Breast Cancer Screening

Ravinder S. Legha¹, Jessica Wai Ting Leung

After skin cancer, breast cancer is the cancer most diagnosed in U.S. women and has the second highest death rate. Breast cancer will develop in approximately one in eight American women during their lifetimes; more than 230,000 new cases of invasive cancer and 40,000 deaths were expected in 2015. Although the incidence and the death rate have declined over 30 years, more than 2.8 million Americans have a current history of breast cancer. Approximately 85% of these cases occur in patients with no family history; the most important risk factors are female sex and increasing age [1].

Although there is variability by subtype and histopathologic features, it is widely accepted that advanced breast cancer with axillary or distant metastases is associated with a poorer prognosis [2]. As reported by the Surveillance, Epidemiology, and End Results Program (SEER) [3], the 5-year relative survival of breast cancer localized to the breast is 98.6%, decreasing to 84.9% after spread to regional lymph nodes and 25.9% with distant metastases. Consequently, the trend toward screening evaluation and early-stage diagnosis has gained increasing importance in the last several decades. Important metrics for the efficacy of a screening examination include sensitivity, specificity, positive predictive value (PPV), and recall rate. In the case of screening mammography for patients 40–89 years old, the Breast Cancer Surveillance Consortium reports sensitivity of 83.5%, specificity of 90.9%, PPV of 4.1%, and a recall rate of 9.3%. Notably, sensitivity, specificity, and PPV for screening mammography all improve with increasing age [4]; sensitivity and specificity decrease with increasing breast density [5].

Screening Mammography

A typical screening mammographic examination includes craniocaudal and mediolateral oblique views of both breasts with strict adherence to patient positioning, examination technique, and quality. Under ideal circumstances, images are acquired with rapid throughput and batch interpreted in an uninterrupted environment, and the results are mailed to the patient and referring physician. In approximately 10% of patients, an abnormality is detected at screening mammography, and a patient is recalled for diagnostic imaging, which consists of additional mammographic views, ultrasound, or both under direct supervision of the radiologist. Recall rates are generally higher after the initial examination compared with subsequent examinations and are typically higher among younger than among older patients [6], likely owing to differences in breast density.

Efficacy of Screening Mammography

Determination of the efficacy of screening mammography is extremely complex. As described by Kopans [7], establishing benefit of evidence, such as improved survival or diagnosis of cancer at an earlier stage, is different from proof of evidence, such as decreased breast cancer mortality. Benefit of evidence can be influenced by bias, which must be minimized to establish proof of evidence. Important forms of bias include lead-time bias, length-bias sampling, and selection bias. As it pertains to screening mammography, lead-time bias is an apparent increase in survival time discerned by identifying cancer earlier by screening but with no alteration in the date of death. Length-bias sampling, also known as prognostic selection bias, refers to the likelihood that slower-growing, indolent cancers will more often be detected with screening mammography than will rapidly growing, aggressive cancers, resulting in better apparent outcomes. Selection bias suggests that healthy women are more likely to participate in screening, also resulting in better apparent outcomes.

The effects of bias can be minimized with prospective randomized controlled trials (RCTs), which in this case seek to establish the statistical significance of screening mammography in reducing death from breast cancer in a randomly selected population that is invited to undergo screening compared with a population that is not invited to undergo screening. To date, eight RCTs, most of which were population based, have been completed to assess the efficacy of screening mammography. Critical features of the RCTs included large sample sizes and long follow-up periods. The trials varied slightly in subgroup ages, techniques compared with mammography, and interval follow-up, but the overall results of the RCTs suggest a statistically significant 20% reduction in breast cancer mortality in the screening population 40–74 years old, including a 22% reduc-
tion among women 50–74 years old and a 15% reduction among women 40–49 years old [4]. There is also a belief that these numbers are conservative estimates of the true value of screening mammography with improvement in techniques and technology [4]. The findings of the RCTs are summarized in Table 1 [8].

The first two RCTs were the Health Insurance Plan (HIP) trial in New York in 1963 and the Malmö trial in Sweden in 1976. In the HIP trial, 18 years after study enrollment, the breast cancer mortality in the intervention group was approximately 25% lower than that in the control group [9]. The Malmö trial revealed an approximately 36% decrease in breast cancer mortality in the intervention group after 19 years [10]. The largest RCT performed was the two-county trial in Sweden, which invited a total population of 163,000 women 40–74 years old and divided them into screening and nonscreening groups. This trial was also notable for performing only single-view mammography (mediolateral oblique view), for screening women 40–49 years old every 2 years and women 50 years old and older every 3 years, and for its long-term follow-up analysis lasting 29 years. The findings revealed a highly significant 30% reduction in breast cancer mortality in the population invited to undergo screening. Furthermore, reduction in breast cancer mortality lasted over the duration of the follow-up period, and the absolute benefit of an invitation to screen improved with time [11]. Most of the breast cancer deaths prevented occurred more than 10 years after the beginning of screening, highlighting the importance of long-term follow-up [4].

