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Radiologic Screening for Breast Cancer: Current Controversies

Carol H. Lee

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Abstract Breast cancer is the most commonly occurring cancer, aside from skin cancer, among American women and the second leading cause of cancer death. Screening with mammography has been used for decades in this country, and since its introduction, there has been a reduction in breast cancer mortality. However, controversy surrounding the use of mammography to screen for breast cancer continues. In addition, the development of newer imaging techniques that can be applied to breast cancer screening has generated further debate about the value and appropriate use of radiologic imaging for breast cancer screening.

Keywords Screening · Breast cancer · Mammography · Tomosynthesis · Breast magnetic resonance imaging · Breast ultrasound

Introduction

Several prospective randomized trials conducted in the US and Europe in the 1970s and 1980s showed statistically significant breast cancer mortality reduction associated with mammographic screening [1–3]. Based on these results, a number of medical organizations in the US have advocated its use. Throughout its history, however, mammographic screening has been the subject of debate, and despite the randomized trials and 30 years of experience, controversy surrounding screening mammography has intensified rather than diminished and polarization between advocates and critics of screening has increased. Proponents of screening mammography point out the decrease in breast cancer mortality, which they say can be directly attributed to screening while opponents state that treatment rather than early detection is responsible for the observed mortality reduction, and there is little justification for mass screening with mammography.

Other areas of controversy include at what age screening mammography should start, how often it should occur and whether the harms of screening, which include false-positive results and overdiagnosis, outweigh the benefits. Finally, increased awareness of the limitations of mammography and the development of other imaging techniques to screen for breast cancer, such as tomosynthesis, ultrasound, and magnetic resonance imaging (MRI), among others, have raised new questions about what modality should be used for which population of women.

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C. H. Lee (✉)
Memorial Sloan-Kettering Cancer Center, 300 East 66th Street, New York, NY 10065, USA
e-mail: leec1@mskcc.org

Controversies Surrounding Screening Mammography

Doubts About Efficacy

Meta-analyses of the randomized controlled trials of screening mammography show a statistically significant 15–22 % reduction in breast cancer mortality among the population invited to screening [4, 5]. Despite this, there are continued challenges to the validity of screening mammography. Goetzche and Olsen in 2000 reviewed the screening trials and declared that all but three had serious flaws in methodology and poor randomization rendering their results unreliable [6]. The three that they deemed to

have proper methodology showed no reduction in breast cancer mortality among the screened population, showing a relative risk of 1.04 (95 % CI 0.94–1.05). Therefore, they stated, screening with mammography is unjustified. Other studies of the efficacy of screening comparing mortality rates in screened groups with those in either historical or geographical controls have yielded varying results despite being based on data that include the same population and same time periods.

In a report from Denmark, mortality rates among screened and unscreened populations were compared and showed a 1 % decline among the screened group but a 2 % decline among the unscreened group [7]. In addition, the greatest decrease in mortality from breast cancer occurred in women who were too young to be eligible for screening. The authors of this study postulated that the decrease in breast cancer mortality was due to improvements in therapy and greater awareness of breast cancer rather than early detection through screening. Similarly, a study of breast cancer mortality trends in four counties in Sweden from 1972 to 2009 found that in two counties, breast cancer mortality trends after screening was introduced was similar to those before the use of screening [8]. The authors concluded that screening mammography had little or no effect on breast cancer mortality.

Finally, a study of screening in Norway compared death rates in regions with and without screening to historical data from the same areas and found that deaths declined by 7.2 deaths/100,000 person-years in the screening group compared to a decline of 4.8/100,000 person-years in the non-screened group [9]. The conclusion of this study was that screening accounted for only a third of the observed mortality reduction.

Countering these studies are others that continue to demonstrate a benefit of screening. A meta-analysis of the randomized controlled trials by an independent panel in the UK (UK) reported a 20 % mortality reduction among screened populations [10••]. An analysis of data from the two-county Swedish trial after 29 years of follow-up reported a statistically significant decline in mortality of 31 % in the screening group [11]. A recent case–control study from Australia reported a 49 % reduction in breast cancer mortality among women receiving screening [12]. In addition, researchers conducted an analysis of 7,301 women with breast cancer in Massachusetts, 609 of whom died of the disease [13•]. They found that 71 % of the deaths occurred in women who had either never been screened or who had not had screening in the past 2 years and concluded that screening is associated with a lower risk of dying from breast cancer.

