# Screening for Breast Cancer

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## Introduction

Screening is defined as the presumptive identification of unrecognized disease by means of tests, examinations, or other procedures that can be applied rapidly. The World Health Organization outlines a number of important prerequisites to justify implementation of an effective screening program [1]:

- Target cancer should have a high prevalence and be associated with a high mortality and morbidity.
- The screening test has to be safe, effective, and acceptable.
- The compliance of the target population in attending initial screening and diagnosis and in follow-up visits has to be high.
- Effective treatment should be available to be delivered to screen positive cases.

An ideal screening test is one which detects a high percentage of cancers [sensitivity] and has low false-positive rate so that disease-free women are not subjected to unnecessary diagnostic tests. A high prevalence of cancer in the target population being screened is an important prerequisite since even the best screening test will be ineffective when deployed in a population with a low prevalence of cancer. National and/or professional or regulatory body guidelines in individual countries for cancer screening should be based on cancer incidence and prevalence statistics. These need to address at what age and how frequent screening needs to be performed; additional influencing factors to be taken into consideration will also include cost-effectiveness of screening strategy. Quality control and assurance to ensure effectiveness, accuracy, and consistency has to be applied to and monitored for health-care personnel performing and interpreting these tests as well as for the equipment used for this purpose. A tested and a robust referral system for women testing positive for cancers needs to be in place. An information system that can send out invitations for initial screening, follow-up visits, and repeat screening at predetermined intervals is a must to ensure success [1].

## Mammographic Screening for Breast Cancer

Randomized clinical trials study the efficacy of a screening methodology; efficacy is thus measured in experimental studies. The effectiveness of a screening modality on the other hand is defined as the extent to which a specific intervention when deployed in routine circumstances does what it is supposed to do in a specific population [2]. 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 77,080 women aged 40–74 years were randomized in geographical clusters and invited to be screened, and 55,985 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 [3]. 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 [3].

A meta-analysis of all the randomized clinical trials [RCTs] 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

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years [4]. How do the results of these RCTs translate to clinical practice, i.e., service screening, effectiveness versus efficacy. This has been studied by Tabar and others. In the age group of women between 20 and 69 years, there were 6,807 who were diagnosed with breast cancer over a 29-year period in two counties in Sweden and 1,863 breast cancer deaths [5]. 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 1988–1996 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 %. The reason for a more significant mortality reduction in service screening compared to RCTs 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 RCTs 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 Two-County trial was 33 months for women aged 50–74 years are additional factors that lead to better results in service screening [5]. A review of seven population-based community screening programs in the USA that included 463,372 women, the sensitivity of mammography was 75 % and the specificity was 92.3 %. Sensitivity was similar to what was shown in RCTs. Breast density contributes to the overall sensitivity with only 63 % sensitivity noted in women with dense breasts and 87 % in women with entirely fatty breasts [6].

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. The controversy regarding benefits of screening mammography and the debate as to when breast cancer screening should commence, how often to screen, 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 the use of biannual mammography for women age 50–69 [7].

## Recommendations for Screening for Breast Cancer with Imaging in the USA [8]

In the USA, the Society of Breast Imaging and the Breast Imaging Commission of the American College of Radiology recommends women at average risk to undergo annual screening mammography starting at age 40 [8]. The recommendations for screening women at average and elevated risk are outlined in Table 2.1. The recommendations are based on presence or absence of risk factors.

**Table 2.1** The American College of Radiology and the Society of Breast Imaging recommendation for breast cancer screening with imaging

| Population to be screened | Age to commence screening |
|---|---|
| *Women at average risk* | |
| Annual screening mammograms | 40 years |
| *Women at an elevated risk* | |
| (a) Women with certain BRCA 1 or BRCA mutations or those who have not been tested but have first degree relatives[Mother, sisters, daughters] with such proven mutations | Yearly starting by 30 years of age but not before 25 |
| (b) Women ≥ 20 % lifetime risk of breast cancer based on maternal or paternal family history | Yearly starting by 30 years of age but not before age 25 or 10 years before diagnosis of youngest affected relative whichever occurs later |
| (c) Women with mothers or sisters with premenopausal cancer | Yearly starting by 30 years of age but not before 25 or 10 years before diagnosis of youngest affected relative whichever occurs later |
| (d) Women with history of mantle radiation usually for Hodgkin's lymphoma received between 10 and 30 years | Yearly starting 8 years after therapy but not before age 25 |
| (e) Women with biopsy proven lobular carcinoma in situ, atypical lobular hyperplasia, atypical ductal hyperplasia, ductal carcinoma in situ, invasive carcinoma, ovarian carcinoma | Yearly from the time of diagnosis regardless of age |

Data from Lee et al. [8]

Annual screening mammography is recommended for women starting at the age of 40 years based on overwhelming evidence showing a benefit with significant mortality rate reduction. In those at risk screening at an earlier age is recommended [8]. There are no data from large clinical trials on the effectiveness of screening for breast cancer in the high-risk population. Screening is recommended in young women with an elevated risk based on the assumption that the risk for developing breast cancer is same or higher than women 40 and older therefore justified to offer screening. Women with personal history of breast cancer have a 5–10 % risk of developing a second cancer in the first 10 years after diagnosis, and those with ovarian cancer have a three- to fourfold increased risk for development of breast cancer; hence, it is reasonable to subject these women to annual mammographic surveillance from the time of diagnosis of breast or ovarian cancer. Those women who have received mantle radiation between the ages of 10 and 30 years have a significantly elevated risk of developing breast cancer; 35 % by the age of 40 years has been reported [8]. Histopathologies that indicate an increased risk for developing breast cancer include lobular

