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Breast cancer screening controversies: who, when, why, and how?

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ABSTRACT

Mammographic screening is effective in reducing mortality from breast cancer. The issue is not whether mammography is effective, but whether the false positive rate and false negative rates can be reduced. This review will discuss controversies including the reduction in breast cancer mortality, overdiagnosis, the ideal screening candidate, and the optimal imaging modality for breast cancer screening. The article will compare and contrast screening mammography, tomosynthesis, whole-breast screening ultrasound, magnetic resonance imaging, and molecular breast imaging. Though supplemental imaging modalities are being utilized to improve breast cancer diagnosis, mammography still remains the gold standard for breast cancer screening.

The menu of available options for breast cancer screening continues to expand. Questions arise regarding why screen, when to screen, who to screen, and how to screen.

Breast cancer is the second most common cancer in the world and by far, the most frequent cancer among women with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers) [1]. Breast cancer ranks as the fifth cause of death from cancer overall, and while it is the most frequent cause of cancer death in women in less developed regions, it is now the second cause of cancer death in more developed regions after lung cancer [1].

It is accepted that screening with mammography prevents deaths from breast cancer, although debate continues about the absolute size of the mortality benefit conferred and the concomitant risks associated with screening [2–6]. To reduce mortality, screening must detect potentially life-threatening disease at an earlier, more curable stage [7]. Effective screening programs therefore should both increase the incidence of cancer detected at an early stage as well as decrease the incidence of cancer presenting at a late stage [7]. However, to be effective in reducing mortality in the population, the proportion of the population screened must remain high. One of the factors limiting success of any screening program is low compliance.

The primary factor limiting compliance with screening mammography is low health literacy. Health literacy represents the degree to which individuals are able to obtain, process, and understand the basics of medical information in order to make necessary health decisions. Socioeconomic factors such as ethnicity, education, income, or employment, are also significant factors in whether or not patients undergo screening [8]. Given that patient compliance with mammography is less than 50%, efforts to increase health literacy are paramount [9].

Though mammography remains the gold standard for initial screening exams to detect breast cancer, limitations exist. Mammography has an overall sensitivity of 85%; however, when a patient has dense breasts, the sensitivity decreases to 68% [10]. This is relevant for 50% of American women, who fall into the category of having dense breast tissue [11]. In addition, critics point to the low specificity of an abnormal screening mammogram stating that many biopsies performed for an abnormal mammogram show no evidence of cancer and lead to unnecessary anxiety and high cost [12]. Proponents for mammography screening agree that an abnormal screening mammogram does not frequently lead to a cancer diagnosis, but point out that less than 10% of patients require additional views for further clarification, and less than 2% of women screened undergo biopsies (30–40% of which show breast cancer) [13].

A number of observational studies have claimed to find low rates of benefit in terms of reducing mortality rates or late-stage disease and high rates of overdiagnosis [7,14] and have stimulated debate in the media [15]. Therefore, supplemental imaging modalities are being utilized to improve breast cancer diagnosis.

1. Reduction in breast cancer mortality

Randomized controlled trials have consistently shown a reduction in mortality in patients screening with mammography [16]. Despite this, recent authors claim screening mammography has only marginally

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reduced the rate at which women present with advanced cancer [7]. These authors point to the data from the Canadian National Breast Screening study in their analysis [17–19]. This contrasts with a recent population-based mammography service screening study which included 2.7 million women from Canada that demonstrated a mortality benefit of 40% for women who participated [20]. Duffy et al. reexamined the four highest profile reviews, the UK Independent Review [3], the Nordic Cochrane review [4], the US Preventative Task Force (USPSTF) review [21], and the EUROSCREEN review of mammography service in Europe [22]. When the authors estimated breast cancer mortality reduction using corrected data that maintained the same screening and follow-up periods, all indicated a substantial reduction in breast cancer mortality with screening [23].

2. Overdiagnosis

Bleyer et al. suggested that there is substantial overdiagnosis, accounting for nearly a third of all newly diagnosed breast cancers over the age of 40 in the United States, and argued that screening has only a small effect on the rate of death from breast cancer [7]. Overdiagnosis is defined as the diagnosis by screening of cancer that would not have been diagnosed in the patient's lifetime if screening had not taken place [24]. This concept is also referred to as lead time, which is the time by which screening advances detection. Overdiagnosis occurs when the time to other causes of death is less than the patient's lead time. Simply put, this means that the patient would have died from other causes before her breast cancer was advanced enough to cause her death.