All of these reports, both in favor of and opposed to screening, are met with criticisms of methodology, underlying assumptions, type of analysis and conclusions by the opposing group. Many of the studies rely on very sophisticated statistical methods that are difficult if not impossible for a non-statistician or epidemiologist to decipher. This has left clinicians and the general public confused as to where the truth lies.

When Should Screening Start?

The age at which regular screening mammography should begin has been a point of contention for many years and is still being debated. This topic was hotly contested in the 1990s, and the argument was re-ignited in 2009 when the US Preventive Services Task Force (USPSTF) revised their previous guidelines to suggest that routine screening should wait until age 50 [14]. They and others cite the lower incidence of breast cancer, the increased proportion of false positives, and the lower sensitivity of mammography among younger women as justification for their recommendation.

Evidence of benefit for women aged 40–49 from the randomized controlled trials was limited, as most were not specifically designed to address this question. A trial that did look at this was conducted in Canada and showed no significant difference in mortality between the screened and unscreened population [15]. In addition, the AGE trial conducted in the UK randomly assigned women aged 39–41 to screening or no screening and after 11 years of follow-up showed a nonsignificant 11 % reduction in mortality among the screening group [16]. The USPSTF performed a meta-analysis of eight screening trials involving women aged 39–49 and found a significant 15 % reduction in mortality [5]. They calculated that the number needed to be screened to save one life among the 40–49-year age group was 1,904 compared to 1,339 among 50–59 year olds and 337 among those aged 60–69. They also found that starting at age 40 resulted in the greatest number of years of life saved. However, citing the number of false positives generated by screening among the younger age group, the USPSF recommended that routine screening start at age 50, and for women in their 40s the decision as to whether or not to screen should be an individual one depending on risk factors and values concerning possible risks versus benefits. In contrast, the American Cancer Society (ACS), American Congress of Obstetrics and Gynecology (ACOG), American College of Radiology (ACR) and the American College of Surgeons (ACoS), in recognition of the benefits of screening in the younger age group, recommend that routine screening begin at age 40. Guidelines in many European countries call for screening of average risk women to begin at age 50. A summary of screening mammography recommendations from a number of organizations in the US and from national screening programs around the world is presented in Table 1.

Table 1 Screening mammography recommendations for average risk women

Country/organization	Age to start routine screening	Age to stop screening	Interval
United States/ACS, ACR, ACOG, ACoS	40	As long as a woman is in good health	Yearly
USPSTF	50	74	Every 2 years
Canada	50	74	Every 2–3 years
United Kingdom	47	73	Every 3 years
European Union[a]	50	69	Every 2 or 3 years
Sweden	40	74	Every 1.5 years 40–49
			Every 2 years $\geq$ 50
Australia	50	74	Every 2 years

ACS American Cancer Society, *ACR* American College of Radiology, *ACOG* American Congress of Obstetrics and Gynecology, *ACoS* American College of Surgeons, *USPSTF* US Preventive Services Task Force

[a] Varies by country, most common strategy listed here

How Often Should Screening Be Performed?

The interval at which screening mammography should be performed is another area of debate. Using six different models and data from the Breast Cancer Surveillance Consortium (BCSC), Mandelblatt et al. [17] weighed the benefits of various screening models against the risks of false-positive exams, subsequent benign biopsies and overdiagnosis. All of the models indicated that the most efficient strategy was for biennial rather than annual screening. Also using data from the BCSC, Kerlikowski et al. [18] evaluated tumor stage, size and lymph node status as a function of age, breast density and screening interval. They found that biennial screening was not significantly associated with adverse tumor characteristics in most women except those aged 40–49 with extremely dense breasts in whom biennial compared to annual screening was associated higher stage disease. In the US, the ACS, ACOG, ACR and ACoS recommend annual screening, whereas the USPSTF recommends biennial screening. In most of Europe, the recommended interval is 2 years, and in the UK it is 3 years (Table 1).

Do the Benefits of Screening Mammography Outweigh the Harms?

The benefit of screening is the potential of avoiding death from breast cancer through early detection. Some of the harms such as discomfort from the exam, radiation exposure and psychological distress from an abnormal interpretation, though important, are not generally regarded as being of sufficient magnitude to outweigh the benefit. Other risks, however, namely false positives necessitating additional imaging and/or biopsy and most notably the risk of overdiagnosis, have generated a great deal of controversy in terms of the balance of harms versus benefit for screening mammography.