The Canadian National Breast Screening Studies (CNBSS) evaluated women 40–49 years old (CNBSS-1) and 50–59 years old (CNBSS-2) [12, 13]. The goal of CNBSS-1 was to test the efficacy of screening mammography with either 4 or 5 years of annual mammography and clinical breast examinations (CBE). The goal of CNBSS-2 was to evaluate the efficacy of screening with mammography and CBE versus CBE alone with either 4 or 5 years of annual examinations.

The trial concluded that more small, node-negative tumors were detected with screening with annual mammography and CBE than were detected with CBE alone, but there was no effect on the death rate after 7 years of follow-up [12, 13]. It is important to note that the blinded randomization in this trial was flawed. Randomization was done only after volunteers accepted invitations to the trial and after CBE had already been performed. In addition, there were serious concerns over the suboptimal quality of mammograms obtained [2].

### Limitations of Screening Mammography

Screening mammography reduces breast cancer mortality, but it has drawbacks. Some of these limitations include ionizing radiation exposure, financial cost, false-positives findings, and anxiety associated with false-positive results and recalls. The concept of overdiagnosis that is often discussed also must be addressed. Radiation exposure in two-view screening digital mammography is estimated at approximately 4.7 mGy, which corresponds to a lifetime attributable risk of five to seven cases of breast cancer per 100,000 and 1.3–1.7 breast cancer deaths per 100,000 [14]. At a similar dose, however, the number of lives saved has been estimated at 350 per 100,000 [15]. Critics of mammography also refer to the high false-positive rate, because there is considerable overlap in the appearance of cancer and benign lesions. Approximately 10% of patients are recalled for additional views and fewer than 2% of women screened undergo biopsies, 30–40% of which result in a cancer diagnosis [16]. The benefit, however, is earlier diagnosis of otherwise advanced breast cancer and reduction in mortality. Recall imaging and need for biopsy to exclude cancer may cause anxiety in some patients. However, although there may be increased short-term anxiety, there is no measurable health utility decrement and no decrease in patients’ intentions to undergo future screening as a result of this potential anxiety [17].

Overdiagnosis of breast cancer is the concept of diagnosing and treating breast cancers that may never become clinically apparent or affect patient lives, such as low-grade ductal carcinoma in situ. In one study [18], it was estimated that as many as 31% of breast cancer diagnoses among U.S. women older than 40 years were related to overdiagnosis. Critics suggest, however, that the data and design of the study were flawed, and it is more likely that the overdiagnosis rate is in the range of 1–10% after accounting for preexisting trends and lead time [4]. Given that it is often not possible to select out the less clinically significant cancers on the basis of imaging findings, and given that RCTs have shown statistically significant mortality reduction, it is important to view overdiagnosis in the appropriate clinical context. That is, mortality reduction is present despite the possibility of overdiagnosis.

### Table 1: Randomized Controlled Trials of Screening Mammography

<table>
<thead>
<tr>
<th>Study</th>
<th>Age Range (y)</th>
<th>No. of Patients</th>
<th>Relative Risk</th>
<th>95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Insurance Plan</td>
<td>40–64</td>
<td>60,995</td>
<td>0.78</td>
<td>0.81–1.00</td>
</tr>
<tr>
<td>Malmö</td>
<td>43–70</td>
<td>60,076</td>
<td>0.78</td>
<td>0.65–0.95</td>
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<tr>
<td>Swedish two county</td>
<td>40–74</td>
<td>133,065</td>
<td>0.68</td>
<td>0.59–0.80</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>45–64</td>
<td>44,286</td>
<td>0.78</td>
<td>0.62–0.97</td>
</tr>
<tr>
<td>Stockholm</td>
<td>40–64</td>
<td>60,117</td>
<td>0.90</td>
<td>0.63–1.28</td>
</tr>
<tr>
<td>Canadian National Breast Screening Service 1</td>
<td>40–49</td>
<td>50,430</td>
<td>0.97</td>
<td>0.74–1.27</td>
</tr>
<tr>
<td>Canadian National Breast Screening Service 2</td>
<td>50–59</td>
<td>39,405</td>
<td>1.02</td>
<td>0.78–1.33</td>
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<tr>
<td>Gothenburg</td>
<td>39–59</td>
<td>51,611</td>
<td>0.79</td>
<td>0.58–1.08</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.80</td>
<td>0.73–0.86</td>
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</tbody>
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whole, the mortality reduction benefit of screening mammography outweighs the drawbacks.

