cancer that will be diagnosed worldwide in 2009, low- and middle-resource countries will be burdened with 45% of breast cancer cases and 55% of breast cancer related deaths [2, 3]. Compounding the problem is the limited data that is available on breast cancer incidence in low resource countries. Data available are often based on those obtained from small geographic areas and then extrapolated to larger areas, a dependable cancer registry such as those available in the USA and Europe are not available [3]. In India, data from the Cancer Atlas reports that amongst the population based cancer registries, Delhi had the highest age adjusted incidence rate of breast cancer at 33.4 per 100,000 females compared to 109.6 per 100,000 white females in San Francisco, California, USA. District wise comparison of minimum age adjusted incidence rates of breast cancer [MAAR] showed that Chandigarh with a rate of 39.5 per 100,000 and North Goa with a rate of 36.8 per 100,000 women exceeded the MAAR of Delhi [4].

Benefits of Mammographic Screening for Breast Cancer

Prior to the emergence of mammography as a screening modality, most breast cancers were being diagnosed by palpation and often the tumors had been palpable for a variable period of time prior to clinical diagnosis. Consequently the outcome of such cancers was poor because of the often systemic nature of the disease at the time of diagnosis [5]. The prime reason for Breast cancer mortality is diagnosis at an advanced stage of disease. The rationale of a breast cancer screening program then is primarily to detect cancer when it is small and impalpable. The interval between mammographic detectability and clinical detectability reflects the tumor growth rate and is variable being

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dependent on the histological type, tumor type and patient's age [5]. This interval called the sojourn time or the preclinical phase of breast cancer is when breast cancers should be diagnosed so as to reduce breast cancer mortality. Treatment of such screen detected small non palpable breast cancers provides an opportunity for curing cancers by local therapy alone [5].

The role of mammography in reducing breast cancer mortality has been demonstrated in multiple randomized clinical trials as well as in organized mammography screening services. The first randomized controlled study to demonstrate a significant benefit of screening mammography was the Swedish Two-County trial. A total of 77080 women aged 40–74 years were randomized in geographical clusters and invited to be screened, 55985 women were assigned to a no invitation group. A single view mammogram was performed every 33 months in women of age group 50–74 years and every 24 months in the age group 40–49 years. In this trial a 30% mortality reduction was achieved when those women who were invited to be screened were compared to those who were not [6]. In the same study when those women who actually attended screening were compared to those who did not, a still higher mortality reduction of 42% was observed [6, 7]. A Meta analysis of all the randomized clinical trials [RCT's] testing the efficacy of screening mammography to date, demonstrated a significant reduction in breast cancer mortality of 20–35% in women of age group 50–69 years [8]. The evidence of reduction of mortality for women between 40 and 49 years is lower yet significant. A study that looked at the data from all 4 Swedish trials for women in this age group reported a 23% mortality reduction at randomization achieved from a median trial time of 7 years, median follow up of 12.8 years and a screening interval of 18–24 months [9].

How do the results of these RCT's translate to clinical practice i.e. service screening? This has been studied by Tabar and others. In the age group of women between 20 and 69 years there were 6807 who were diagnosed with breast cancer over a 29 year period in two counties in Sweden and 1863 breast cancer deaths [10]. These investigators reported a 63% mortality reduction in mortality from incident breast carcinoma in women ages 40–69 years during the service screening period of 1988 to 1996 compared with breast cancer mortality during the time period when no screening was available (1968–1977). The reduction in mortality observed during the service screening period when adjusted for selection bias was 48% [10]. The reason for a more significant mortality reduction in service screening compared to RCT's can be attributed to a number of logical factors. These include significant improvements in mammographic techniques since the randomized trial era, and the inherent limitations of RCT's in quantifying

mortality reduction due to compliance and contamination rates, and prevalence screen. The number of screening rounds, length of follow up and length of screening intervals which in the Swedish tow county trial was 33 months for women aged 50–74 years are additional factors that lead to better results in service screening [11].