False Positives

As with any screening test, mammography can result in an abnormal reading that requires further evaluation, usually consisting of additional mammographic views and/or ultrasound. On occasion, a biopsy is necessary to exclude malignancy. The degree to which false-positive interpretations occurs varies from location to location, but in the United States is generally on the order of 10 % [19]. Christiansen et al. [20] estimated the cumulative risk for an abnormal reading to be 43 % after nine rounds of screening. False positives have been cited as a reason for not screening the 40–49 year age group and are also given as a reason to screen biennially rather than annually. In the modeling study by Mandelblatt et al. [17], biennial screening resulted in similar stage distribution of cancers detected, but nearly 50 % reduction in false-positive readings and benign biopsies.

Abnormal findings on screening mammography have been reported to be associated with anxiety, and this has been cited as a "harm" associated with screening [14]. However, the reported degree of psychological distress and the significance of this anxiety varies among different reports [21], and acceptance of false-positive results among the public seems to be high. In one survey of 503 American women, 63 % felt that 500 false positives were reasonable to save one life, and 37 % would tolerate 10,000 or more [22].

Overdiagnosis

Overdiagnosis of breast cancer is defined as detection of disease that is so biologically innocent that it would never be life-threatening. The possibility of overdiagnosis has been cited as a major harm associated with screening, but

the degree to which this occurs is difficult to determine, and it ranges from less than 1 % to more than 50 % [23, 24]. Recently, Bleyer and Welch [25•], using Surveillance, Epidemiology and End Results data, determined that in the 30 years since screening mammography has been used in the US, the incidence of early stage cancer has doubled, but the incidence of late stage disease has only decreased by 8 %. They concluded that this is due to overdiagnosis, which they estimated accounts for 31 % of all breast cancers diagnosed. In contrast, Yen et al. [24] looked at the incidence of cancer in one of the Swedish counties involved in an early randomized controlled screening trial and found no excess incidence among the screened population after 29 years of follow-up. They concluded that overdiagnosis occurred rarely if at all. In addition, a study of screening mammography in Norway estimated that overdiagnosis occurred in 2.3 % of targeted women [26]. In the UK, an independent panel examining existing information on the efficacy of screening concluded that mammography reduces breast cancer mortality by 20 %, but is associated with overdiagnosis on the order of 19 % of cancers diagnosed [10••]. Based on their calculations, the panel postulated that for every breast cancer death avoided through screening, three cases were overdiagnosed. Finally, the USPSTF in their analysis concluded that overdiagnosis likely occurs in $\sim$10 % of cases and is more of a consideration in older women in whom slowly growing cancers may be detected by screening [5].

The discrepancy among published studies in the estimates of overdiagnosis is undoubtedly due to differences in methodology and in underlying assumptions. The crux of the problem of overdiagnosis is the inability to discern the biologic significance of cancers that are found through screening. Rather than addressing overdiagnosis by abandoning screening, as has been suggested by some, development of ways to identify which cancers are potentially lethal and which are not should be the goal.

Other Screening Modalities

The development of screening modalities other than conventional mammography has provided new opportunities for detection of breast cancer, but also new areas of controversy. Questions raised by other screening modalities include when and on whom they should be used and whether they are cost-effective.

Tomosynthesis

Digital breast tomosynthesis (DBT) is a digital mammography technique in which multiple low-dose mammographic images are acquired as the X-ray tube moves in an arc. The images are then processed to create a simulated three-dimensional rendering of the breast that can be displayed as slices, similar to a computed tomography (CT) scan. Unlike CT, however, tomosynthesis images are not truly three-dimensional as one of the axes is computer generated from two-dimensional (2D) data. The theory behind DBT is that by viewing slices of breast tissue and eliminating overlying tissue, cancers might be seen more easily (Fig. 1).