Some studies have claimed overdiagnosis from increasing incidence rates of breast cancer [7,25,26]. However, these estimates were derived with no information on which individuals were screened or which cancers were screen detected [23]. The Bleyer and Welch [7] study, for example, estimated that 31% of breast cancer patients over the age of 40 years in the United States were overdiagnosed. However, this study was based on registry data, and the authors had to make assumptions and extrapolations, as the registry did not include data as to whether or not the patients had their cancers diagnosed with mammography. In addition, the study failed to account for underlying incidence trends [15]. In fact, the average lead time corresponding to this study was shown to be 9 years [27] compared to an average lead time of 2–4 years for invasive breast cancers. The study by Kalager [26] included only 2.2 years of follow up. Since the benefit of screening is not realized until 3–5 years after a program has been initiated, this study likewise did not adjust for lead time [28]. Moreover, the authors did not make clear that before their study was begun, a substantial portion of patients in the population were already being screened, potentially altering the background mortality rate (and decreasing measured benefit of screening).

There is disagreement over the extent of overdiagnosis in breast cancer screening, but the case for high rates of overdiagnosis rests on analyses that were biased by lead time and incidence trends occurring independently of screening [23].

The majority of overdiagnosis in breast cancer screening may be related to Ductal carcinoma in situ (DCIS) [29] rather than invasive disease. Some have argued that the possibility of overdiagnosis should be part of an informed decision-making process [30]. However, overdiagnosed tumors may represent around 5% of prevalence screen tumors and a much smaller proportion of incidence screen cases [31], rates which certainly do not contraindicate screening.

3. Ideal screening candidate

Another area of debate includes the optimal age to begin and end screening and the potential for replacing general screening recommendations based on age with individually tailored risk-based screening [21,32–34].

In 2009, the USPSTF recommended biennial screening mammography for women aged 50–74 years and an individualized decision to start screening mammography for women in their 40s [12]. The task force also concluded that there was insufficient evidence to assess the benefits and harms of screening mammography for women aged 75 years or older [12]. Multiple public objections to the methodology of the task force were written by the Society of Breast Imaging/American College of Radiology leadership.

In the past, the major point of debate over mammography screening was whether or not to offer the examination to women aged 40–49 years [35]. Arguments against offering screening to this age group included the lesser relative reduction in breast cancer mortality observed in the trials in this age group, the lower incidence at ages 40–49 years compared with women aged 50 years and over, and the comparatively lower efficiency of screening women in this age group due to dense breast tissue of younger women [36]. Unfortunately, age grouping played a significant role in the interpretation of studies arguing against screening of women at the age of 40. By grouping women ages 40–49 and ages 50 and over, there appeared to be a sharp increase in breast cancer incidence at the 50-year mark [37] rather than a gradual increase in incidence with age progression. In addition, follow-up of the randomized trials indicates an unequivocal breast cancer mortality reduction with the offer of screening in age group of 40–49 years of age [31].

Furthermore, in Sweden, at the time of introduction of nationwide mammography screening, the policy makers chose age 40 years as the lower age limit in approximately half of the counties in the country, and 50 in the remaining half. At the 16-year observation, mortality from breast cancers diagnosed at ages 40–49 years was significantly lower in those counties that offered screening starting from the age of 40 years [32].

4. Optimal imaging modality for breast cancer screening

4.1. Mammography

Mammography has undergone greater scrutiny than almost any other medical intervention. The trials of mammographic screening provide conclusive evidence that the policy of offering screening is associated with a significant and substantial reduction in breast cancer mortality [2,3,35,38–40]. The pooled estimate from all trials and all age groups is a breast cancer mortality reduction of 20%, which is highly statistically significant [31].

When screening is introduced into a population, deaths from breast cancer decline [41–43]. Newer modalities for screening are not being introduced to replace mammography but, instead, to increase the diagnosis of early cancer in those patients for whom mammography is less sensitive.

4.2. Tomosynthesis

Digital breast tomosynthesis is a newer clinical imaging modality that allows for reconstruction of planes from breast tissue volume. Inherently, this overcomes any limitation posed by 2D imaging caused by overlapping normal and pathologic breast tissue. Numerous studies investigating tomosynthesis demonstrate a reduction in recall rates and increase in cancer detection rate [44–47]. In fact, retrospective studies show that tomosynthesis offers specificities similar to ultrasound in characterizing breast lesions seen on mammography [48]. Tomosynthesis in combination with standard screening digital mammography increases invasive cancer detection by more than a third compared with mammography alone, while reducing false positives by 15% [44]. This improvement in specificity may decrease the false positive rate of screening mammography.

4.3. Automated whole-breast ultrasound

Given the current national trend toward adopting legislation requiring the reporting of breast density to women undergoing mammography, there is a need for an efficient, reproducible method to provide supplemental screening to women with dense breasts.

Ultrasound is an attractive screening tool because it is relatively inexpensive, readily available, and requires no injected contrast or ionizing radiation. As a supplemental screening modality, ultrasound has been shown to find increased number of smaller cancers in dense-breasted women compared to mammography alone [49–58]. Mammographically occult cancers detected on supplemental ultrasound have an average size of 10 mm and are often node negative [58]. Sonographically detected cancers are most often invasive tumors, and their detection will not increase the rate of "overdiagnosis" of DCIS seen at mammography. However, the shortage of qualified personnel, lack of uniformity, and time and skill necessary to detect small, nonpalpable tumors via hand-held ultrasound limits universal implementation [58].