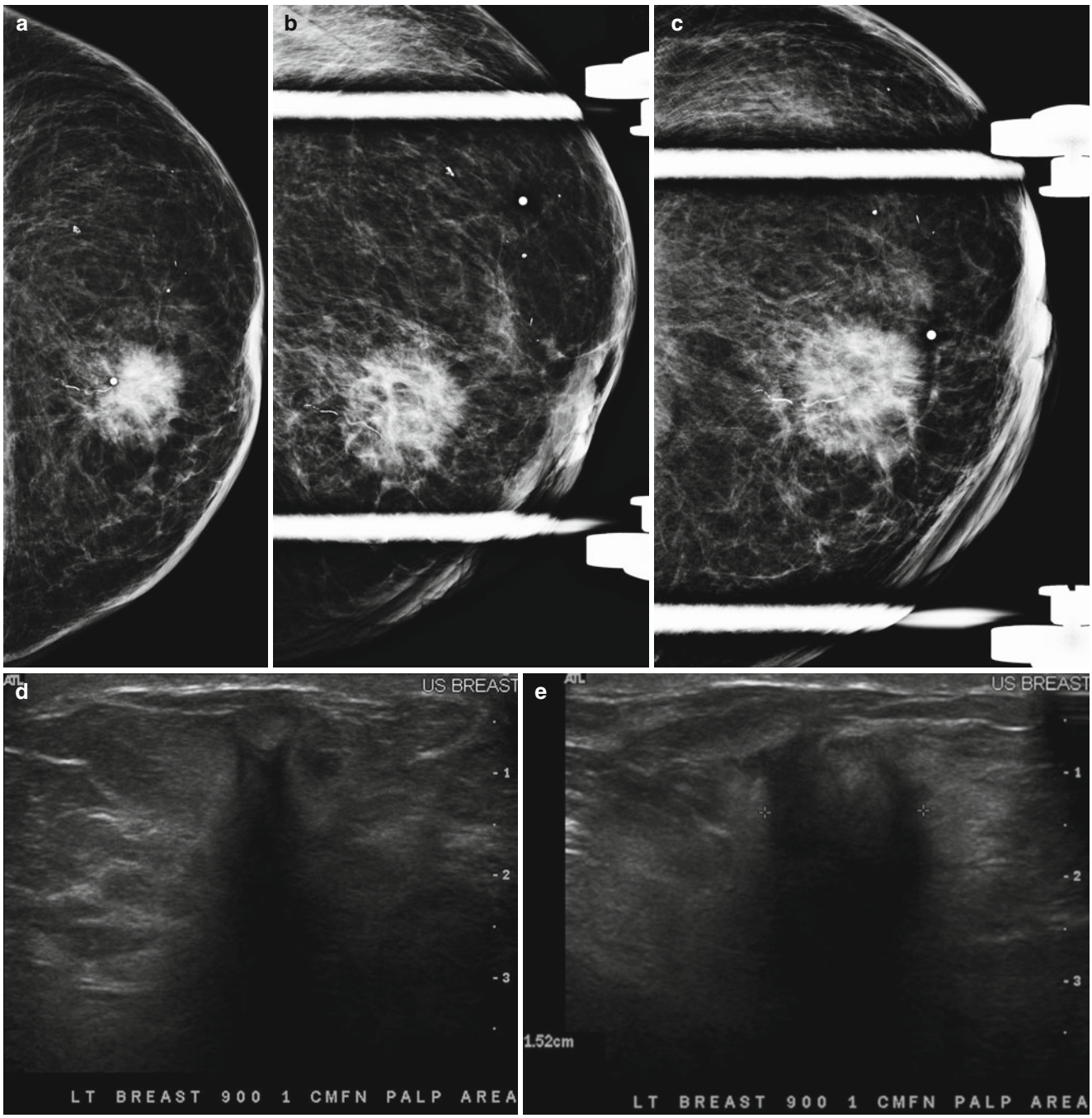


**Fig. 2.1** (**a**–**e**) A 95-year-old with a palpable lump in left breast. (**a**) Left mediolateral view shows a 1.5 cm irregular mass. (**b**, **c**) Spot compression views show a spiculated mass. (**d**, **e**) Radial and antiradial ultrasound images demonstrate a 1.5 cm mass with malignant features. Histology showed an invasive ductal carcinoma

neoplasia, and atypical ductal hyperplasia is a justifiable indication to commence screening before the age of 40 years. Hereditary breast cancer is caused by several genetic mutations. BRCA 1 mutation carries a 19 % risk for breast cancer by the age of 40 years and a lifetime risk of 85 %, BRCA 2 mutation carries a similar lifetime risk, but cancer tends to occur at a later stage, and screening should start by 30 years of age [8]. Although there are no specific recommendations as to when screening should be stopped, it is generally desirable to offer screening mammograms until there is at least a 7 years of life expectancy remaining. In our practice occasionally we receive requests for screening in women in their 80s, and we had recently a case of an unsuspected cancer found on a screening mammogram in a 95-year-old woman (Fig. 2.1a–e). It is also not uncommon to find larger cancers in women who have skipped several years of undergoing screening mammograms (Figs. 2.2a–c and 2.3a–d).