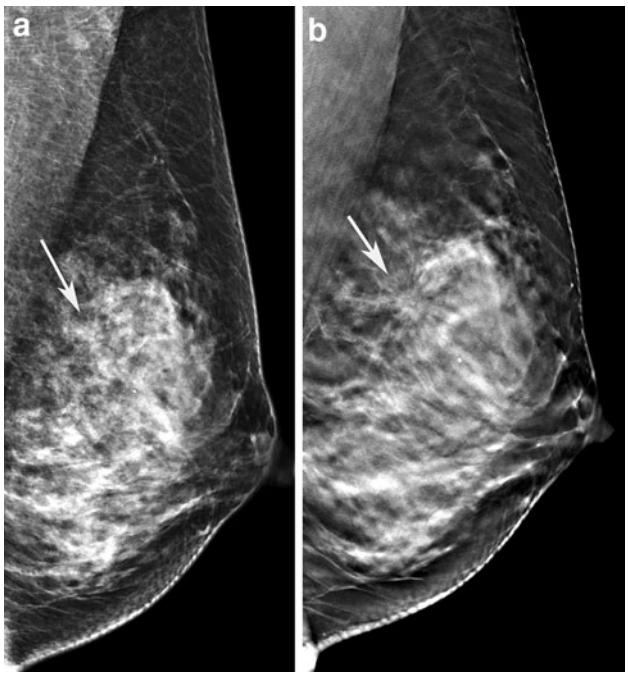

Fig. 1 Example of tomosynthesis image. **a** Standard 2D left MLO view; **b** slice from tomosynthesis study obtained at the same time as the standard 2D view. The cancer in the breast is more clearly seen on the DBT image

In 2011, the Food and Drug Administration (FDA) approved the first device for clinical use in the US. Approval was granted for DBT to be used only in addition to, not as a substitute for, standard 2D mammography. This was because it could not be demonstrated that the use of DBT alone increased cancer detection over standard 2D mammography alone. The radiation dose from a single DBT view is approximately equal to that of a 2D view. Therefore, women who have DBT as part of their screening examination receive twice the radiation dose of a 2D study.

Since its introduction, DBT is increasingly being adopted by practices in the US. Information on its performance is still limited. Several studies have shown that tomosynthesis reduces the number of false-positive interpretations at screening [27–29]. In one of the earliest reports on DBT, Poplack et al. [27] found a 40 % reduction in the recall rate with the use of tomosynthesis in addition to standard mammography. Multi-reader studies conducted

under the auspices of the equipment manufacturer and published in the peer-reviewed literature reported an increase in sensitivity when DBT was added to 2D mammography and a statistically significant decrease in recall for non-cancer cases among all of the readers [29]. Recall among cancer cases, however, was mixed, with some of the readers showing an increase, others no change, and in some an actual decrease.

Early results of two randomized prospective trials of DBT for screening have recently been published. In one being conducted in Norway, comparison of 12,631 cases read with and without the addition of DBT showed a 27 % increase in the cancer detection rate (6.1/1,000–8/1,000) accompanied by a 15 % decrease in the recall rate (61.1/1,000–53.1/1,000) [30•]. Similarly, a study from Italy showed a statistically significant increase in cancer detection from 5.3/1,000 with 2D mammography to 8.1/1,000 with the addition of DBT. They also showed a 17.2 % reduction in recalls [31].

These results are promising, but two additional reports of DBT as used in routine clinical practice in the US are not as favorable. In one study by Rose et al. [32], the results of screening using 2D plus DBT in 9,499 women were compared to results obtained from screening in 13,856 women prior to the introduction of DBT. There was a significant decrease in recall rate from 8.7–5.5 %, but there was no statistically significant change in cancer detection rate. A study by Haas et al. [33] had similar results. In this study, DBT is used with 2D at some but not all sites, and screening results from the sites using DBT were compared to results from those that do not. The recall rate was 12 % at sites not using DBT and 8.4 % at sites that did. This difference was statistically significant. The cancer detection rate, however, was similar with and without DBT at 5.7/1,000 with DBT and 5.2/1,000 without. The final word on how DBT can best be used will be determined by further experience and data on its performance in the clinical setting.

In May 2013, the FDA approved the use of a synthesized 2D mammogram produced from the DBT images as a replacement for the standard 2D mammogram. This obviates the need for obtaining a separate 2D examination during screening, thus lowering the radiation dose associated with the use of DBT. Whether this synthesized image will be efficacious in replacing the 2D image remains to be demonstrated, but if it does, one of the major disadvantages of DBT, namely the increased radiation dose, will no longer be a factor.

