4 Screening and Early Diagnosis of Breast Cancer: Proven Methodology and an Optimized Strategy for Developing Countries

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Abstract

Breast cancer is emerging as a major health care challenge in developing countries. Most recent data show that breast cancer is the most frequently diagnosed cancer in women and the leading cause of mortality from cancer. Breast cancer incidence in developing countries accounts for 51 % of the worldwide incidence. Younger women, i.e., between the ages of 15 and 49, are diagnosed with breast cancer in developing countries in a higher proportion than in developed countries (23 % to 10 %). Cost-effective health care interventions are urgently needed to reduce the increasing mortality rate from breast cancer. This chapter provides an overview of methods that have been extensively studied and whose benefits have been validated to screen for breast cancer in developed countries. Screening mammography is discussed in detail, and its benefits and potential harms are presented with an outline of the challenges of implementation and extensive resources that an organized or an opportunistic program involves. Potential low cost alternatives that may be more relevant in low resource settings such as clinical breast examination (CBE) and breast self-examination are presented. Finally, an optimal strategy for screening for breast cancer is described. This involves improved awareness of breast health among women through education and self-awareness, and periodic screening CBE performed by a trained health care professional combined with a focused sonographic evaluation of screen positive women. A detailed discussion of the use of ultrasound in characterizing palpable abnormalities in the breast and its role in optimally triaging patients who need diagnostic tissue sampling, thereby minimizing false positives, is presented. Finally, the pros and cons of fine needle aspiration biopsy and large core needle biopsy in the assessment of palpable solid masses that need tissue diagnosis are discussed.

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M.K. Shetty (ed.), *Breast and Gynecological Cancers: An Integrated Approach for Screening and Early Diagnosis in Developing Countries*, DOI 10.1007/978-1-4614-1876-4_4,

Introduction to Breast Cancer Screening

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, diagnosis, and 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 that detects a high percentage of cancers (sensitivity) and has a 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 frequently 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 of effectiveness, accuracy, and consistency has to be applied to and monitored in health care personnel performing and interpreting these tests as well as in the equipment used for this purpose. An effective and 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, for follow-up visits, and repeat screening at predetermined intervals is a must to ensure success [1].

Global incidence of breast cancer increased from 641,000 in 1980 to 1.64 million in 2010. Breast cancer has killed 425,000 women, of whom 68,000 were women younger than 49 in developing countries [2]. Breast cancer is now the leading cause of cancer in women and the leading cause of cancer mortality. Fifty-one percent of breast cancer cases occur in developing countries [2], which have a higher mortality rate for breast cancer than developed countries due to diagnosis at a late stage as well as due to lack of availability of effective treatment. Screening for breast cancer is justified considering the fact this cancer has a documented preclinical stage that can be diagnosed. Early diagnosis has a better prognosis, requiring less treatment with consequent benefit to the individual and the society. Numerous clinical trials have been undertaken in developed countries over the last several decades to test the efficacy of breast cancer screening in reducing breast cancer mortality. It remains to be seen whether these results can be reproduced in developing countries or if it is feasible to implement an organized, robust program on a large scale in developing countries [3]. Screening for breast cancer can be either population-based, organized screening as is in place in some European countries, or it can be opportunistic screening as is in place in the USA. An organized screening program is very resource intensive and rarely justified in a country where the prevalence rates are not high. Opportunistic screening refers to screening tests, usually a mammogram outside of a national or regional screening program. Here, the patient and the referring doctor assume responsibility for further testing if screening results are positive. Such screening programs require enormous financial and human resources, involving: a massive information campaign that effectively reaches out to the target population; building a health care infrastructure to provide screening, diagnosis, and treatment of cancers; and creating a continuous supply of trained health care professionals, specifically mammography technologists, nurses, pathologists, and radiologists. Many of the developing countries do not offer training to radiologists in breast imaging. Breast cancer screening implementation has several

competing health care priorities that can be tackled at much lower cost. An organized mammographic screening program is not feasible in the foreseeable future in developing countries.

Early detection is distinct from screening and is more practical for developing countries. The aim of such an approach is to identify cancer at a relatively early stage, with the potential of curing with the least physical effects. In a typical scenario, a woman presents with a symptom and is assessed appropriately by a health care professional. Early diagnosis, however, requires education of women so that they understand the signs and symptoms and seek care; it also requires trained health care workers, particularly in rural settings, who appropriately evaluate women presenting with breast symptoms. Breast cancer may be diagnosed at an earlier stage, possibly Stage II or lower, with a prognosis significantly better than the currently prevailing situation of presentation of a large number of women at Stage III and Stage IV of the disease. Such an approach requires only limited resources and is an appropriate first step. This has been outlined in the Breast Health Global Initiative Guidelines as an option when level of resources are basic, and it includes breast health awareness consisting of educating women, self-examination, and clinical breast examination (CBE). The evaluation goal is for a baseline assessment and repeated survey [4]. Three of the most commonly studied methods for breast cancer screening, i.e., screening mammography, clinical breast exam, and breast self-examination, are discussed next in this chapter, followed by a suggested strategy optimal for developing countries.

Screening Mammography

Randomized clinical trials (RCTs) 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 [5]. The role of mammography in reducing breast cancer mortality has been demonstrated in multiple RCTs 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; 55,985 women were assigned to a no-invitation group. A single view mammogram was performed every 33 months in women in 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 invited to be screened [6]. In the same study, when those women who actually attended screening were compared to those who did not, a still higher mortality reduction of 42 % was observed [6, 7].

A meta-analysis of all the RCTs testing the efficacy of screening mammography to date demonstrated a significant reduction in breast cancer mortality of 20–35 % in women in age group 50–69 years [8]. How do the results of these RCTs translate into clinical practice, i.e., service screening, i.e., effectiveness vs. efficacy? This has been studied by Tabar et al. In the age group of women between 20 and 69 years, there were 6,807 women who were diagnosed with breast cancer over a 29-year period in two counties in Sweden, and there were 1,863 breast cancer deaths. These investigators reported a 63 % mortality reduction in mortality from incident breast carcinoma in women ages 40–69 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, are additional factors that lead to better results in service screening [9]. In 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 [10].

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 rage on. The Council of the European Union and the International Agency for Research on Cancer Expert Working Group have recommended use of bi-annual mammography for women age 50–69 [11]. In the USA, the Society of Breast Imaging and the Breast Imaging Commission of the American College of Radiology recommend an annual screening mammography for women of average risk starting at age 40 [12].

Limitations of 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 over-diagnoses cancer, leading to unneeded treatment interventions, comprise some of the issues. Approximately 95 % of women with abnormalities on the screening mammogram do not have breast cancer [13]. 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 [14].

Screening Women in Their 40s

Women in their 40s have denser breast and a lower incidence of breast cancer accounting for decreased sensitivity of mammography; nevertheless, in this age group, women tend to have faster growing cancers [13]. 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, median follow up of 12.8 years, and a screening interval of 18–24 months [15]. About 18 % of cancers, both in-situ and malignant, are reported in women between the ages of 40–49 in the USA. A longitudinal cohort study in 1977 of 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 %) was seen over time, with a consequent increase in lower stage disease detection and decrease in higher stage disease [16]. A study of 31,814 average risk women reported that the positive predictive value for further evaluation was 1–4 % for women ages 40–49, 4–9 % for women ages 50–59, 10–19 % for women ages 60–69, and 18–20 % for women ages 70 or older [17].

Harms of Mammography Screening

Overdiagnosis refers to diagnosis of cancers, particularly DCIS which may have never progressed to an invasive stage and resulted in death. Such patients would have undergone surgery, chemotherapy, and/or radiotherapy along with their consequent harm [18]. The presumptive evidence for "over-diagnosis" 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 RCTs. This assertion is contentious because diagnosing more breast cancer cases cannot be somehow construed to be a bad thing. It has been shown without question that mortality rate reduction 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 for the fact that we do not know which ones proceed to invasive stage and which ones do not.