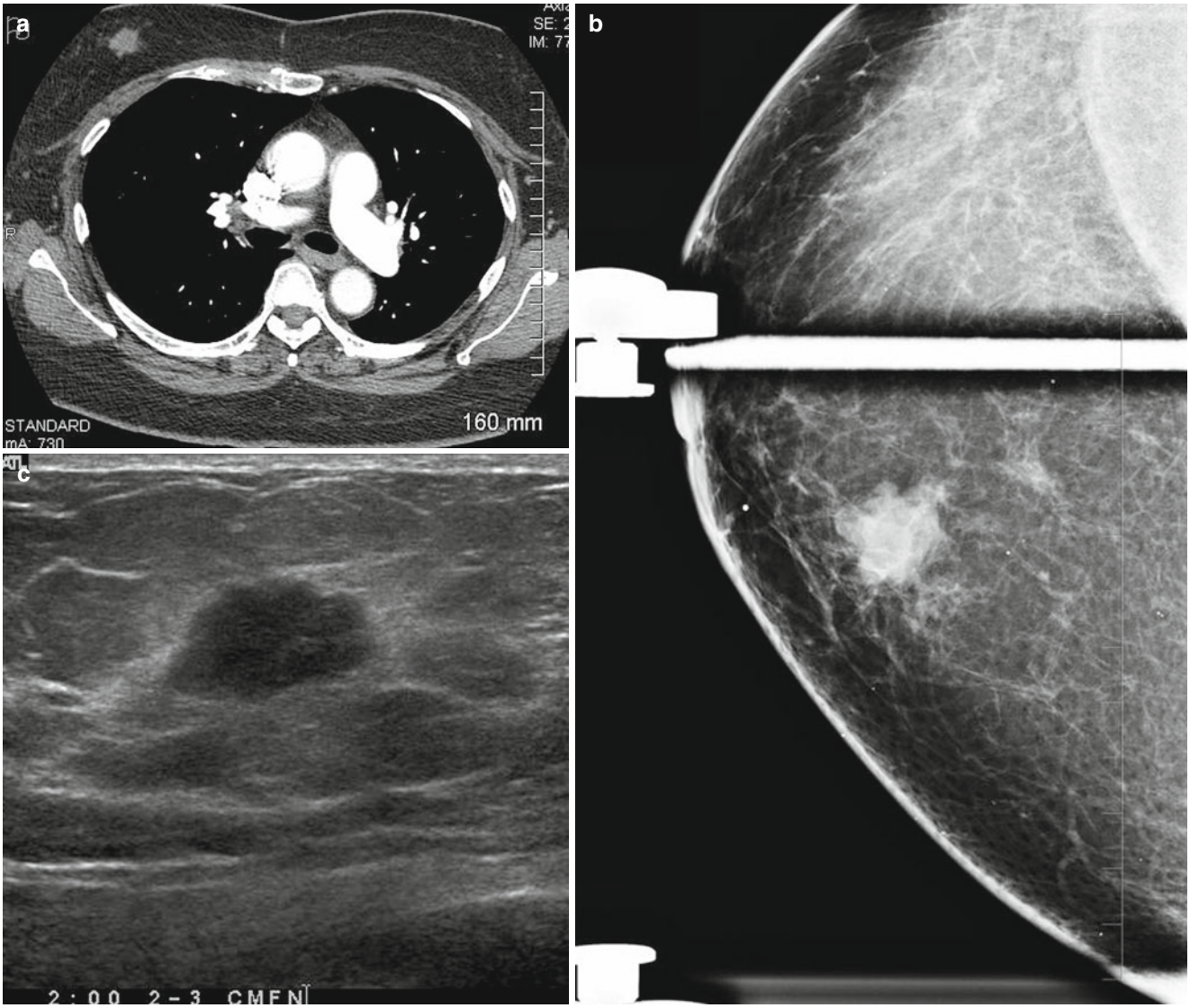


**Fig. 2.2** (**a**–**c**) A 60-year-old who had not undergone screening mammogram in 4 years. (**a**) CT pulmonary angiogram performed for chest pain reveals a 2 cm mass in right breast. (**b**) Spot compression craniocaudad view of the right breast shows an irregular mass in the inner right breast. (**c**) Sonography reveals a 2 cm mass with irregular borders suggestive of malignancy. Histology showed an invasive ductal carcinoma

## Limitations and Potential Harm from Screening Mammography

There are some who question the benefit of screening mammography. Controversies regarding the false positives resulting from mammography, the benefit of performing screening in women in their 40s, and whether mammography overdiagnoses cancer, leading to unneeded treatment interventions, are some of the issues. Approximately 95 % of women with abnormalities on the screening mammogram do not have breast cancer [9]. In a review commissioned by the US Preventive Services Task Force, the sensitivity of mammography for a 1-year screening interval was found to be 71–96 % and substantially lower for women in their 40s. The specificity was 94–97 %; it has to be borne in mind that false positive meant recall of the patient for additional views and resolution of the abnormality in most instances without the need for a biopsy or surgical intervention. The positive predictive value of one-time mammography ranged from 2 to 12 % for abnormal results requiring further evaluation and from 12 to 78 % for abnormal results requiring biopsy. There is continued increase in predictive value with age [10].

### Screening Women in Their 40s

The mammographic sensitivity is lower in women in their 40s mostly due to increased prevalence of dense breast tissue in this age group. The incidence of cancer in this age group is lower about 140 per 100,000 compared to 500 per

100,000 in women older than 50 years. An evidence-based analysis from Canada concluded that there is Level 1 evidence that screening mammography in women aged 40–49 years at average risk for breast cancer is not effective in reducing mortality [11]. The Canadian Task Force of Preventive Services supports neither the inclusion nor the exclusion of screening mammography for women in their 40s. In the USA there is disagreement among nation organizations regarding the benefit of screening in their 40s. The National Institutes of Health, the American Association for

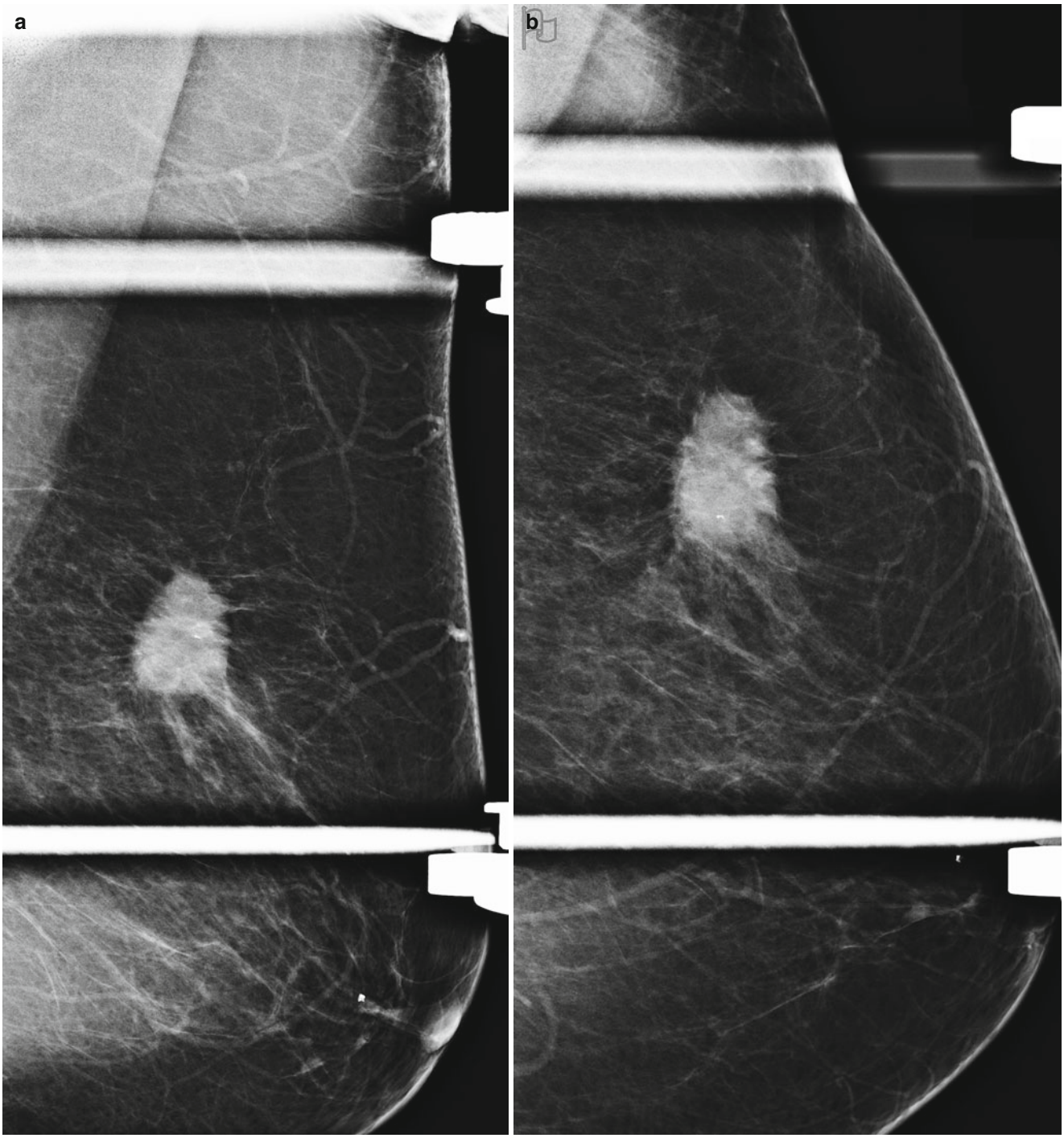


**Fig. 2.3** (**a**–**d**) A 72-year-old woman not screened in 6 years. (**a**) Left breast mediolateral oblique view with spot compression demonstrates an irregular spiculated mass. (**b**) Left breast craniocaudad view with spot compression. (**c**, **d**) Left breast ultrasound shows a 3 cm mass with malignant features. Histology showed an invasive ductal carcinoma