Ultrasound

Screening with ultrasound has a number of advantages over other screening modalities. It does not require compression or intravenous contrast and does not deliver ionizing radiation. Ultrasound is widely available and relatively inexpensive, and a number of studies have reported additional cancers detected when screening ultrasound is added to mammography [34–37]. Despite this, the adoption of screening ultrasound has, until recently, been limited in the US largely because of the fact that the study is very operator dependent and relatively time consuming in terms of image acquisition. However, the use of screening breast ultrasound is increasing rapidly in this country because of legislation in a number of states requiring direct patient notification of a woman's breast density after a mammogram. The controversy surrounding screening with ultrasound is not so much whether this modality is effective but whether there should legislation mandating direct patient notification of breast density, which results in increased demand for screening with ultrasound. These laws have been the result of a grassroots movement started by women whose cancers were not detected by mammography because the cancers were obscured by dense tissue [38••]. Currently, 12 states have direct density notification, and another 6 state legislatures are considering similar bills (Fig. 2). In addition, a bill has been introduced in the House of Representatives to make notification a national mandate.

The Breast Imaging Reporting and Data System (BI-RADS) of the ACR describes four categories of breast density: almost entirely fat, scattered fibroglandular densities, heterogeneously dense and extremely dense (Fig. 3) [39]. Approximately 10 % of women have predominately fatty breasts, 40 % have scattered fibroglandular tissue, 40 % have heterogeneously dense breasts, and, in about 10 %, breast tissue is extremely dense [40]. Breast density is significant in that it is associated with increased risk of breast cancer, and dense breast tissue can obscure cancers, making them harder to detect by mammography. Carney et al. [41] showed sensitivity for screening was 88 % in fatty breasts and 62 % in women with extremely dense breasts. In the Digital Mammographic Imaging Trial that compared film-screen to digital mammography, the sensitivity of film-screen mammography in women with extremely dense breasts was only 55 % [40]. The sensitivity of ultrasound is not decreased by breast density, and with increased awareness among the public of the limitations of mammography, utilization of ultrasound in addition to mammography for screening women with dense breasts has been increasing.

Data from a number of single-center ultrasound screening series and one large multicenter trial have all reported a supplemental yield of screening of ~3/1,000 women screened [34–37]. For all but one of these studies, the ultrasound examinations were radiologist-performed. In three more recent reports of screening ultrasound, all from Connecticut, which was the first state to pass density