Two observational studies of 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 has been shown in RCTs of 30–40 % for women in their 40s. In fact, RCTs tend to underestimate the benefit of 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 it does 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 a one view mammogram only was obtained which limits the cancer detection rate [19].

Mammographic Interpretation and Quality Assurance in Mammography, Medical Audit, and Benchmarks

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 [20]. 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 we next address ways of achieving this objective.

The US Congress enacted the Mammography Quality Standards Act (MQSA) to ensure that all women have access to quality mammography for the detection of breast cancer in its earliest, most treatable stages, and it charged the Federal Drug Administration with developing and implementing the MQSA regulations [21]. The scope of the act included establishing minimum national quality standards for mammography facilities to ensure safe, reliable, and accurate mammography. All facilities had to undergo periodic certification by accredited bodies to ensure compliance with federal standards. This included adequate training of both radiologists and technologists. European guidelines for quality control and quality assurance in breast cancer screening and diagnosis were developed. The purpose of such a rigorous quality assurance program in breast cancer screening was to diminish the potential harm that can result from mammography such as unnecessary anxiety and morbidity, inappropriate economic cost, and the use of ionizing radiation [11]. A screening program should strive to reduce and avoid unnecessary work up of clearly benign abnormalities, to reduce anxiety, and to maintain a cost-effective program. Somewhat similar to the mandated requirements in the USA, the European guidelines for quality assurance recommended the need for QA on all mammography units, implementation of a robust accreditation of all screening programs,

and emphasized the need for all staff to hold professional qualifications to perform and interpret mammograms and to undertake specialist training and participate in CME, updates, and external quality assessment schemes. Each screening unit should have a lead professional to oversee overall quality assurance and performance of the screening mammography program. Strict adherence to such national and regional guidelines are critical for a successful screening program, and many countries where screening programs are in place or are being implemented adopt similar measures to ensure quality.

Mammography Interpretation Benchmarks

A screening program must have benchmarks to serve as minimally acceptable criteria for interpretive performance. This was recently studied by Carney et al. [22]. The study was aimed to identify minimally acceptable performance standards for interpreting screening mammograms. They reported that a sensitivity of less than 75 %, specificity less than 88 % or greater than 95 %, recall rate less than 5 % and greater than 12 %, PPV 2 of less than 20 % or greater than 40 %, and cancer detection rate of 2.5 per 1,000 interpretations indicate low performance [22]. If underperforming physicians moved into the acceptable range by additional training, detection of an additional 14 cancers per 100,000 women screened and a reduction in the number of false positive examinations by 880 per 100,000 women screened would be expected [22]. Radiologists interpreting moderate (1,001–2,000) and those with high volume (>2,000) had a higher sensitivity [22]. It is of interest to note that the recall rate in the USA is twice the recall rate in the United Kingdom (e.g., 12.5–14.4 % vs. 7.6 %), with no difference in cancer detection rate [23]. This may have to do at least in part to the practice of defensive medicine in the USA rather than interpretive skills since failure to diagnose breast cancer is the leading cause of malpractice litigation in the USA. Among other things, MQSA mandated implementation of the American College of Radiology BIRADS™ (Breast Imaging Reporting and Data System, ACR, Reston, VA) recommendations for mammogram interpretation and final assessment categories have helped to standardize mammographic reporting in the USA [24]. Per the BIRADS reporting system, a standard mammogram report should include a description of the breast composition, i.e., breast composition is almost entirely fat (<25 % glandular), there are scattered fibroglandular densities (25–50 % glandular), breast tissue is heterogeneously dense (51–75 % glandular), and breast tissue is extremely dense (>75 % glandular) [24]. This is important since it gives an idea about the volume of attenuating tissue in the breast and hence an idea of the relative sensitivity of the examination. The next step in the interpretation of a mammogram is a description of significant findings such as a mass (size, morphology), calcifications (morphology and distribution), architectural distortion, and special cases (dilated ducts, intramammary lymph nodes, global and focal asymmetry) [24]. Both category 1 and 2 indicate absence of mammographic evidence of malignancy. The BIRADS™ three probably benign category is used when there is a finding that has a less than 2 % risk of malignancy. Most mammographers follow a sequence of 6, 12, 24, and 36 months of mammographic surveillance for women in this assessment category. During mammographic reading, understanding the normal variation in the mammographic patterns as well as identifying the subtle signs of malignancy are equally important. The subtle signs are often faint microcalcifications and indirect signs of malignancy such as areas of architectural distortion, focal asymmetry, solitary dilated duct, and small developing densities. Increasing the true positives is more important than reducing false positives. An important goal of the mammographer should also be to increase cancer detection rate. The importance of comparison with prior mammograms is very important. An analysis of 48,281 consecutive mammography examinations for which previous mammography (9,825 diagnostic, 38,456 screening) had been performed between 1997 and 2001 reported that, for screening mammography, comparison with previous examinations significantly decreases false positive and permits detection of cancers at an earlier stage. For diagnostic mammography, comparison with

previous examinations increases true-positive findings. In the diagnostic setting, comparison with previous examinations increases the biopsy yield from 38 to 51 % and the overall cancer detection rate from 11/1,000 to 39/1,000. A significant decrease in the frequency of axillary node metastasis and the cancer stage for screening mammography was observed [25, 26].

The National Cancer Institute outlines a "discovery-development-delivery" approach to cancer research [27]:

> Discovery is the process of generating new information about fundamental cancer processes from the genetic to the population level. Development is the process of creating and evaluating tools and interventions that are valuable in detecting, diagnosing, predicting, treating, and preventing cancer. Delivery involves promoting and facilitating the application of evidence-based cancer interventions [27].

The Breast Cancer Surveillance Consortium was established by the NCI in 1994. The benefits of screening mammography have been well established in large RCTs; however, the effectiveness of screening mammography had to be studied in routine clinical practice. It was also recognized that useful information could only be obtained by linking screening patterns and performance parameters as outlined by national bodies and professional societies such as the American College of Radiology with cancer outcomes. At the present time, seven data collection and research centers and the statistical coordinating center comprise the BCSC. A key program of NCI's Division of Cancer Control and Population Sciences focuses on the delivery component, and its research wing aims to promote adoption of proven intervention methods in clinical and public health practice. The BCSC links surveillance data on breast screening practices with data from population-based cancer registries. Most recent data which includes data on screening mammography performed from 2002 to 2006 and analyzed in 2009 show a cancer detection rate of 4.6 per 1,000 women amongst 1,960,500 mammograms performed. Sensitivity and specificity for 2,264,089 screening mammography examinations from 2002 to 2006, based on BCSC data as of 2009, was as follows: sensitivity: 84.1 %; specificity: 90.4 %. The recall rate was 10 %. PPV 2 was 23.6 % (cases where biopsy was recommended) and PPV 3 was 28.9 % (cases where biopsy was performed within 1 year) [27]. An analysis of the results of 47,798 screening and 13,286 diagnostic mammograms found that radiologists that are specialized in breast imaging detected more cancers and more early stage cancers, recommended more biopsies, and had lower recall rates than did the general radiologists. Cancer detection rate of specialists was 6 % compared to 3.4 % for generalists. A database of such large samples of screened population allows the Consortium to study and publish several key features of community based breast cancer screening programs such as characteristics of women that affect the performance of screening mammography, characteristics of radiologists, radiology facility, or mammographic technologists affecting performance of screening mammography, and characteristics of mammography equipment that affects the performance of screening mammography. The low-contrast detectability was studied using a full-field digital mammography system and was compared with results obtained from an optimized screen-film system. Results showed that using a softer X-ray beam for thin breasts and a harder X-ray beam for thick breasts improved digital mammography's ability to detect low-contrast lesions when the average glandular dose was kept constant. Under this constraint, optimum low-contrast lesion detection with digital mammography was superior to that of conventional screen-film mammography (SFM) for all but the thinnest breasts.