Now that automated whole-breast ultrasound (ABUS) has been Food and Drug Administration-approved for use in screening for breast cancer as an adjunct to mammography, it is a viable option to provide widespread screening ultrasound to fulfill the newly developing demand for adjunctive breast cancer screening. Moreover, ABUS has been shown to be effective not just in the academic setting but by community radiologists [57]. In one study, the addition of ABUS to mammography in women with greater than 50% breast density resulted in the detection of 12.3 per 1000 breast cancers, compared to 4.6 per 1000 by mammography alone [59].

The SomoInsight study showed that not only does screening ultrasound detect more cancers with mammography when compared to mammography alone but, also, that nearly all cancers detected with additional ABUS were Stage IA or IB at diagnosis [60]. ABUS discovers clinically important small invasive tumors that are mammographically occult.

The positive predictive value for biopsy in patients undergoing ABUS in addition to mammography is consistently lower when compared to those undergoing solely mammography, ranging from 7% to 21% versus 25%–38% [52,58,61]. While the technique is easily tolerated, requiring only minimal compression and no radiation, there is as surprisingly low patient compliance (28%) when screening ultrasound is offered in addition to mammography [61].

4.4. Magnetic resonance imaging

Magnetic resonance imaging (MRI) has been recommended for women with a >20% lifetime risk of breast cancer [62]. Although MRI has a very high true positive rate, MRI has a callback rate of 8–17%, a relatively low positive biopsy rate of 20–40%, requires the injection of intravenous gadolinium, and is expensive, averaging 5–10 times the cost of screening mammography [63–67]. In addition, studies have shown poor patient compliance with MRI, with many patients reporting claustrophobia as the main reason for declining MRI for supplemental breast cancer screening [58].

4.5. Molecular breast imaging

Preliminary data suggest that high-resolution nuclear medicine imaging such as breast-specific gamma imaging may be beneficial in detecting mammographically occult breast cancers in high-risk women or women who cannot undergo MRI [68,69]. Scintimammography, also known as breast-specific gamma imaging, is a noninvasive nuclear medicine study that involves the intravenous injection of Technetium 99-labeled sestamibi, a radiotracer that accumulates more in breast cancer tissue than normal breast tissue. Images are taken with a gamma camera, which detects areas of increased radiotracer uptake.

Multiple studies have demonstrated the potential utility of scintimammography. In a 3-year investigation involving 94 women with a calculated 1.66% risk of developing breast cancer, mammographically occult lesions measuring less than 1 cm were detected on scintimammography with a specificity of 85%. Negative predictive value was 100%, demonstrating that a high-resolution breast-specific gamma camera may play a role in distinguishing between benign and malignant lesions in this population of women [68]. A retrospective study performed by Tadwalker et al. suggested that scintimammography should be an adjunct to screening mammography. In this study, 139 females with known invasive carcinoma and an average tumor size of 1.8 cm underwent scintimammography. Of the known 149 cancers, 146 were identified with breast-specific gamma imaging, resulting in an overall sensitivity of 98% [70].

A study that compared breast-specific gamma imaging versus MRI in women with indeterminate breast findings seen on mammography demonstrated no statistically significant difference in the sensitivity of cancer detection between breast-specific gamma imaging and MRI [71]. Breast Specific Gamma Imaging demonstrated greater specificity and equal sensitivity when compared to MRI for the detection of breast cancer [71].

5. Conclusion

Mammographic screening has been shown to be effective in reducing the mortality from breast cancer. The benefit of screening mammography for women ages 40–75 has been documented by multiple, quality, randomized controlled trials. In this era of evidenced-based medicine, it is critically important that effectiveness of a practice be established when issuing clinical practice guidelines and other population-level policies. The issue is not whether mammography is effective but whether the false positive rate and false negative rates can be reduced. By improving both sensitivity and specificity, the benefit for screening will be even greater than it is today. Initial data show that breast tomosynthesis is able to reduce call-back rates (decreasing false positives) and increase cancer detection rates (increasing sensitivity). The positive predictive value rises, and the need for additional testing is diminished. Therefore, the addition of breast tomosynthesis is a step forward for women being screened with mammography. The issue of dense breasts is more complicated. Screening breast ultrasound increases the cancer detection rate in dense breasts but comes with a higher cost of false positives. The advantage is that it is readily available, lower cost than MRI and, in the automated environment, is quick to perform. MRI has the advantage of including physiologic data (enhancement) and carries the highest sensitivity for the detection of breast cancer. However, it is limited by low specificity, high cost, and is a time-intensive procedure. Continued progress in the refinement of these additional screening tools is being made, and these imaging methods, in addition to mammography with tomosynthesis may become the best tools for addressing patients at higher risk for development of breast disease.

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