**Screening Modalities**

Although the original RCTs were performed with film-screen mammography, the current standard for mammography is full-field digital mammography (FFDM). Because image acquisition and display are separated in FFDM, both features can be optimized because contrast can be adjusted and display optimized. In 2005, the Digital Mammographic Screening Trial sought to quantify the differences in film-screen mammography and FFDM over a 2-year period with a 50,000-patient enrollment [19]. The investigators concluded that digital mammography was superior to film-screen mammography in the detection of breast cancer in premenopausal and perimenopausal women and in women with dense breasts. Though breast cancer mortality was not assessed, it can be inferred that digital mammography may decrease mortality by affording earlier detection. Notably, no statistically significant difference in diagnostic utility was observed between film-screen mammography and FFDM in the general population or other subgroups. Nevertheless, digital mammography has additional advantages, including improved access and transmission of images, lower average radiation dose, and the ease of applying computer-aided detection [19]. Although increased cost was a significant concern in the conversion to digital mammography, currently more than 97% of accredited mammography units in the United States use FFDM [20].

Although mammography is the only screening modality proven in RCTs to be associated with a decrease in breast cancer mortality [6], there are potential roles for adjunctive screening with other imaging modalities. Because mammographic images are 2D, both suspicious and benign findings can be obscured by adjacent structures with similar attenuation, particularly in dense breast tissue. At the same time, overlapping (benign) structures may cause pseudolesions. These phenomena lead to both decreased sensitivity and an increased rate of false-positive findings. Digital breast tomosynthesis (DBT) is an emerging technology developed to solve this problem by projection of multiple low-dose x-rays through an angled arc around compressed breast tissue. The projections are reconstructed into 1-mm cross-sectional slices of breast tissue, which can be viewed sequentially, as on a CT scan [5].

The U.S. Food and Drug Administration approved the use of tomosynthesis for two-view mammography in 2011. DBT has been found to reduce the false-positive rate and increase the rate of detection of invasive cancers [21] and the PPV [22]. With DBT, it may also be possible to more readily differentiate masses and asymmetry, characterize margins, and detect architectural distortion. Concerns about DBT include increased radiation dose, limited perception of microcalcifications, a paucity of long-term data, and an increase in interpretation time, data requirements, and cost.

The Oslo Tomosynthesis Screening Trial is the largest DBT study to date, enrolling more than 12,000 patients. In the study, standard two-view FFDM images are compared with a combination of two-view DBT and two-view FFDM images [21]. The results show a 40% increase in detection of invasive cancer, a 27% increase in cancer detection rate, and a 15% decrease in recall rate. No increase in detection of ductal carcinoma in situ was observed, addressing concerns about the possibility of overdiagnosis. Not surprisingly, the interpretation time was twice as long with combined DBT and two-view FFDM [21].

The Tomosynthesis Mammographic Screening Trial is a randomized clinical screening trial underway at more than 30 sites for 5 years. The primary aim is to compare tomosynthesis and digital mammography with respect to numbers of advanced cancers detected. Advanced cancers are considered all tumors diagnosed at stage II or higher and all tumors larger than 6 mm that have markers suggesting they are aggressive [23]. One concern about the trial is that there will be no control group of unscreened women, limiting the assessment of breast cancer mortality.

The uses of breast ultrasound for targeted evaluation of a clinical symptom and further evaluation of an abnormal mammographic finding are well established. However, screening whole-breast ultrasound is not universally accepted. Potential indications for screening breast ultrasound include being at high risk and unable to undergo screening MRI and dense breast tissue screening of women with extremely dense (10% of women) or heterogeneously dense (40% of women) breasts [24]. The sensitivity and specificity of mammography decrease with denser breast tissue, going from 87% and 97% among women with fatty breasts (Fig. 1) to 63% and 89%, among women with dense breasts [25] (Fig. 2). In addition,
dense breast tissue has been reported to be associated with increased risk of development of breast cancer [26]. Twenty-four states have enacted breast density notification laws [27], which require radiologists to inform patients if they have dense breast tissue and advising them to discuss these findings with their referring physicians. The most important limitation of screening breast ultrasound is its unacceptably high false-positive rate [28]. Other drawbacks include operator dependence and increase in costs and time.