Recall rate of women undergoing mammography is one of the audit benchmarks, since performing additional imaging to rule out cancer increases false-positive rates. False-positive mammograms also lead to anxiety, excess costs, and morbidity from subsequent biopsies, many of which result in a benign diagnosis. The false-positive rate for screening mammography is higher in the USA than in European countries. In a study that looked at three groups of radiologists interpreting mammograms; the sensitivity in the group considered high volume readers, which included those who read >301 mammograms

each month, was significantly higher than in those who read <100 or those who read between 100 and 300 mammograms. The specificity was also better among high volume readers although was not statistically significant. In the USA, the minimum number of mammograms required is 480/year compared to 5,000/year required in the UK [28, 29]. Others have also shown that increasing minimum interpretive volume requirements in the USA while adding a minimal requirement for diagnostic interpretation could reduce the number of false-positive work-ups without hindering cancer detection [30].

About two-thirds of all mammography equipment in the USA is digital, predominantly full-field digital systems. A study of total of 49,528 asymptomatic women presenting for screening mammography at 33 sites in the USA and Canada underwent both digital and film mammography [31]. The overall diagnostic accuracy of full-field digital mammography (FFDM) and SFM as a means of screening for breast cancer was found to be similar, but digital mammography was found to be more accurate in women under the age of 50 years, women with radiographically dense breasts, and premenopausal or perimenopausal women [31]. Another study that compared the miss rate of breast cancer found no difference in those who underwent SFM from those who underwent FFDM. The missed cancers in the SFM group of 52,444 women had microcalcifications on the prior mammograms in 34 % compared to 18 % in the FFDM group of 35,127 women; focal asymmetry at the site of cancer was seen more frequently at the site of missed cancers in women who underwent FFDM, 27 % compared to 10 % in those who underwent SFM [32].

Screening by Clinical Breast Exam

Most professional societies that issue recommendations for screening mammography also recommend physician or health care worker perform periodic CBE. CBE 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 [33]. 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; 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 policymakers and payers, cost effectiveness is an important factor in decisions about the allocation of finite resources [8].

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 on mammography. There has been no RCT 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 RCTs 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 [13, 34–36]. The sensitivity of CBE in clinical practice has been reported to be considerably lower compared to the Canadian National Breast Cancer Screening Study: a sensitivity of 28–36 % only in clinical practice compared to 63 % achieved with CNBCSS [13].

A cost effectiveness analysis of screening mammography and CBE in India reported that a single CBE at age 50 lead 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.$1,341. 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 [37]. It has been pointed out that health policy makers are critical of BSE and CBE and more tolerant towards inconsistent and negative findings of mammographic screening [38]. CBE 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 CBE, 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

Breast self-examination has the advantage of being patient centered and noninvasive, and can be carried out by women in the comfort of their home. If the challenges of educating women on breast self-awareness and of training to perform structured BSE are overcome, it makes sense to implement this method as part of a breast cancer screening strategy. Compliance will be the greatest challenge, and even in the USA only one-third of women perform regular BSE; the reported sensitivity is also low (20–30 %), and the prospects in developing countries may be even more challenging [39]. 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. 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 [40]. The first large scale clinical trial conducted in Russia also did not show any benefit in reducing breast cancer mortality in women undergoing BSE. This trial has been criticized for not having practiced BSE well and for the lack of critical analysis of cluster randomization data [41, 42]. 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 [43]. 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 [44]. 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 [44].

Optimal Strategy for Breast Cancer Screening in Developing Countries

The fundamental prerequisite when formulating a strategy to implement programs aiming to diagnose breast cancer at an early stage with an aim to improve mortality is to have data on the prevalence of breast cancer in the target population. The existing cancer burden is taken into account while crafting the most cost-effective strategy that would be appropriate for the resources of the country and relevant to the cancer burden of the target population. Effective strategy will have to be

tailored to a country or region based on prevalence of cancer and resources available in that particular country: there can be no one-size-fits-all developing country strategy. Breast cancer statistics in developing countries are sketchy, incomplete, and may not be accurate. A starting point in the breast cancer-control strategy would require developing countries to assess the existing cancer burden by setting up accurate statistics to determine the breast cancer incidence and mortality [45]. The strengths and limitations of the existing health care systems will have to be assessed, and a cancer-control strategy has to be put in place once both system inefficiencies and patient barriers are identified. The release of the Cancer Atlas of India is an example of one such effort at establishing a cancer registry [46]. Cancer statistics and data in developing countries are sparse, but a definite upward trend is apparent particularly in urban areas where a more westernized lifestyle has led to an increase in the incidence of breast cancer [47]. In Mumbai, India, over a 30 year period, the incidence of age standardized rate of breast cancer increased 1.1 % per year in women in age group 30–64 years, similar to that in Shanghai, China, and other urban areas in mid and low resource countries. The rate is still about one-third of those seen in Caucasian women in the USA. In Mumbai, India, breast cancer represented 32 % of cancer burden in women in the 2001–2005 period, compared to 18 % for cervical cancer which has decreased in incidence over the years and ovarian cancer which has remained steady and accounted for 7 % of the cancer burden [47, 48]. The changing pattern reflects adoption of a more sedentary life style, dietary changes of increased consumption of alcohol and meat combined with fertility pattern changes of delayed age of first child birth, fewer children, and shortened breast feeding time [47, 48]. In a mid resource setting, the screening strategy adopted in an urban setting with a more affluent population may have to be different than one adopted in the rural population. In rural areas, the degree of existing breast health awareness as well as expected compliance with a newly initiated screening program will be more challenging than in an urban area. The infrastructure and health care expertise available in urban areas such as Mumbai, Shanghai, or Manila may allow setting up of comprehensive screening and diagnostic breast centers similar to those that exist in developed nations. Opportunistic screening using mammography and work up of abnormalities utilizing diagnostic mammography and sonography may be feasible in urban areas. Funding mechanism in these sprawling urban areas is largely expected to be one involving a combination of government supported and individually supplemented. The strategy described next, on the other hand, is one that will be suited to the low resource countries and the rural population that is government funded, keeping in mind the limited resources available [47, 48].

The age distribution of breast cancer is reportedly lower in low resource countries than in high resource countries. A recent publication of global breast and gynecological cancer data reported that 23 % of breast cancer cases occurred in age group 15–49 in developing countries compared to 10 % in developed countries [2]. Increased incidence of breast cancer in younger women has been attributed by some to the average lower age of women in the population rather than to a higher age-specific incidence [45]. It may still be advisable to start screening at an earlier age in these settings. The target population to be screened should probably include women in the age group 40–69 years. The proposed methodology would include an annual CBE followed by focused diagnostic breast sonographic evaluation of screen positive women. Those women in whom a palpable solid mass is seen and determined to be suspicious based on ultrasound morphologic features undergo ultrasound-guided biopsy for optimal sampling [48–50]. Tissue sampling can be achieved using fine needle aspiration biopsy or large core needle biopsy. The rationale of this suggested methodology is explained next. Following a screening CBE, further assessment of screen positive cases is most optimally carried out by diagnostic sonography rather than by diagnostic mammography for many reasons [48–50] (Tables 4.1 and 4.2). Mammography has limitations in the evaluation of the symptomatic woman, particularly in those with dense breasts.