Mammographic Screening Recommendations

The literature supporting the benefits of screening mammography in reducing mortality from Breast cancer is extensive and the overwhelming body of evidence is strongly in favor of offering this service to women in countries with a high prevalence of breast cancer. Nevertheless, the controversies and the debate as to when breast cancer screening should commence, how often to screen women, and when to stop screening, rages on. The council of the European Union and the International agency for Research on Cancer expert working group has recommended use of bi-annual mammography for women age 50–69 [12]. In the USA, the Society of Breast Imaging and the Breast Imaging Commission of the American College of Radiology recommends annual screening mammography for Women at average risk to undergo annual screening mammography starting at age 40 [13]. For women with certain BRCA1 or BRCA2 mutations or for those who are untested but have a first degree relative who is BRCA positive, annual screening mammography is recommended starting at age 30 years. Women with either a >20% lifetime risk for breast cancer based on family history or those with mothers or sisters with premenopausal breast cancer are advised to undergo annual screening starting at age 30 or 10 years earlier than the age of diagnosis of the youngest affected relative whichever is later [13]. Women with histories of mantle radiation usually for Hodgkin's disease are advised to commence screening yearly starting 8 years after radiation therapy but not before age 25. And finally women with a biopsy proven Lobular carcinoma in situ, atypical lobular hyperplasia, atypical ductal hyperplasia, ductal carcinoma in situ, invasive breast cancer or ovarian cancer are advised to undergo yearly screening from the time of diagnosis regardless of age [13].

The recently announced United States Preventive Services Task Force [USPSTF] revised recommendations for screening mammography created widespread controversy in both the medical and public arena in the USA. The recommendation stated that there was no significant additional benefit gained by starting screening at age 40 years rather than at age 50 and recommended against routine screening for women in their forties [14]. The task force went on to state that the decision to start regular biennial screening mammography before the age of 50 years should be an

individual one. They recommended against teaching breast self examination and concluded that current evidence is insufficient to assess benefits and harms of clinical breast examination [14]. There was an immediate and resounding denunciation of these new recommendations by the American College of Radiology as well as from the leading Breast Imaging experts in the USA. In a sobering editorial published in *Radiology*, Berlin and Hall commented that: ‘Response of the radiologic medical community to the new USPSTF guidelines for screening mammography was needlessly confrontational and not in the best interest of everyone’s fight against breast cancer. Because these critical views are not shared by the bulk of the medical community, we fear a backlash against our specialty’. They emphasized that medical screening are more of societal issues rather than purely scientific, costs are important components in any population based health care decision. Prevention no doubt saves lives but a cost benefit analysis is critical [15].

Quality Assurance in Mammography Screening

The United States Congress enacted the Mammography Quality Standards Act [MQSA] to ensure that all women have access to quality mammography for the detection of breast cancer in its earliest, most treatable stages and charged the Federal Drug Administration with developing and implementing the MQSA regulations [16]. The scope of the act included establishing minimum national quality standards for mammography facilities to ensure safe, reliable, and accurate mammography. All facilities had to undergo periodic certification by accredited bodies to ensure compliance with federal standards. This included adequate training of both radiologists and technologists [16]. The European Union against cancer developed a European guideline for quality control and quality assurance in breast cancer screening and diagnosis. The purpose of such a rigorous quality assurance program in Breast cancer screening was to diminish the potential harm that can result from mammography such as unnecessary anxiety and morbidity, inappropriate economic cost and the use of ionizing radiation [12]. A screening program should strive to reduce and avoid unnecessary work up of clearly benign abnormalities to reduce anxiety and maintain a cost effective program. Somewhat similar to the mandated requirements in the USA, the European guidelines for quality assurance recommended the need for QA on all mammography units, implementation of a robust accreditation of all screening programs, and emphasized the need for all staff to hold professional qualifications to perform and interpret mammograms, and to undertake specialist training and participate in CME and updates and

participate in external quality assessment schemes. Each screening unit should have a lead professional to oversee overall performance. Strict adherence to such national and regional guidelines are critical for a successful screening program and many countries where screening programs are in place or are being implemented adopt similar measures to ensure quality.

Mammography Interpretation Benchmarks

A screening program must have benchmarks to serve as minimally acceptable criteria for interpretive performance. This was recently studied by Carney and others. The study was aimed to identify minimally acceptable performance standards for interpreting screening mammograms. They reported that a sensitivity of less than 75%, specificity less than 88% or greater than 95%, recall rate less than 5% and greater than 12%, PPV2 of less than 20% or greater than 40% and cancer detection rate of 2.5 per 1000 interpretations as indicating low performance [17]. If underperforming physicians moved into the acceptable range by additional training, detection of an additional 14 cancers per 100 000 women screened and a reduction in the number of false positive examinations by 880 per 100 000 women screened would be expected [17].