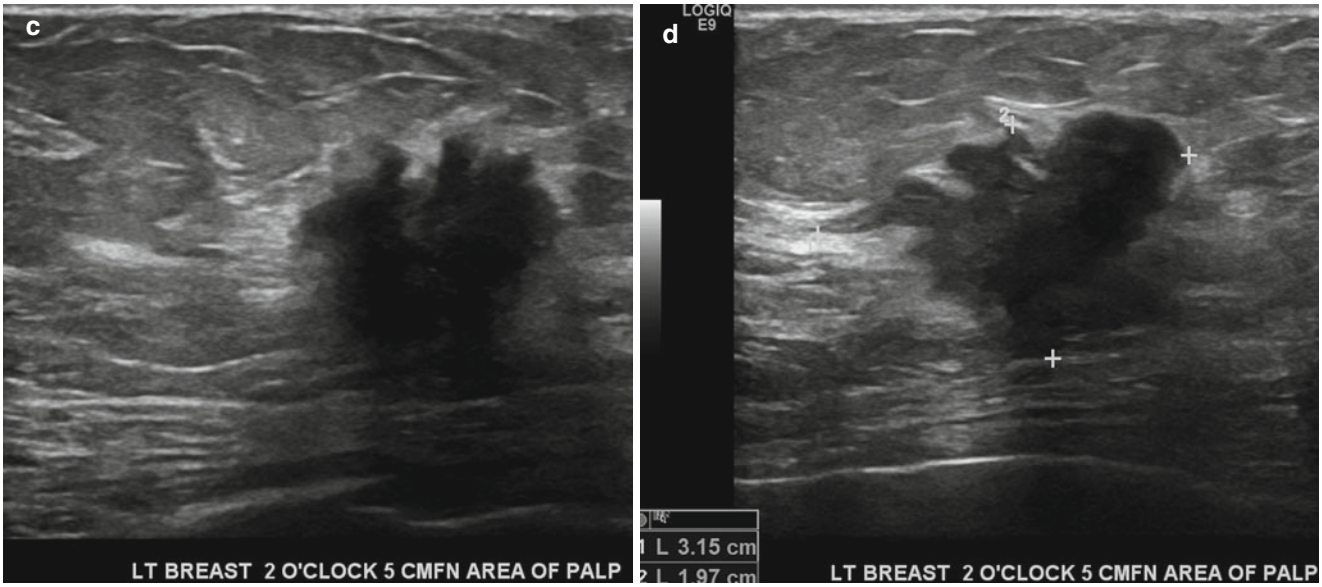


**Fig. 2.3** (continued)

Cancer Research, and the American Academy of Family Physicians do not recommend screening women in their 40s, whereas the National Cancer Institute, the American Cancer Institute, the American Cancer Society, the American College of Radiology, and the American College of Obstetricians and Gynecologists do.

Although women in their 40s have denser breast and a lower incidence of breast cancer accounting for decreased sensitivity of mammography, in this age group, women tend to have faster growing cancers [9]. 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 four Swedish trials for women in this age group reported a 23 % mortality reduction at randomization achieved from a median trial time of 7 years, a median follow-up of 12.8 years, and a screening interval of 18–24 months [12]. About 18 % of cancers both in situ and malignant are reported in women between the ages of 40 and 49 in the USA. A longitudinal cohort study of 1977 women in this age group who had primary breast cancer was undertaken over an 18-year period. A significant increase in the percentage of mammography-detected cancer was seen over time (28–58 %), and a concurrent decline in patient- and physician-detected breast cancer (73–42 %), with a consequent increase in lower stage disease detection and decrease in higher stage disease [13]. A study of 31,814 average-risk women found that the positive predictive value for further evaluation was 1–4 % for women aged 40–49 years, 4–9 % for women aged 50–59 years, 10–19 % for women aged 60–69 years, and 18–20 % for women aged 70 years or older [14].

## Harms of Mammography Screening

Overdiagnosis refers to diagnosis of cancers particularly DCIS [ductal carcinoma in situ] which may have never progressed to an invasive stage and resulted in death. Such patients would have undergone surgery, chemotherapy, and/or radiotherapy with consequent harm to women [15]. The presumptive evidence for "overdiagnosis" is suggested by the fact that breast cancer diagnosis in the screened group remained persistently higher even after many years when compared to the control group of non-screened women in large randomized clinical trials. This assertion is contentious because diagnosing more breast cancer cannot be somehow construed to be a bad thing, and mortality rate reduction which has been shown beyond question should be the one and only benchmark of success of screening mammography. Despite the criticism that mammography may find DCIS that may never become invasive is a moot point since the same detractors of screening have no answer to the fact that we do not know or have a means of determining which cases of DCIS will progress on to the invasive stage and which ones do not.

On the other hand two observational studies among women who underwent the current standard technique of a two view mammography and included millions of person years of observation reported a much stronger mortality reduction than what has been shown in RCTs of 30–40 % for women in their 40s. In fact RCTs tend to underestimate the benefit from screening mammography because it includes all women in the screened group who are invited to be screened including those who do not actually end up getting a

mammogram and do not exclude women in the control group who may end up getting a mammogram outside the trial. As has been previously pointed out, in several RCTs, the mammographic quality was not comparable to the current standards, and one-view mammogram only was obtained which limits the cancer detection rate [16].

Interpretive accuracy varies among radiologists, especially in mammography. A study that examined the relationship between radiologists' confidence in their assessments and their accuracy in interpreting mammograms found that confidence in mammography assessments was associated with better accuracy, especially for low-volume readers. Asking for a second opinion when confidence in an assessment is low may increase accuracy [17]. The other significant potential harm resulting from screening mammography is from false-positive results that lead to unnecessary patient anxiety and unneeded breast biopsies. Although this is a shortcoming of mammography, it is a given that any screening modality is bound to have some false positive as no test is perfect. However, much can be done to minimize the false positives, and the following section addresses ways of achieving this objective.