Table 4.1 Limitations of mammography as a screening modality in developing countries

Resource-intense modality, expensive to set up and maintain
Poor sensitivity in women with dense breasts
Screen detected abnormalities may require additional evaluation with sonography
Substantial recall rate would mean repeat clinic visit
Discomfort from breast compression may affect patient compliance
Screen-film mammography is not optimal for telemedicine reads or consultation
Image-guided biopsy of mammographic abnormalities is cumbersome and requires additional investment in stereotactic biopsy units

Table 4.2 Advantages of sonography in breast cancer screening and diagnosis

Several large clinical studies such as the ACRIN 6666 have shown that US can detect small cancers not seen on mammography due to dense breast tissue
Cost-effective modality: initial capital expenditure and operational expense are considerably lower than mammography
Ultrasound can be used for screening and diagnosis of other cancers in women
Telemedicine feasible modality
Portable equipment easy to transport and for use in mobile clinics
No need to recall for additional imaging evaluation as in mammography
Sonographic examination of the breast is better tolerated by women due to lack of the need for breast compression
Fine needle aspiration biopsy feasible: procedure is cytology based and similar to PAP smears. US is used as the imaging guide to obtain the sample

A false-negative rate of 16.5 % has been reported for mammography in patients with a palpable breast abnormality (Fig. 4.1a, b) [51]. Mammographic abnormalities identified in a symptomatic woman usually require additional diagnostic ultrasound work up, and, in those with a suspicious palpable solid mass seen on a mammogram and a sonogram, the latter is a better modality for tissue sampling (Fig. 4.4c). Overall, diagnostic ultrasound is superior and a cost-effective alternative to diagnostic mammography for the assessment of the symptomatic patient in a LRC. Ultrasound is a safe, well-tolerated, relatively inexpensive modality that can be readily used in the evaluation of a palpable lump in a woman where a positive physical finding was detected during the course of a screening CBE. Ultrasound has also the added potential of being used to stage breast cancer [49, 50].

The recommendations for triple assessment of symptomatic women at a breast clinic traditionally consisted of physical assessment, diagnostic mammography, and Fine Needle Aspiration Biopsy (FNAB) [52–56]. As stated previously, substituting diagnostic mammography with diagnostic ultrasound is particularly suitable in low resource settings. There are data to support the fact that findings of cytology are best considered in combination with imaging morphology and characterization of solid masses. Such an approach will improve the PPV, thereby allowing for optimal management of symptomatic women with suspicious findings at imaging and cytology. In a consecutive series of 2,334 women, PPV for cytology findings of atypical, suspicious, and malignant was 55, 95.9, and 99.4 %, respectively. However, when an atypical finding at cytology is seen in combination with a suspicious finding on imaging, the PPV improved to 83.3 % and PPV for suspicious lesions increased to 98.5–98.7 %, potentially allowing for management decisions of open biopsy and/or planning surgery [57]. Core needle biopsies have been reported to be more accurate than FNAB [54]; in a LRC, the latter may be preferred as a less invasive and a more cost-effective alternative. FNAB has the advantages of being a minimally invasive procedure, well tolerated with minimal complications and patient discomfort and providing rapid results. FNABs are usually performed using a 21–25-gauge needle and a 10-mL syringe mounted on an aspiration device. However, as stated next, FNAB requires an experienced cytologist for interpretation. This proposed strategy is discussed in greater detail, including the role of ultrasound in women with a palpable abnormality of the breast and the biopsy of those palpable masses that are deemed to be suspicious.

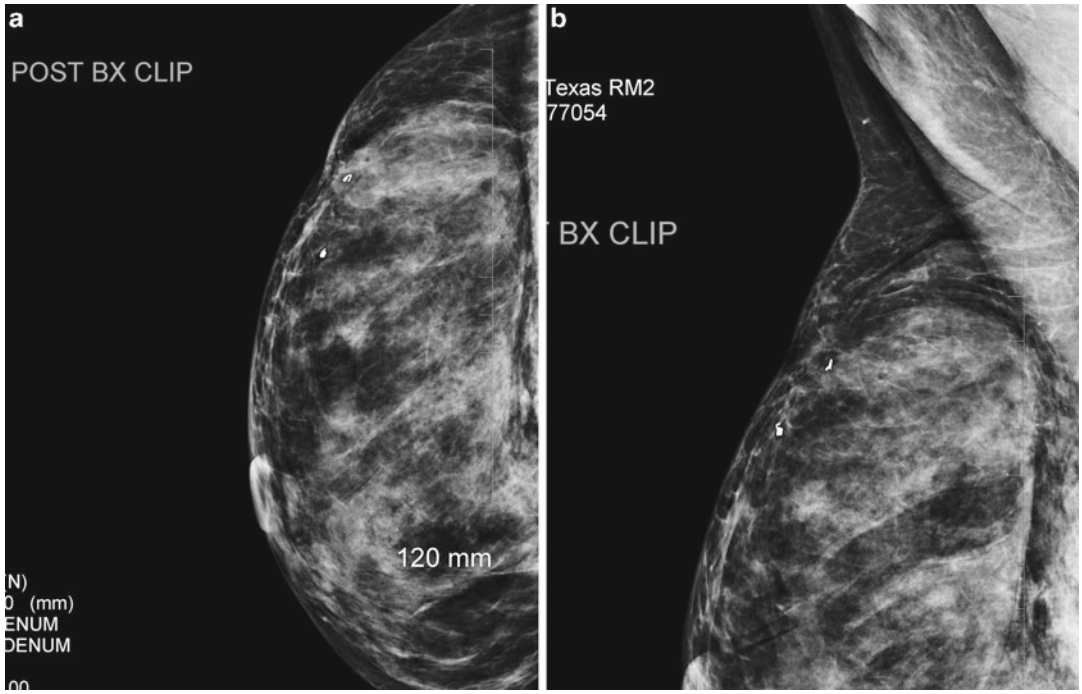

Fig. 4.1 False-negative mammogram in a patient with a palpable cancer (ultrasound image of the palpable mass is shown in Fig. 4.4c). (**a**) Craniocaudal view demonstrating no mammographic evidence of malignancy. Post ultrasound biopsy clips are seen at the site of solid palpable mass proven to be an invasive ductal cancer. (**b**) Mediolateral oblique view also showing no abnormal finding at the site of biopsy proven palpable cancer

Sonographic Evaluation of Palpable Breast Masses

Palpable abnormalities of the breast have a predominantly benign etiology, particularly in young women. Malignancy has been reported in 3.4–6 % of cases [58, 59]. In one series of 605 women under the age of 40, a cancer rate of 5 % was reported [60]. Imaging is critical to avoid unnecessary intervention and to improve accuracy of diagnosis. Focused sonography is quick, cost effective, and accurate in the assessment of a palpable abnormality. It is ideally combined with physical examination and provides a benign diagnosis with no further intervention needed in most instances [61]. Benign etiologies that are readily identified under ultrasound include cysts (Fig. 4.2a), benign lymph nodes (Fig. 4.2b), dermal lesions such as an infected epidermal cyst (Fig. 4.2c), fat lobules, palpable ridge of normal tissue [62], as well as the rare entity of Mondor's disease (Fig. 4.2d) where patient presents with a painful palpable cord. Sonographic diagnosis of superficial thrombophlebitis is diagnosed using real-time and color Doppler assessment of the palpable finding [63]. We have reported these characteristic findings in a small series of five patients. A majority of palpable lumps represent cysts, 25 % in a series of 300 [64]. In a series of women presenting with a palpable abnormality that we have published, 36.7 % (151/411) of palpable abnormalities were proven to be cysts, with a benign diagnosis provided by sonography in 39.4 % of cases precluding any further intervention [58]. In the same series, 168 palpable lumps had negative findings on sonography (45.1 %). Overall, only 14.6 % of women with a palpable abnormality had a solid mass to account for the palpable finding, excluding nearly 85 % of women from further intervention, demonstrating the value of ultrasound in the management of a woman presenting with a palpable lump [58].