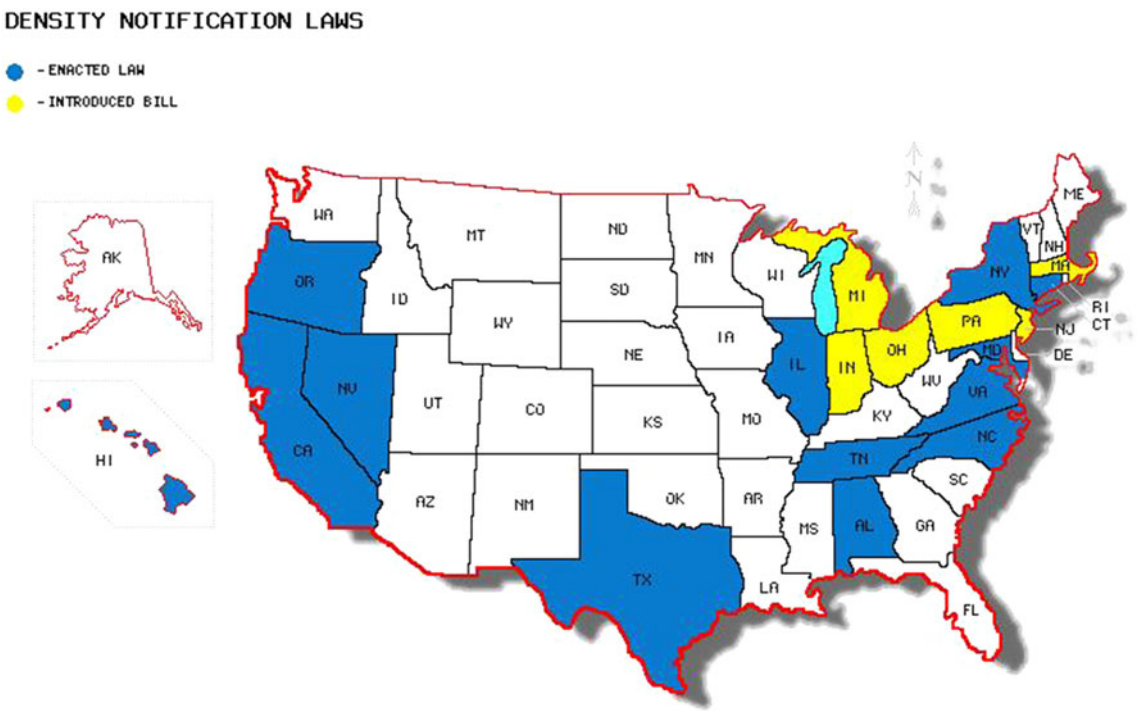

Fig. 2 Direct patient notification of breast density

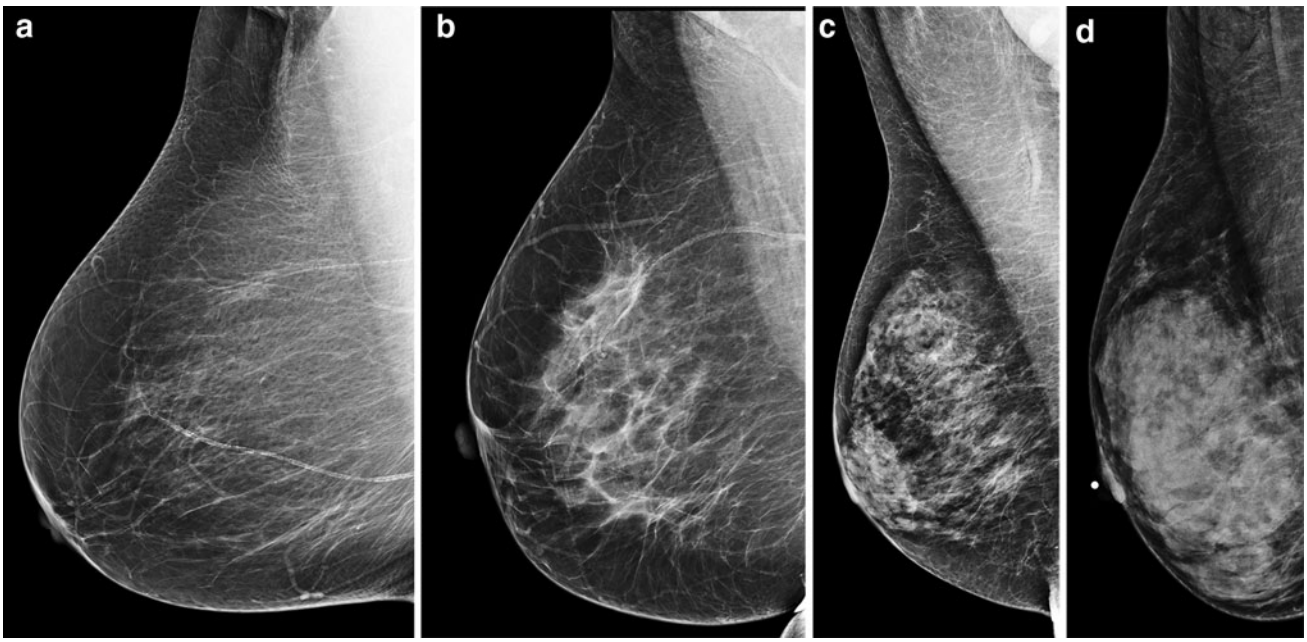

Fig. 3 BI-RADS density categories. **a** The breasts are almost entirely fatty; **b** there are scattered areas of fibroglandular density; **c** the breasts are heterogeneously dense, which may obscure detection of small masses; **d** the breasts are extremely dense, which lowers the sensitivity of mammography

notification legislation, the screening exams were technologist-performed, and they reported incremental cancer detection rates of about 2–3/1,000 [42•, 43, 44].

Despite these results, there is controversy as to whether screening ultrasound is a valid screening test. Major disadvantages are the relatively large amount of time required to perform the examination, which puts a strain on personnel resources, the high false-positive rate and the very low positive predictive value (PPV) of biopsy recommendations. The PPV for ultrasound detected findings is

~10 % or less. In the large American College of Radiology Imaging Network 6666 study, the PPV was 8 %, and for the three Connecticut studies, it was 5–6 % [37, 41–43]. In addition, in the study by Hooley et al. [42•], the BI-RADS 3 rate where short interval follow-up was recommended was 20 %, meaning that one in five women was recommended to have a 6-month follow-up ultrasound examination for a probably benign finding, further adding to the drain on resources. In addition, there is not yet evidence that the use of screening ultrasound results in mortality reduction. It is clear, however, that with the increased awareness of breast density and its contribution to decreased sensitivity on mammography, more screening ultrasound examinations will be performed in this country even without evidence of mortality reduction.