The most recent review of the benefits and potential harms of breast cancer screening was performed by an independent panel in the UK [18].The review was performed based on the UK screening program which offers screening for women 50 years or older once every 3 years. The review included assessment of the relative mortality benefit in women who were invited to be screened and looked at 11 randomized clinical trials with a 13-year follow-up, a mortality rate reduction of 20 % was noted, and the benefit is higher among women who underwent screening as opposed to those who were invited to and did not undergo screening. This increased benefit is difficult to ascertain. This panel looked only at RCTs that were conducted 20–30 years ago, and since then there has been significant improvement in both the quality of mammographic technique and interpretive accuracy. More recently published studies have been observational studies, namely, ecological studies, case control studies, and incidence-based mortality studies that showed a greater benefit but were not included in the review. The absolute mortality benefit is variable but was estimated to be one breast cancer death prevented for 180 women screened [18].

The overdiagnosis rate is hard to quantify and varied from 0 to 36 %. Of more importance is the fact that neither the woman nor her physician has any means of knowing which of the screen detected DCIS or invasive cancer is an "overdiagnosed case." If it was somehow possible to distinguish at screening those cancers that would not lead to death if left untreated from those cancers that would, the overdiagnosis problem would be solved. Even DCIS that is often diagnosed on screening does not inevitably equate to overdiagnosis since 10 % of DCIS leads to subsequent development of invasive cancer even when treated with wide local excision [18]. The sources of data for overdiagnosis are few, and data are mostly based on indirect estimates. Data from three RCTs that did not screen the control group and followed them for several more years showed an estimated rate of overdiagnosis in order of 11 % from a population perspective and about 19 % from the perspective of a woman invited to screening. It has been estimated that for every 10,000 women invited to screening from 50 years onward for 20 years, there will be 681 cancers, estimated overdiagnosis rate is 129 cases, but 43 deaths from breast cancer will be prevented. An expert opinion panel after an exhaustive review of data opined that benefits of screening and benefits of better treatment are independent. Uncertainty as to whether some of the benefits in mortality rate reduction are due to better treatment is not a justification to stop screening [18].

The benefits of screening mammography have been questioned, and it has been suggested that RCTs were fundamentally flawed in design and that the results are not scientifically valid [19, 20]. An opposing view on the benefits of screening mammography that was recently published claimed that a review of clinical trials with adequate randomization did not show a statistically significant mortality rate reduction at 13 years [20]. The total rate of lumpectomies, mastectomies, and radiation therapy was increased in the screened group. When seven trials including 600,000 women were reviewed, the mortality rate reduction was seen to be only 15 % with a significant overdiagnosis and overtreatment which was estimated to be at 30 %. These authors concluded that for every 2,000 women invited for screening throughout 10 years, one breast cancer death will be prevented and ten healthy women will be treated unnecessarily. About 200 women will be subjected to anxiety and distress due to false-positive findings [20].

## Nonmammographic Screening for Breast Cancer

Mammography is still the gold standard for breast cancer screening of the general population [2–5].

Breast MRI and whole breast ultrasound survey have been shown to be of greater sensitivity than mammography in the early detection of breast cancers [9, 21–39]. However, unlike mammography, these two modalities have not been proved to reduce breast cancer mortality. Proof of mortality rate reduction will require a randomized controlled clinical trial involving a large number of women receiving screening with the new modality, who will then have to be followed for at least 15 years and be matched with a control group of women who

receive the current standard care. The new modality being tested would have to show mortality rate reduction over and above what has been achieved with screening mammography; this is unlikely to be the case anytime in the near future [9]. At the present time, ultrasound and MRI are being used to supplement mammography for breast cancer screening in women with an elevated risk for cancer. The role of ultrasound for this reason is discussed next; the role of MRI in breast cancer screening is discussed in the chapters on breast MRI (Chaps. 8 and 9). A brief discussion on two additional examinations that have been used as supplemental tools or primary means for screening, namely, breast self-examination and clinical breast examination, follows.

## Supplemental Screening with Ultrasound in Women with an Elevated Risk for Breast Cancer

In North America, breast ultrasound has been predominantly used as a targeted examination for a clinical or mammographic problem, whereas in Europe whole-breast ultrasound survey has been more prevalent [26]. It is not uncommon to identify incidental nonpalpable cancers during diagnostic sonographic evaluation of a mammographic or physical finding [26]. Mammography is known to have a limited sensitivity in women with dense breast tissue. The use of breast ultrasound as a supplemental modality for breast cancer screening has been studied in women with dense breast tissue and in those with an elevated risk for breast cancer. Dense breast tissue is by itself considered a risk factor for breast cancer [27]. It has been suggested that in women with a threefold relative risk compared with women without any known risk factors, it is enough to be categorized in the high-risk group [29]. To date, none of the major professional societies in the USA or elsewhere recommend the use of screening ultrasound for breast cancer.

A systematic search and review of studies involving mammography and ultrasound performed for screening of breast cancer found 6 cohort studies, of which only two had follow-up on patients with negative or benign findings. Screening ultrasound performed in women with American College of Radiology breast density types 2–4 identified primarily invasive cancers in 0.32 % of women. The mean tumor size was 9.9 mm, and 90 % of the cancers were node negative. Biopsy rate was high at 2.3–4.7 %, with positive predictive value of 8.4–13.7 % for those biopsied because of an abnormal finding on the ultrasound examination. The added benefit of using ultrasound to screen for breast cancers in women with a negative mammogram might be lower in women aged 50–69 years [23].

The most notable and the largest clinical trial of screening ultrasound to date is the American College of Radiology Imaging Network trial 35 (ACRIN 6666). This study was a prospective multicenter trial randomized to a group receiving ultrasound and mammographic screening and one to mammographic screening alone to compare the diagnostic yield of performance of breast ultrasound and mammography versus mammography alone in women with elevated risk of cancer [22].The criteria used in this study to determine an elevated risk for breast cancer included a personal history of breast cancer, prior atypical biopsy, and elevated risk based on the Gail or Claus model or both. A standard protocol and interpretive criteria were used. Mammography and ultrasound were performed and read independently, allowing for reducing potential biases in patient recruitment and interpretation. Data were analyzed from 2,637 patients who underwent imaging. Thirty-one cancers were detected in the study group, 11.8 per 1,000 women; the increase in the cancer detection rate because of addition of ultrasound was 4.2 per 1,000 women. The diagnostic accuracy for mammography was 0.78, for ultrasound was 0.80, and for combined mammography and ultrasound was 0.91. Ultrasound hence proved a useful supplemental modality, identifying additional small node-negative invasive cancers in this cohort of women at an elevated risk for breast cancer [22].