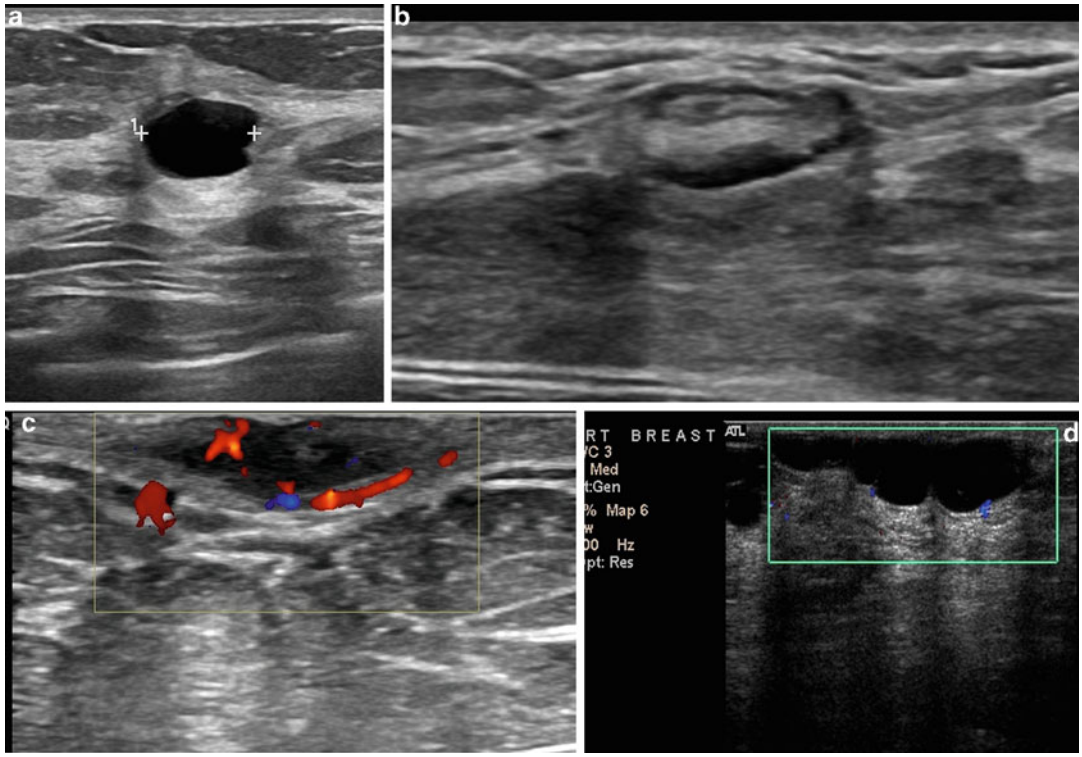

Fig. 4.2 Benign causes for palpable lumps diagnosed by sonography, no further work up is needed. (**a**) Cyst. (**b**) Lymph node. (**c**) Infected epidermal cyst. (**d**) Thrombosed superficial vein in Mondor's disease of the breast

When a palpable solid mass is seen, characterization based on previously published reports allows a mass to be categorized in one of three groups: benign, probably malignant, or indeterminate. For a mass to be considered benign, one of three groups of findings have to be present: intense uniform hyperechogenicity, ellipsoid shape with a thin echogenic capsule, two to three gentle lobulations with a thin echogenic capsule (Fig. 4.3a–c). The negative predictive value of intense uniform hyperechogenicity was 100 %, a thin echogenic pseudo capsule was 99.2 %, ellipsoid shape was 99.1 %, and four or fewer gentle lobulations was 98.8 % [62].

There are nine malignant features described by these investigators. These included the following (positive predictive value for each of the malignant feature is within parenthesis):

Spiculation (91.8 %)
A solid mass that is taller than it is wide (81.2 %)
A mass with angular margins (67.5 %)
One that demonstrates posterior acoustic shadowing (64.9 %)
A mass that demonstrates a branching pattern [61]
Hypoechogenicity (60.1 %)
Calcifications (59.6 %)
Duct extension (50.8 %)
Microlobulations (48.2 %)

A solid mass is initially interrogated for presence of malignant features (Fig. 4.4a–f), and, when absent, these described benign features are sought. If benign characteristics are seen, a solid mass is classified as being benign. Solid masses which do not demonstrate malignant or specific benign features are then classified as indeterminate with a recommendation for tissue diagnosis (Fig. 4.5) [62].

Description of Benign Features [62]

Intense and uniform *hyperechogenicity* (Fig. 4.3a) refers to markedly hyperechoic tissue compared to the echogenicity of fat. Hyperechogenicity should be uniform and usually corresponds to

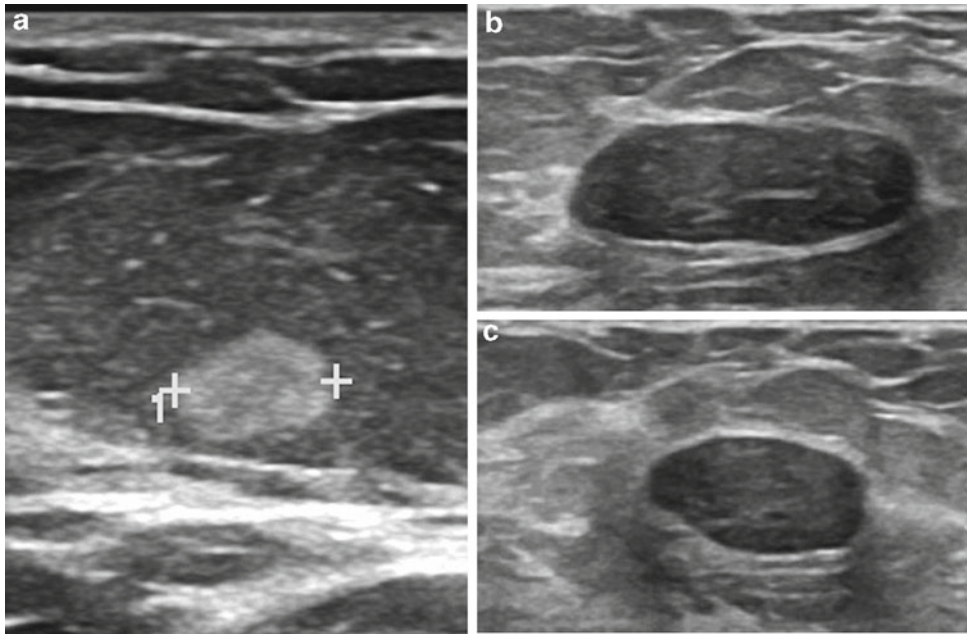

Fig. 4.3 Palpable solid masses demonstrating benign sonographic features. (**a**) Circumscribed uniformly hyperechoic mass. (**b**) Ellipsoid shaped solid mass with benign features. (**c**) Ellipsoid shaped solid mass with benign features

fibrous tissue; this criterion cannot be applied to masses that have areas of decreased echogenicity within other than fat lobules or ducts, or terminal lobular ductal units that are larger than 4 mm.

An *ellipsoid shape* (Fig. 4.3b) or a mass that is taller than wider refers to a sagittal and transverse diameter that is greater than the aneroposterior dimensions. A *thin echogenic capsule* (Fig. 4.3b) indicates a slow growing lesion; in order to demonstrate this finding in its entire extent, the transducer will have to be angled and studied in real time in multiple planes. *Gentle lobulations* are gently curving, smooth, and few in number (3 or less) as opposed to microlobulations that are features of a malignant mass. Since some purely intraductal cancers may have a thin echogenic capsule and a few malignant ellipsoid masses with gentle lobulations do not have a thin echogenic capsule, using these criteria in combination improves the accuracy of characterizing breast masses [5].