The American College of Radiology Imaging Network (ACRIN) 6666 trial was conducted to investigate the added effects of supplemental annual screening with handheld ultrasound performed by expert physicians in conjunction with screening mammography [26]. The trial also evaluated the effects of screening breast MRI in a subset of women who had three consecutive rounds of negative results of screening mammographic and ultrasound examinations. The participants had dense breast tissue and increased risk of breast cancer. Thus, there was no control group for assessing the effects on mortality, and there was no assessment of women at average risk. On average, 4.3 additional cancers were detected per 1000 women screened. However, recommendations for follow-up (BI-RADS category 3) and biopsy were also increased with decreased PPV. Furthermore, the decrease in PPV persisted during the incident screening rounds.

Overall, ACRIN 6666 showed the number of screening examinations needed to detect one cancer with mammography to be 127, with screening ultrasound after negative mammographic findings to be 234, and with screening MRI after negative results of screening mammography and ultrasound to be 68 [26]. During the screening MRI round, 14.7 additional cancers were found per 1000 women screened, approximately four times as many as for the addition of ultrasound to screening mammography. The trial investigators concluded that though additional cancers are detected with the addition of screening ultrasound, even more cancers are detected with screening MRI. Furthermore, there is no need for screening ultrasound if screening MRI is performed. However, either examination must be performed in conjunction with screening mammography [26]. In considering whether a facility should perform screening ultrasound, the benefits of additional cancer detection must be weighed against the drawbacks of false-positive results and additional procedures.

MRI certainly has a role in screening, particularly of patients at high risk with BRCA mutations, a family history of breast cancer (lifetime risk ≥ 20%), and a history of mantle radiation [29]. A more complete discussion of screening MRI and other modalities, such as automated breast ultrasound and molecular breast imaging, is beyond the scope of this chapter.

**Screening Mammography Recommendations and Controversy**

Differing interpretations of the data from the RCTs have resulted in different screening recommendations by different organizations. A central topic of debate relates to the age-specific benefits of screening mammography and at which age screening should begin. The age of 50 years is often arbitrarily selected as the division between premenopausal and postmenopausal status. Although there is improved sensitivity, specificity, PPV, and mortality reduction with increasing age, mammographic screening of women 40–50 years old reduces mortality 15% according to RCT results and as much as 24–29%, according to several other studies [30, 31]. The American College of Radiology [32], American Cancer Society [33], American College of Obstetricians and Gynecologists [34], and National Comprehensive Cancer Network [35] all call for routine annual screening beginning at the age of 40 years. The U.S. Preventive Services Task Force (USPSTF) [36] recommends routine biennial screening for women 50–74 years old.

The American College of Radiology offers additional recommendations for earlier screening mammography for populations at high risk [37]. The USPSTF, an independent volunteer panel in the fields of evidence-based medicine and public health, recommends biennial screening for women 40–49 years old who have no risk factors other than being in the target age group.

![Fig. 2—Screening mammograms of extremely dense breast. Mammographically occult cysts are present but obscured by dense tissue. A, Craniocaudal projection. B, Mediolateral oblique projection.](image-url)
of preventive medicine and primary care, most recently issued a C grade for screening mammography before the age of 50 years [38]. A C grade suggests that there is at least moderate uncertainty that the net benefit is small [39]. The task force therefore recommends that the decision about screening before the age of 50 years “be an individual one and take patient context into account, including the patient’s values regarding specific benefits and harms” [36].

The task force recommendations not to start routine screening until age 50 has drawn considerable criticism from experts in different organizations. Of note, a C recommendation by the USPSTF may result in denial of insurance coverage, limiting access to screening for women younger than 50 years, even if the woman wants to undergo screening after considering her personal values regarding specific benefits and harms. The conclusions of the USPSTF may be flawed because of questionable data analysis techniques, including observational modeling and meta-analyses of theRCTs—which tend to underestimate the benefit of screening of younger patients and overestimate the drawbacks associated with screening [4]—and overreliance on potentially flawed studies such as the CN-BSS [2]. Notably, no radiologists, oncologists, surgeons, or pathologists are part of the task force [40]. It has been estimated that considerably fewer lives would be saved if the USPSTF guidelines were followed [41]. As the breast cancer screening debate continues, it remains paramount for radiologists to remain experts on the subject and to educate patients about the benefits and drawbacks of breast cancer screening so that they are able to make informed decisions about their care.

REFERENCES
15. Hauge IH, Pedersen K, Olerud HM, Hole EO, Hofvind S. The risk of radiation-induced breast cancers due to biennial mammographic screening in women aged 50–69 years is minimal. Acta Radiol 2014;55:1174–1179