Radiologists interpreting moderate (1001–2000) and those with high volume (>2000) had a higher sensitivity [17]. It is of interest to note that the recall rate in the United States is twice the recall rate in the United Kingdom (eg, 12.5%–14.4% vs. 7.6%), with no difference in cancer detection rate [18]. This has to do more with practice of defensive medicine rather than interpretive skills since failure to diagnose breast cancer is the leading cause of malpractice litigation in the USA.

Mammographic Interpretation

Amongst other things, introduction and MQSA mandated implementation of the American College of Radiology BIRADS™ [Breast Imaging Reporting and Data System] recommendations for mammogram interpretation and final assessment categories have helped to standardize mammographic reporting in the USA [19]. These state that a standard mammogram report should include a description of the breast composition i.e. breast composition is almost entirely fat (<25% glandular), there are scattered fibroglandular densities (25 to 50% glandular), breast tissue is heterogeneously dense (51–75% glandular), and breast tissue is extremely dense (> 75% glandular [19]. This is important since it gives an idea about the volume of attenuating tissue in the breast and hence an idea of the relative sensitivity of the examination. The next step in the

interpretation of a mammogram is a description of significant findings such as a mass (size, morphology), calcifications' (morphology and distribution), architectural distortion and special cases (dilated ducts, intramammary lymph nodes, global and focal asymmetry) [19]. The final assessment categories contained in the BIRADS Atlas appear in Table 1. Both category 1 and 2 indicates absence of mammographic evidence of malignancy. The BIRADS™ Probably benign category is used when there is a finding that has a less than 2% risk of malignancy. Most mammographers follow a sequence of 6, 12, 24 and 36 months mammographic surveillance for women in this assessment category.

During mammographic reading, understanding the normal variation in the mammographic patterns, as well as identifying the subtle signs of malignancy is both important. The subtle signs are often faint Microcalcifications, and indirect signs of malignancy such as areas of architectural distortion, focal asymmetry, solitary dilated duct and small developing densities. Increasing the true positives is more important than reducing false positives. An important goal of the mammographer should also be to increase cancer detection rate. The importance of comparison with prior mammograms is very important. An analysis of 48,281 consecutive mammography examinations for which previous mammography (9825 diagnostic, 38,456 screening) had been performed between 1997 and 2001 reported that for screening mammography, comparison with previous examinations significantly decreases false-positive and permits detection of cancers at an earlier stage. For diagnostic mammography, comparison with previous examinations increases true-positive findings. In the Diagnostic setting, comparison with previous examinations increases the biopsy yield from 38% to 51% and the overall cancer detection rate from 11/1000 to 39/

1000. A significant decrease in the frequency of axillary node metastasis and the cancer stage for screening mammography was observed [20].

Non Mammographic Screening for Breast Cancer

Clinical Breast Examination and Breast Self Examination

Clinical Breast Examination [CBE] and Breast self examination [BSE] has been extensively studied as a low cost alternative to mammographic screening aiming to reduce mortality by early detection. Breast cancer mortality reduction has been proven in RCT's for use of CBE's. An estimate based on all randomized clinical trials reported sensitivity of CBE for detection of breast cancer at 54% and specificity at 94% [21]. On the other hand evidence for benefit of BSE is lacking and studies show there may be more harm caused due to increased biopsy rate [22]. A large clinical trial conducted in China, which included 26600 women showed no benefit of BSE on breast cancer mortality after 10 years of follow up, the rate of biopsies due to false positive findings doubled in the instruction group when compared to the control group [22]. The American Cancer Society no longer recommends routine breast self examinations.