Description of Malignant Features [62]

Spiculation (Fig. 4.4f) is seen as alternating hyperechoic and hypoechoic lines that radiate from the surface of a mass. The appearance of these spicules is modified depending on whether hyperechoic tissue surrounds the mass. A mass that is *taller than wide* (Fig. 4.4b) is when any part of a mass is greater in its aneroposterior dimension than in its sagittal or transverse dimension, indicating that the tumor is aggressive and transgressing the normal tissue planes of the breast. *Angular margins* refer to the junction between the hypoechoic central portion of the solid mass and the surrounding tissue; this interface may be acute, obtuse, or 90°. *Branching pattern* (Fig. 4.4a) in a solid mass is akin to duct extension and refers to presence of multiple broad based projections extending from the surface of the mass. *Marked hypoechogenicity* (Fig. 4.4c) is a finding described in comparison to the surrounding tissue. *Duct extension* (Fig. 4.4d) is said to be present when there is radial extension of the tumor either within or along a duct coursing in the direction of the areola. *Posterior acoustic shadowing* (Fig. 4.4e) is considered present even when mild or present behind a small portion of the mass. *Calcifications* refer to punctate calcifications seen in a mass; these are more suggestive of a malignant process. Calcifications are more apparent when a mass is

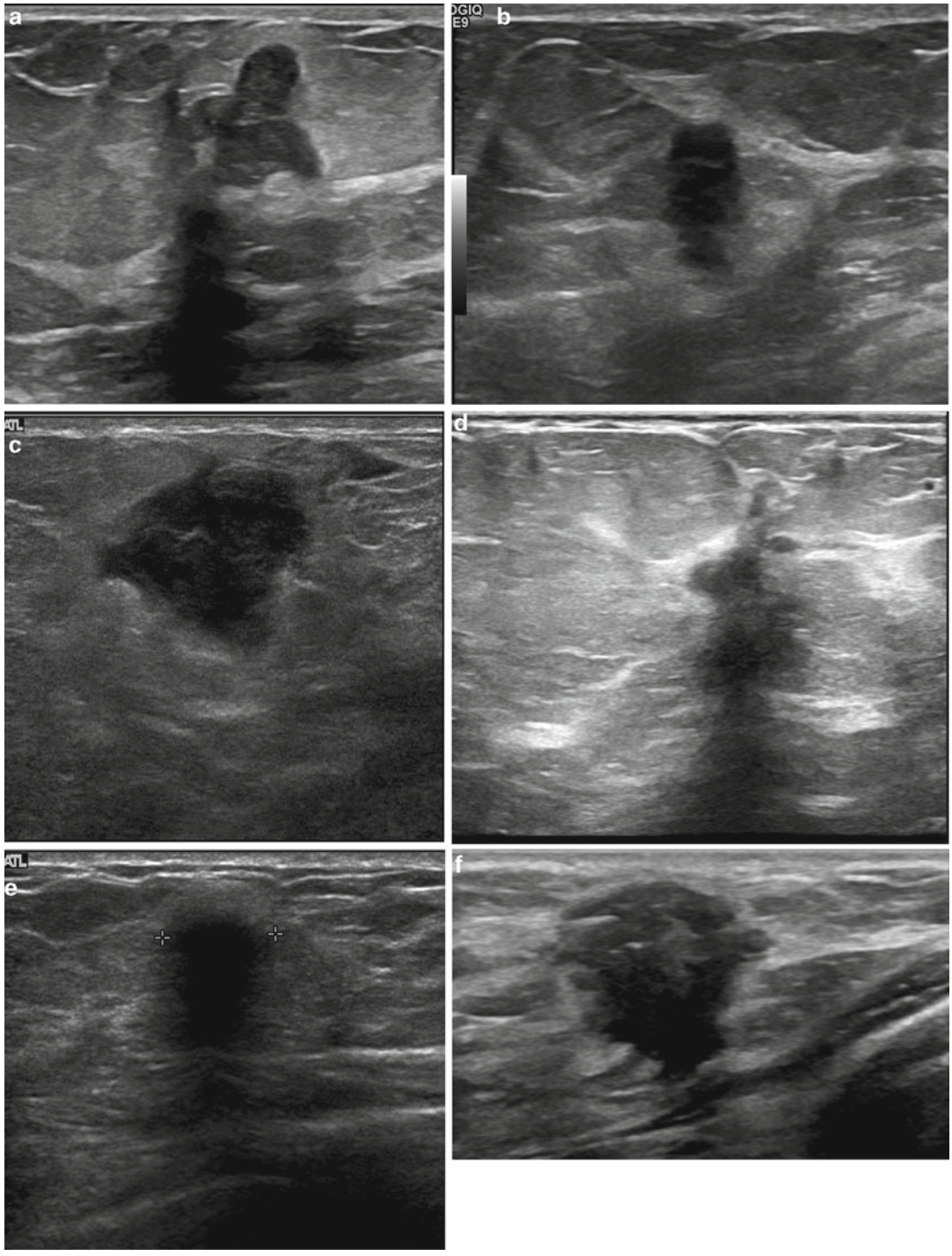

Fig. 4.4 Palpable solid masses demonstrating malignant morphological features and histologically proven to be invasive cancers at core needle biopsy. (**a**) Solid mass with a branching pattern. (**b**) Solid hypoechogenic mass that is taller than wide. (**c**) Intensely hypoechogenic mass. (**d**) A palpable mass with intraductal extension. (**e**) A solid mass with posterior acoustic shadowing. (**f**) A palpable solid mass with a spiculated margin

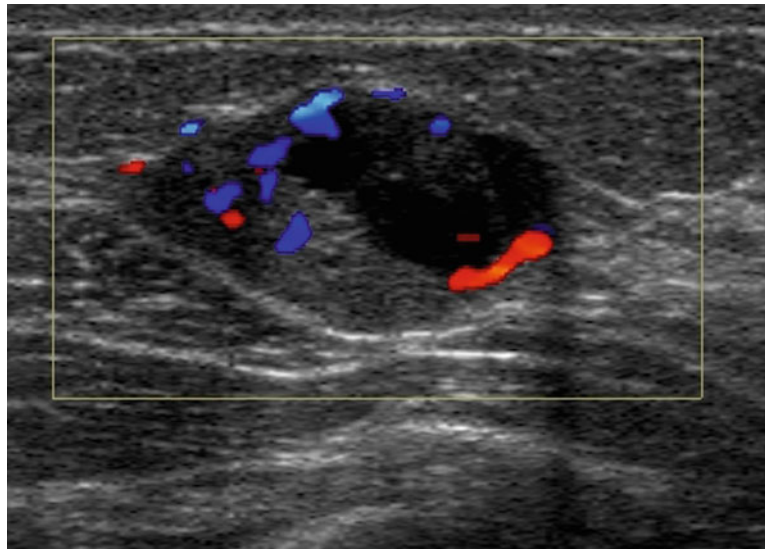

Fig. 4.5 Palpable right breast mass showing indeterminate sonographic features. US-guided core biopsy confirmed a fibroadenoma

intensely hypoechogenicity. *Microlobulations* refer to presence of 1–2 mm lobulations on the surface of a solid mass.