Breast sonography has never been studied or been advocated to be used as the only modality to screen for breast cancer. The rationale against such an approach is sound; not the least is the low yield of ultrasound alone detected breast cancers. There is, however, some data from a study in Japan that demonstrate the value of sonography when used as the only modality for screening of breast cancer in women less than 40 years of age [29]. This study was undertaken in the Ibaraki prefecture of Japan where the breast cancer screening recommendations include performing annual screening ultrasound and CBE in women of ages 30 through 56 and biannual mammography in women of ages 40 through 65. There were 12,359 women in the age group of 30–39 years who received annual screening breast ultrasound and did not undergo mammographic screening. Of these, 4,501 women also received annual CBE in addition to whole breast screening ultrasound. In young women, i.e., younger than the age of 40 years, as expected, the cancer yield was low, with a cancer detection rate of 0.04–0.07 % [34]. In those women between the ages of 40–56 years in whom both mammography and ultrasound were used, the cancer detection rate ranged from 0.13 to 0.16 % for sonography and 0.1–0.22 % for mammography. Overall, 41,653 women underwent mammography, and 48,294 women underwent CBE and breast ultrasound. The rate of detection of stage I cancers was 72 % by ultrasound, 66 % by mammography, and 42 % by CBE. Cancer detection by mammography and ultrasound was complementary. Approximately one-third of cancers would have been missed if only one of these modalities were used, which once again proves the value of supplementing

ultrasound with mammography, as has been shown in the ACRIN 6666 trial [29]. There have been other studies conducted in Japan, where a significant proportion of women tend to have small breasts with dense parenchyma and are better suited for whole breast ultrasound survey. These studies have also validated use of ultrasound in the detection of small cancers in women with dense breasts [30, 31].

### Breast Ultrasound: Pros and Cons (Table 2.2)

The benefits of ultrasound as a screening modality are that it does not use ionizing radiation, is well-tolerated, does not require intravenous contrast administration, and is optimally amenable for percutaneous biopsy guidance. Ultrasound is able to identify small nonpalpable masses while undeterred by presence of dense breast tissue, which is an inherent limitation of mammography. More than 90 % of cancers identified at sonography are in women with >50 % of dense breast tissue [32, 33]. In addition ultrasound is a useful supplemental tool in identifying small cancers with subtle findings on a mammogram (Fig. 2.4a–e).

Due to its ability to detect intraductal calcifications associated with DCIS, mammography is able to identify intraductal cancers with a high degree of accuracy (Fig. 2.5). However, unlike mammography, the vast majorities of cancers that are seen on ultrasound are invasive cancers; DCIS is not usually identified by sonography [23]. On the other hand, MRI has been shown to readily identify DCIS [33]. Nevertheless, it is debatable whether a screening examination that identifies small node-negative cancers is adequate or whether detection of DCIS is a more critical requirement of a screening test. There are limitations for the use of ultrasound in screening for breast cancer. Ultrasound has never been proven to reduce mortality from breast cancer. Because the incidence of cancers seen on ultrasound is low, to prove mortality rate reduction, a large cohort will have to be studied in a randomized blinded controlled clinical trial [9]. These studies are unlikely to be conducted anytime in the near future, leaving this important question of whether ultrasound screening will lead to breast cancer mortality rate reduction unanswered. Ultrasound is an operator-dependent examination; standardization of the examination and having a skilled, adequately trained sonologist are critical for performance of a whole breast ultrasound [26]. This is compounded by intraobserver and interobserver variability when follow-up for probably benign lesions is recommended. Perhaps one of the most significant drawbacks for the use of ultrasound is the time that is takes to perform a high-quality bilateral breast ultrasound, which was reported to be a median of 19 min [26]. That compares very poorly with mammographic interpretation time. A breast radiologist might read up to 50 mammograms in the time taken to perform three breast ultrasounds [21]. Another limitation of ultrasound is the high rate of false-positive studies; the positive predictive value in those cases in which biopsy was performed was 8.8–8.9 %, compared with 23 % with mammography [22]. In this context it is worthwhile keeping in mind that a false-positive ultrasound might not have the same consequence as that of a false-positive mammogram. As Kuhl points out in an editorial, a suspicious finding on a mammogram requires a much more expensive and time-consuming biopsy procedure than an ultrasound-guided core biopsy or a fine-needle aspiration biopsy that can be performed often immediately after the ultrasound examination [21].

**Table 2.2** Screening breast ultrasound: Pros and cons

| Advantages | Disadvantages |
|---|---|
| Identifies small node-negative cancers that are missed by screening mammography | Operator dependent |
| Better tolerated by the patient, no ionizing radiation, no patient discomfort | Requires longer physician time compared to interpreting mammograms |
| May be beneficial as a supplemental modality in women with an elevated risk for breast cancer and/or in women with a dense breast | High false-positive rate |
| Biopsy of a suspicious abnormality is easier to perform than for mammographically identified abnormalities | Mortality rate reduction has not been proven in a randomized clinical trial as has been shown with mammography<br>Lower sensitivity in identifying DCIS compared with mammography |

### Supplemental Screening with Ultrasound in Women with Dense Breasts

In the USA, there has been a movement that aims to make it a requirement to notify patients of their breast density on a mammogram when it is heterogeneously dense or very dense so their physicians could offer them supplemental screening with breast ultrasound and/or MRI depending on their risk factors [http://www.areyoudense.org/]. A handful of states like Texas, California, and Connecticut have passed such laws. In Connecticut, insurers are required to pay for supplemental screening with breast ultrasound. Connecticut Public Act 09–41 requires that radiologists inform patients with heterogeneous or extremely dense breasts at mammography that they may benefit from supplemental ultrasound or breast MRI [34]. In a report of 935 such women undergoing supplemental screening ultrasound, majority of whom were at low risk [65 %], 5 % were categorized as BI-RADS 4, and 63 interventions lead to a malignant diagnosis of three, all of which were small less than 1 cm cancer. There was one cancer each in the low-, intermediate-, and high-risk groups. As shown in multiple studies, the yield of cancer in a screening ultrasound is expected to be higher in women at elevated risk for breast cancer. Cancer detection rate was 3.2 per 1,000, and the positive predictive value was only 6.5 %. Another