Breast MRI and Breast Ultrasound

Sonography has been studied in high risk patients and in those women with a dense breast parenchymal pattern in whom sensitivity of mammography is expected to be lower. In both these scenarios breast ultrasound was studied as an adjunct to mammographic screening. MRI has also been studied extensively as a screening modality in women with elevated risk of breast cancer. The gold standard for determining the effectiveness of a cancer screening modality is the proof of mortality reduction shown in randomized clinical trials. This is also confounded by the fact that mortality reduction may be due to a combination of early detection as well as more effective treatment. It is very highly unlikely that either of these imaging modalities will ever be studied to show this benefit because RCT's requires studying thousands of women with one group receiving standard care and the other receiving screening using a new modality, these women will have to be followed for at least 15 years. Furthermore since mammography is already the standard of care and has been shown to be effective it will be difficult to demonstrate any additional benefits from mortality reduction from use of these newer modalities [23].

Berg and others studied the use ultrasound in addition to mammography to screen 2809 women at high risk for

Table 1 Birads™ final assessment categories and recommendations [19]

Birads final assessment	Recommendation
Category 0	Incomplete Assessment. Need additional imaging evaluation and or prior mammograms for comparison
Category 1: Negative	Routine Screening Mammography
Category 2: Benign	
Category 3: Probably benign Finding	Initial short interval follow suggested
Category 4: Suspicious Abnormality	Biopsy should be considered
Category 5: Highly suggestive of malignancy	Appropriate Action should be taken
Category 6- Known Biopsy-Proven Malignancy	

breast cancer [24]. Ultrasound demonstrated a 55% increase in diagnosing breast cancer compared to mammography alone, detection rate increased from 7.6 per 1000 to 11.8 per 1000 due to use of ultrasound in addition to screening mammography. Sensitivity for detection of breast cancer increased to 77.5% from 49% due to addition of screening sonography. All of this comes at a price, the main disadvantages of using ultrasound as a screening tool is the high false positive rate. In this study only 8.6% of the biopsies were positive for cancer, the positive biopsy rate for mammography in this study group was also a low at 14.7% [24]. It is important however to understand that a suspicious finding on mammography requires a more expensive and resource intensive technique such as a vacuum assisted stereotactic biopsy, whereas positive findings on ultrasound can be sampled by simpler faster and less expensive procedures and sometimes by means of fine needle aspiration [25]. The other drawback with the use of ultrasound is time to perform a whole breast ultrasound which has been reported to be between 10 and 20 mins per bilateral examinations [24, 26–28]. It requires about 20 min performing a meticulous bilateral screening ultrasound; this drawback imposes a limitation of the number of screening studies that can be performed by a radiologist.

The use of Breast MRI as a screening modality is severely limited by cost which is several multiples that of a screening mammogram, availability of Breast MR and ability to perform MRI guided intervention for abnormalities seen only on MRI. The American Cancer Society recommends annual MRI screening in the following group of women with elevated risk of breast cancer: Women with BRCA mutation, in those with a first degree relative of a BRCA carrier, but untested, in those with a life time risk of breast cancer of 20–25% or greater, those who have received radiation to the chest between age 10–30 years and women with rare syndromes putting them at high risk for breast cancer such as Li-Fraumeni syndrome and first-degree relatives, Cowden and Bannayan-Riley-Ruvalcaba syndromes and first degree relatives [29]. MRI has been consistently shown to have significantly higher sensitivity than any other modality in women with breast cancer. The specificity is somewhat lower. In one study on 1909 women at increased risk the sensitivity of CBE, Mammography and MRI was 17.9%, 40% and 71% respectively and specificity was 98.1%, 95% and 89.8% respectively [30].

Conclusion

To date Mammography remains the only screening modality that has been proven to reduce mortality from Breast

Cancer based on multiple randomized clinical trials, by virtue of this fact it remains the gold standard for early detection of breast cancer. It is unlikely that mammography will be replaced by any other screening modality, since mortality reduction by conducting similar large clinical trials will be nearly impossible to undertake. For low resource countries, where significant increase in incidence of breast cancer has been noted, with a higher mortality rate than seen in developed countries, implementation of an organized mammographic screening program is not expected anytime soon. Mammographic screening is resource intensive, requires a stringent, enforced quality assurance, both for the technical component as well as for interpreting physicians. Allocation of funding that will be needed for such a program may not get the budgetary priority needed. Low cost alternates such as Clinical Breast examination, breast health education aimed at increasing awareness among women would be a more cost effective health care intervention at the present time.

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