Using this criteria, Stavros and others, in a series of 750 solid masses, characterized 625 masses as benign (83 %) and 125 as malignant. Mammography did poorly compared with sonography in characterizing a malignant mass. Mammography did not identify 24/125 malignant masses that were correctly characterized by sonography; an additional five malignant masses were classified as probably benign based on mammographic features [62]. The high negative predictive value of sonography in excluding malignancy in a solid mass was proven in this study where only two (0.5 %) of the 426 solid masses that were characterized as benign were malignant, one of which was a metastasis from lung cancer [62]. The malignancy rate amongst masses classified as malignant was 73 %, and the cancer rate in the group considered as indeterminate was 12.3 % [62]. Others have studied the accuracy of ultrasound in being able to distinguish benign from malignant masses with similar results [65–67]. The value of sonography in diagnosing malignant palpable masses was reported in a multi institutional study of palpable masses undergoing sonography; all 293 of 616 palpable masses were correctly characterized as probably malignant by sonography [65]. In a retrospective series of 162 masses undergoing biopsy, three most reliable discriminatory features of a benign mass were round or oval shape (67/71, 94 % benign), circumscribed margins (95/104, 91 % benign), and a width to aneroposterior dimensions >1.4 (82/92, 89 %) [66]. Morphological features most suggestive of a malignant mass were an irregular shape (19/31, 61 %), width to aneroposterior ratio of <1.4 (28/70, 40 %), microlobulations (4/6, 67 %), and spiculation (2/3, 67 %). Like others, these investigators found that internal echotexture of a mass and presence of posterior acoustic enhancement does not help in the distinction between a benign or malignant mass. Uniform hyperechogenicity, although a very useful feature in characterizing a mass as benign, is not very helpful since it is a finding uncommonly encountered in a mass [66]. Some of the descriptors of a mass, such as a thin echogenic capsule, are a finding that may be subject to considerable interobserver variability [66, 67]. If the three most useful sonographic features of a benign solid mass were strictly applied, the positive biopsy ratio would potentially increase from

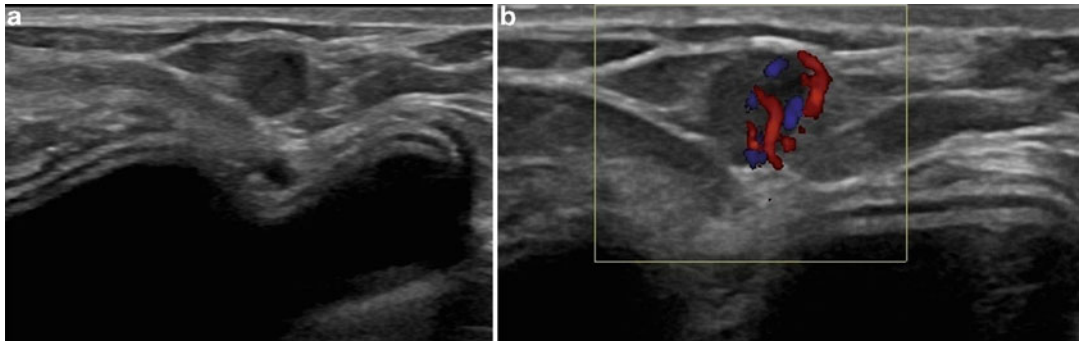

Fig. 4.6 Color Doppler imaging. (**a**) Solid palpable round mass with indeterminate morphological features in a patient with an implant. (**b**) Color Doppler imaging demonstrated rich vascularity. US-guided core biopsy confirmed an invasive ducta

23 to 39 % [66]. Using benign mass criteria of an oval or lobulated shape, circumscribed margins, internal echogenicity of isoechoic, mildly hypoechoic or hyperechoic, a mass that was wider than tall, and a non-shadowing mass or one with increased posterior echoes, 144 of 844 solid masses were categorized as benign; there was only one malignant mass in this group, indicating that biopsy avoidance is a feasible alternative when clearly benign sonographic features are demonstrated in a solid mass [66, 67].

Supplemental Tools to Real-Time Sonography to Characterize Solid Palpable Masses

Color Doppler

Neovascularization is a feature of malignant tumors, and hence color and power Doppler imaging has been proposed as a complementary tool in the evaluation of a solid breast mass [68–72].

Color Doppler imaging reflects the mean intravascular frequency shift caused by the Doppler effects of flowing red blood cells, whereas the power Doppler represents the intensities of the Doppler signals within a time period. On ultrasound images, hypervascularity (92.9 %) and presence of irregular vessels (73.2 %) are features of malignant tumors (Fig. 4.6a, b). Other associated features in a malignant mass indicative of a malignant mass are presence of rich vascularization (vessel mass ratio >10 % in 54.2 % of cases) and more than one vascular pole [69]. Typical color Doppler signs of malignancy are intratumoral vessels that are central (86 % in malignancy vs. 51 % in benignity), penetrating (65 % vs. 34 %), branching (56 % vs. 22 %), and disordered (42 % vs. 8 %). Power Doppler imaging can be used to depict a significant intratumoral increase in blood flow ($P \leq 0.0001$) compared with the flow in normal breast tissue [72]; an increased vascularity on power Doppler images in the area of a possible isoechoic nodule in fat increases confidence that the finding indicates an abnormality [73]. However, such a finding is not useful until the presence of a focal isoechoic mass is suspected. False-negative findings at B-mode US screening of the breast are not improved by using Doppler imaging [69]. Isoechoic lesions surrounded by fat can result in false-negative interpretations and a delayed diagnosis of breast cancer. Color and power Doppler imaging in combination with spatial compound imaging, tissue harmonic imaging, elastography power Doppler fremitus imaging, and contrast agent enhancement have been proposed as supplemental techniques to aid in identification of such isoechoic masses [73].

Elastography

Sonoelastography is a method that attempts to distinguish benign from malignant masses [74–76]. Tissue compression results in tissue deformation;

the extent of this deformation is measured. It is based on the premise that elasticity of a malignant tissue is harder than benign masses. Hence, malignant masses will have a greater elasticity coefficient. The color map of tissue elasticity is superimposed on the real-time greyscale ultrasound image, with each color representing a certain level of elasticity. The more commonly studied method utilizes an elasticity score that is categorized from 1 to 5; softer lesions that are likely benign have a score of 1–3, and harder masses that are more likely malignant [75]. The value of elastography is dubious, and biopsy avoidance based on findings of elastography is unlikely to be widely accepted in clinical practice. As Dempsey points out in an editorial opinion:

> We cannot, therefore, afford to continue to function in a mindset where we try at all cost to avoid doing a simple, rapid, and accurate needle biopsy by which a definite histologic diagnosis can be made. We must not attempt to substitute one or more time-consuming, physician-inefficient, costly, and often inaccurate imaging studies that, based on data currently available, accomplish nothing more than producing a needless procrastination in a timeline that should be efficiently targeted to quickly establishing a firm diagnosis from which proper patient management can be promptly initiated [77].