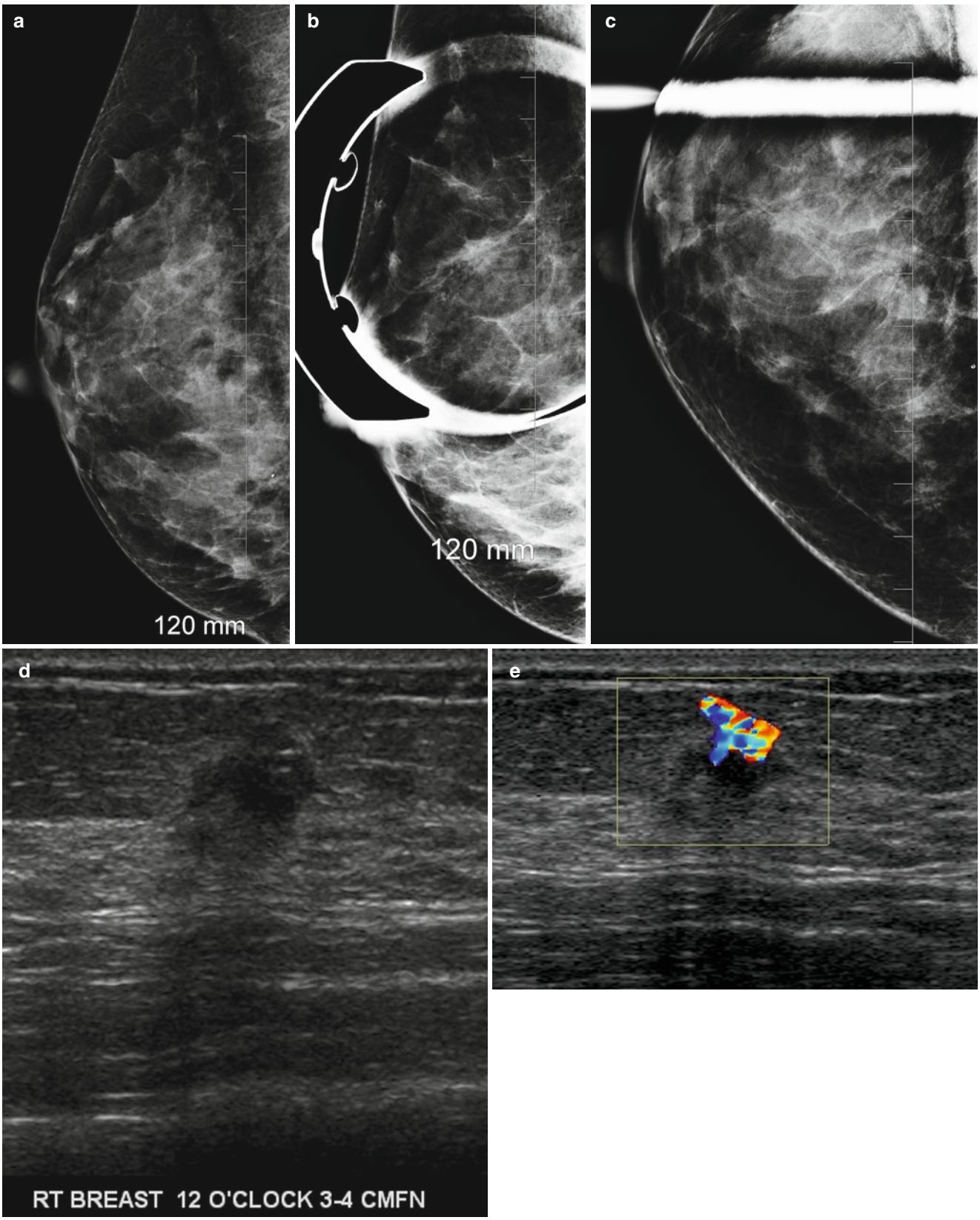


**Fig. 2.4** (**a**–**e**) Mammographically subtle invasive ductal cancer in a 45-year-old female. (**a**) Mediolateral oblique view demonstrates a small focal asymmetry in the upper breast. (**b**) Spot compression mediolateral oblique view shows an irregular focal asymmetry. (**c**) Abnormality is barely visible on spot compression view in the craniocaudad projection. (**d**) Ultrasound demonstrates an irregular small mass with malignant features. (**e**) Color Doppler imaging demonstrates the mass to have prominent vascularity

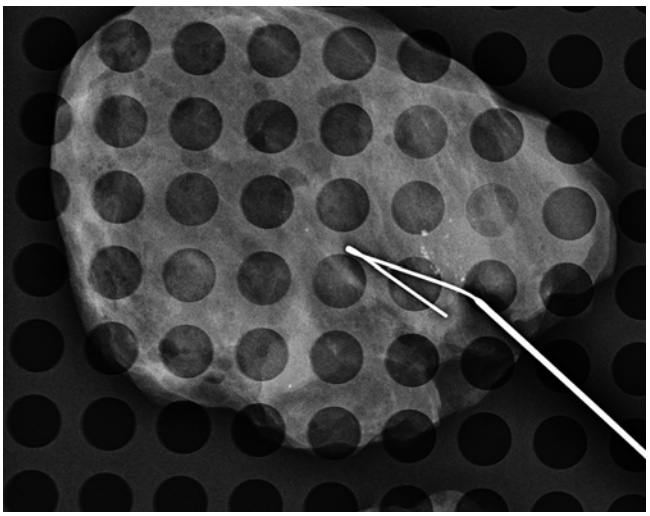

**Fig. 2.5** Ductal carcinoma in situ appearing as clustered crushed stone type of pleomorphic microcalcifications in a specimen radiograph from an excisional biopsy. Localizing wire is seen within the specimen

study undertaken in Connecticut which included 8,647 screening breast ultrasound exams, 5 % were BI-RADS 4 or 5. There were 28 cancers in 418 of 429 in the BI-RADS 4/5 group for a positive predictive value of 6.7 %. The additional yield of cancers in women without an elevated risk was 3.25 per 1,000 [35].

A cancer detection rate of 4.4 per 1,000 has been reported in women with dense breasts in a study from Europe in women with average risk [36]. A systematic review of studies performed between 1995 and 2012 was undertaken to study the benefit of mammography supplemented with ultrasound as compared to mammography alone. There were no controlled studies undertaken to date. Extrapolation of results from women with an elevated risk for breast cancer suggested that the false-positive sonography could exceed 98 %. There is no sound evidence for routine use of ultrasound as a supplement to mammography. In clinical practice the use of supplemental ultrasound should be limited to women with dense breasts and/or in those with an elevated risk of breast cancer with a stronger justification for its use when both criteria exist [35, 38]. The role of ultrasound and/or MRI will remain debatable until controlled clinical trials are conducted to examine their efficacy as a supplemental tool particularly in women at average risk. Mammography will remain the gold standard methodology for screening for breast cancer [39].

## Screening by Clinical Breast Exam

Most professional societies that issue recommendations for screening mammography also recommend that physician or health-care worker perform periodic clinical breast examination. Clinical breast examination in such a setting plays a complementary role. The number of women in the USA undergoing mammography has increased steadily since 1990, especially in women with limited access to health care [40]; In 1997, 71 % of women in the USA older than 41 years reported having undergone mammography in the previous 2 years compared to 54 % in 1989. Women and their physicians are making decisions about screening, and they need information about the underlying risk of the condition being screened for, the effectiveness of the procedure in preventing an untoward outcome such as death, and the potential ill effects of screening, such as false-positive tests. For policy makers and payers, cost-effectiveness is an important factor in decisions about the allocation of finite resources [2].