MRI

In 2007, the ACS issued guidelines for the use of MRI as a screening tool in addition to mammography [45]. Based on the published literature and expert opinion, women at high risk for breast cancer, including those with a 20 % or greater lifetime risk of breast cancer, BRCA mutation carriers and their untested first degree relatives as well as women with a past history of chest irradiation received between the ages of 10 and 30 were recommended to have annual MRI screening in addition to mammography. MRI has been shown to have higher sensitivity for breast cancer than mammography in these populations [46–48].

Because of the high level of risk in these women and the demonstrated poor performance of mammography in BRCA mutation carriers, there is little controversy about the use of MR despite the fact that there is no proven reduction in mortality associated with its use. What is more controversial is whether MR should be used in women with a moderate lifetime risk of 15–20 % for whom the ACS guidelines state there was not enough evidence to advise either for or against the use of screening MRI. This group includes women with biopsy-proven lobular carcinoma in situ (LCIS), those with a personal history of breast cancer and women with extremely dense breasts. There are no data on the use of MRI for women whose only risk factor is dense breasts. There is, however, information that has been published after the ACS issued their guidelines in 2007 suggesting that MRI screening may be useful in women with a personal history of breast cancer and women with prior biopsy-proven LCIS. Two studies on screening MRI in women with a past history of LCIS showed similar supplemental cancer yields of 3.7 and 4.4 %, respectively [49, 50]. A study of screening MR in women with a personal history of MR showed a cancer yield of 12 % [51].

The downsides of screening with MR are high cost, need for intravenous contrast administration, variable insurance coverage and the fact that not all women are candidates for the examination because of claustrophobia, the presence of pacemakers or other metallic objects in the body, and renal impairment that precludes the use of contrast. Despite this and the fact that it too has not been shown to reduce breast cancer mortality, MRI is becoming increasingly utilized for supplemental screening of very high risk women.

Molecular Breast Imaging

With the development of gamma cameras with a limited field of view designed specifically for breast imaging, the use of nuclear medicine techniques using 99mtechnicium sestamibi for screening became a possibility. Rhodes et al. [52] at the Mayo Clinic studied 936 women with dense breasts and additional risk factors with both mammography and molecular breast imaging (MBI) using technicium 99m sestamibi dedicated breast imaging. A total of 11 cancers were detected, 1 with mammography alone, 8 with sestimibi alone and 2 with both. These results are promising, but MBI at the currently used standard dose of 25 mCi technicium 99m sestamibi delivers a relatively high radiation dose to the breast as well as a high total body dose. The risk of radiation-induced cancer death is 20 times higher with MBI than for mammography at age 40 [53]. Therefore, it is difficult to justify the use of MBI at the current doses. Work is being done to reduce the dose while maintaining sensitivity, but until this is achieved, there is reluctance to use this technique for screening.

Conclusion

Despite its use for nearly 30 years in the US, screening mammography remains controversial, and the debate between advocates and opponents of screening is becoming increasingly acrimonious. Depending on the data used, the underlying assumptions and method of analysis, different conclusions as to the harms versus the benefits of screening mammography have been reached. What is not debated, however, is that mortality from breast cancer which had been increasing steadily in the years before screening was introduced, has decreased by ~30 % since its introduction [54]. It is very difficult to believe that screening has not had a role in this dramatic reduction and would be extremely unfortunate if the controversy surrounding screening mammography results in decreased utilization and a reversal of the gains achieved in morality reduction. Screening mammography has become integrated into routine health care for millions of American women and is unlikely to be abandoned, despite continuing controversy.

At the same time that screening with mammography is being challenged and recommendations for less rather than

more screening are being issued, there is increased demand for supplemental screening with alternative imaging modalities including ultrasound and MRI. The role of these tests in screening and the effect, if any, on breast cancer mortality and health care costs remain to be established.

Compliance with Ethics Guidelines

Conflict of Interest Carol H. Lee declares that she has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- •• Of major importance

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