Clinical breast examination [CBE] has been studied as a low-cost alternative to mammographic surveillance to reduce mortality by early detection of breast cancer. CBE identifies about 60 % of cancers that are detected by mammography and a few that are not seen at mammography. There has been no randomized clinical trial undertaken to evaluate the efficacy of CBE in the early diagnosis of breast cancer by comparing women who received CBE and those who did not. An estimate based on all randomized clinical trials reported sensitivity of CBE for detection of breast cancer at 54 % and specificity at 94 %. Indirect evidence of its value comes from the Canadian National Breast Screening Study, where women were divided into two groups, one that received screening with physician-performed CBE alone and a second group that received both CBE and screening mammography. There were 39,405 women enrolled in this clinical trial. These investigators found that in the two groups, breast cancer mortality and nodal involvement was similar [2, 9, 41–43]. The sensitivity of CBE in clinical practice has been reported to be considerably lower compared to the Canadian National Breast Cancer Screening Study [CNBCSS]. A sensitivity of 28–36 % only in clinical practice compared to 63 % achieved with CNBCSS [42].

A cost-effectiveness analysis of screening mammography and clinical breast examination in India reported that a single CBE at age 50 leads to a 2 % decrease in breast cancer mortality rate and had an estimated cost-effectiveness ratio of Int.$793 per life year gained, a 16.3 % mortality rate reduction was possible with biennial CBE at a cost-effectiveness ratio of Int.$1341, and CBE performed annually from ages of 40–60 years was estimated to be as effective as screening mammography for reducing breast cancer mortality at a fraction of the cost [44]. It has been pointed out that health policy makers are critical of BSE and CBE and more tolerant toward inconsistent and negative findings of mammographic screening [44]. Clinical breast examination may find tumors that are not seen on mammography or in breast tissue that is not imaged at mammography, such as in the axilla or the chest

wall above the breast an area that may not show up well or get excluded on routine mammographic views. The value of CBE which requires no special equipment should not be discredited particularly in developing countries. Failure to demonstrate efficacy in controlled clinical trials may not mean that an intervention is not effective particularly when can be implemented at a low cost. It is, however, imperative that primary care providers and health-care workers be well versed in the method of clinical breast examination, so that women who present with a complaint or in whom a lump is discovered are then offered appropriate further imaging with ultrasound.

## Screening by Breast Self-Examination [BSE]

Breast self-examination has the advantage of being patient centered noninvasive and can be carried out by women in the comfort of their home. If the challenge of educating women on breast self-awareness, training to perform structured BSE, is overcome, it makes sense to implement it as part of a breast cancer screening strategy. Compliance is the greatest challenge, and even in the USA, only one-third of women perform regular BSE, and the reported sensitivity is also low [20–30 %]; the prospects in developing countries may be even more challenging [45]. A large randomized controlled trial in Shanghai, China, that included 266,064 women who worked in textile factories provided half of the women with intensive initial instruction that included practice with breast models, regular reminders, and practice examinations under supervision biannually for 5 years [46]. There was no change in breast cancer mortality in the intervention group at 10 years of follow-up. There was a significantly higher rate of biopsy due to false-positive findings [1.8 % in the instruction group compared to 1 % in the control group]. However, these findings have to be interpreted with caution, since the study group had a high percentage of young women [40 % in their 30s]; in this age group, no method of screening has ever been shown to be effective in reducing mortality, and also a higher false-positive rate is to be expected due to the hormonally induced cyclical changes in the breast tissue. The time to measure mortality change in this large clinical trial may have been too short [47]. The first large-scale clinical trial conducted in Russia also did not show any benefit in reducing breast cancer mortality in women undergoing BSE [48]. This trial has been criticized for not having practiced BSE well and the lack of critical analysis of data of cluster randomization [49, 50]. A case–control study within the CNBSS women showed that in those with a higher score, there was a lower score of being diagnosed with advanced breast cancer and thereby lower odds of death from breast cancer [51]. A similar benefit was seen in a cohort of nearly 30,000 women in Finland, where a relative risk of 0.75 for breast cancer mortality relative to that expected from the general population was found [47]. This study suggested that a well-performed BSE combined with a physician visit to act on the findings of BSE was critical in providing this benefit [47].

### Conclusion

Screening mammography has proven benefits in reducing mortality from breast cancer, and this is independent of the benefits of improved therapy. The controversy regarding whether screening for breast cancer is justified, if it is when to start screening and how often to screen are controversies that will continue to rage on. The number of women needed to be screened to prevent one breast cancer death using the cancer intervention and surveillance modeling network [CISNET] is lower than the model based on RCTs that was used by the US Preventive Services Task Force [USPSTF]. For instance, for women between the ages of 40 and 49, the number of women to be screened to avoid one breast cancer death was 746 based on the CISNET model, whereas if the model based on RCTs was utilized, it is 1,904. The difference is attributed to two factors because RCTs do not account for nonattendance among women invited to be screened or for crossover of uninvited control group who end up being screened [52–55]. Only 67–68 % of women invited to be screened actually attended screening in the first year, and this number progressively decreased during subsequent years. In the control group as 20–30 % of women can undergo at least one round of screening [54]. The second confounding factor is that most of the large RCTs were performed in the 1970s and 1980s and therefore do not reflect current mammography technology, screening practice, or interpretation skills and therefore are likely to underestimate the current benefit of screening mammography. A recent publication reported that only 84 women needed to be screened annually between 40 and 84 years to save one life from breast cancer, and 5.3 need to be screened annually to gain one life-year from breast cancer [55]. The evidence in favor of mammographic screening is overwhelming. While there is a need to define and set benchmarks of performance for interpreting physicians to avoid unnecessary biopsy and optimize false positive, the rationale for screening women annually from 40 years of age is sound and scientifically validated.

It is generally recommended that screening mammography should be continued until that age where life expectancy is at least 7 years on the basis of age or comorbid conditions or when abnormal results would not result in intervention because of age or comorbid conditions. All the RCTs included women under the age of 74 years; however, it is known that mammographic sensitivity and specificity increases with age, and a study of 690,000

women aged 66–79 years showed a significant reduction [43 %] in the incidence of metastatic cancer in the screened versus the non-screened group [56]. These findings justify continuing screening beyond 74 years in otherwise healthy women.

In women with an elevated risk, there is proven benefit for supplementing screening with breast ultrasound and breast MRI particularly in women with dense breasts where mammographic screening may be compromised. Ultimately reduction in breast cancer mortality will require a multipronged approach, effective use of screening, and optimal treatment, and reduction of risk factors such as obesity would be the best approach [57]. The benefits of screening mammography in clinical practice has been also validated in a study just published that showed that 71 % of deaths from breast cancer occurred in women who were not screened for breast cancer and the median age of diagnosis of these fatal cancers was 49 years [58].

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