Follow Up of Sonographically Identified Solid Masses

To improve specificity of sonographic evaluation of solid palpable breast masses, it is imperative to characterize masses that have predominantly benign features as benign and to adopt a surveillance strategy; this is particularly important in a screening program in developing countries. The number of false-positive biopsies in such settings has to get as low as reasonably possible. In these situations where compliance is a challenge to begin with, the perception that attending such screening clinics results in excessive and/or unnecessary biopsies may threaten the success of a breast cancer screening program. However, unlike in mammography where studies have established criteria for follow up of certain findings such as circumscribed masses, grouped punctuate microcalcifications, and focal asymmetry [78], similar large prospective studies other than the one published by Stavros have not been carried out for sonographic findings. Interobserver variability has also been an issue with specific sonographic morphologic features as pointed out previously; nevertheless, several retrospective studies have established the value of utilizing sonographic morphology in classifying solid masses as benign and thereby avoiding biopsy [62, 66, 67, 79, 80]. A mass that is oval or macrolobulated, demonstrates circumscribed margins of the entire circumference, has width greater than height, and is isoechoic or mildly hypoechoic fulfills the criteria of a benign mass. Using these criteria, 445 solid, non-palpable masses were classified as probably benign and followed 2–5 years; the first follow-up was at 6 months. There was only one cancer in this group, resulting in a negative predictive value of 99.8 % [79]. A retrospective study of palpable masses also had comparable results [80]. These investigators used the criteria of round, oval, lobular masses with circumscribed margins, homogenous echo texture, and no malignant features. There were 372 solid palpable masses identified by sonography. Follow up was either clinical or imaging; an advantage of palpable masses is that they can be followed up for interval enlargement by clinical examination. There was only one cancer in the 375 solid palpable mass that was recommended for follow-up; in a 2.5 mm round hypoechoic mass that was considered a cyst or a solid mass, a 1.5 mm focus of DCIS was found surrounded by fibrocystic change. Therefore, one single false negative was likely an incidental focus of intraductal cancer. The cancer incidence, even taking into account this single case, was 0.3 % [80].

Breast Cancer Staging with Ultrasound

Breast ultrasound is a useful tool not only to diagnose breast cancer but can also be used to stage the cancer and hence can play an important role in the management of a patient diagnosed with breast cancer. Local and regional staging of

breast cancer involves documentation of primary tumor size, identifying multifocality and multicentricity, and assessing regional nodal status. Multifocal disease is diagnosed when there are two cancers in one quadrant of the breast, and multicentricity is when there are two or more cancers in different quadrants of the breast [81].

Multicentricity precludes breast conservation surgery and results in mastectomy. Lymph node status is the single most important prognostic factor in a breast cancer patient and is very easily and accurately assessed by sonography. Axillary ultrasound and sonographic-guided fine needle aspiration biopsy of abnormal lymph nodes allow one to diagnose axillary nodal metastasis; in positive cases, a sentinel node biopsy is not needed and patients undergo axillary lymph node dissection. Mammography, on the other hand, images the axilla incompletely. Routine sonographic assessment of ipsilateral axillary, infraclavicular, internal mammary, and supraclavicular nodal basins is recommended [81–86].

Ultrasound-Guided Biopsy of Solid Palpable Masses

Large Core Needle Biopsy

Percutaneous biopsy under imaging guidance has nearly replaced open surgical biopsy for nonpalpable as well as palpable lesions identified during screening mammography or diagnostic sonography. This has served to minimize the harm resulting from the often touted false positive surgical procedures resulting from screening women with mammography. Presurgical localization is now performed for selected indications, such as in those patients with a biopsy proven cancer, in those who have imaging pathological discordance at core needle biopsy, in those with high risk lesions such as atypical ductal hyperplasia, radial scar, papillary lesions diagnosed at percutaneous biopsy, or where core needle biopsy is not an option or fails to provide a definitive histological diagnosis [87]. The malignant open biopsy rate has decreased from 2.04 per 1,000 women in 1996/1997 to 0.40 per 1,000 women in 2008/2009, as the nonoperative diagnosis rate for cancers has increased from 63 % to a substantial 95 % [88, 89]. Percutaneous image-guided large core needle biopsy is preferably performed under ultrasound guidance. Mammographic guidance requires a stereotactic biopsy system which can be an add-on device to existing mammography equipment. This is obviously not an option when mammography services are unavailable or limited in availability in developing countries. Apart from this reason, ultrasound-guided biopsy is quicker, is better tolerated, and is a natural choice for all abnormalities seen on a breast ultrasound examination. We recommend sonography as the preferred modality for assessing palpable abnormalities of the breast whether discovered during BSE or during CBE. For this reason, it is the optimal imaging modality for guidance. The recognized gold standard in developed countries is use of 14-guage needle with a throw or excursion of at least 2.2 cm. There have been encouraging results with use of smaller gauge needles, which may represent better choices in developing countries [90–92].

A consecutive series of US-guided core needle biopsies in 1,532 lesions had discordance in only 62 lesions; there were seven malignancies in 55 of those lesions that underwent vacuum-assisted percutaneous biopsy with larger needles. There were 12 cancers diagnosed at repeat biopsy confirmed at surgery [90]. In a consecutive series of 1,069 lesions biopsied using a 16-guage needle under ultrasound guidance, there were only 28 lesions with discordance, only six lesions were malignant, and all were diagnosed at repeat biopsy using a large 10-guage needle and using vacuum-assisted biopsy [91]. In one series of 235 lesions where a routine postfire needle tip position was confirmed in the orthogonal plane to confirm satisfactory sampling, the sensitivity of US-guided core needle biopsy using an 18-guage needle for breast cancer was 96 % (199/207 lesions) [92].

Fine Needle Aspiration Biopsy

Fine needle aspiration biopsy has been well established in the diagnosis of breast lesions. Its advantage is that it is quick, inexpensive, has minimal to no complications, and is well tolerated

by patients. Its usefulness has been documented in several studies [93, 94]. Fine needle aspiration cytology (FNAC) is an established and accurate method for diagnosing breast lesions. In recent years, there has been increased use of core needle biopsy [94]. The challenges for routine use of fine needle aspiration biopsy are lack of experienced cytopathologist, availability during the procedure to check adequacy of sampling so that repeat sampling can be performed, reliable distinction of invasive from in-situ cancer, and difficulty in equating cytomorphologic features in aspirates with histologic classification system especially for benign lesions [94]. A study that looked at 4,367 FNABs for which histologic correlates were available for 1,275 lesions reported that the false positive and false negative for FNAB was 1.7 % (7/404) and 7.1 % (45/635), respectively, compared to 0 and 5.7 % for core needle biopsy. Inadequate sampling was seen in 15.1 % of lesions undergoing FNAB and was attributed to presence of collagenous lesions and to physicians inexperienced in performing FNAB [94]. Core needle biopsy is the preferred method when FNAB provides inadequate specimen for fibrotic or collagenous lesions such as lobular cancer or radial scar [94]. A meta-analysis of 46 studies was performed to assess the value of FNAB [93]. FNAB is quicker, better tolerated, and cheaper to perform than a core needle biopsy, and its results can be obtained within hours, a potentially great advantage in developing countries, particularly in rural settings or where a woman has traveled a distance to participate in a screening program. In situations where compliance may suffer if multiple clinic visits are needed, same visit results seem to be inherently advantageous. However, core needle biopsy is more robust, accurate, and reliable when compared to FNAB; the false-negative rate and the rate of insufficient samples are significantly lower. Advantages of FNAB over CNB are a lower complication rate, lower incidence of hematoma, and the rare pneumothorax. Many institutes in the USA, UK, and Canada now prefer CNB to FNAB; however, the latter still retains its use in parts of Europe and Asia [93].

The National Cancer Institute recommendation for the diagnosis of breast aspiration cytology is:

C1 = unsatisfactory

C2 = cells present all benign; no suspicious features

C3 = cells suspicious but probably benign

C4 = cells suspicious but probably malignant

C5 = definitely malignant

C3 and C4 require further testing for confirmation, and C5 can undergo surgery based on the cytology findings. The meta-analysis included 29 studies from Asia and 17 from North America and Europe. When C1 (unsatisfactory samples) was excluded, the sensitivity was 92.7 % and the specificity was 94.8 %. Unsatisfactory sample was treated as positive so that a potential breast cancer diagnosis was not delayed [93]. Underestimation rate in the unsatisfactory sample group was 27.5 %. Therefore, it is strongly recommended that unsatisfactory samples undergo either CNB or open surgical biopsy [94]. Vacuum-assisted biopsy is routinely used in the USA for stereotactic and MRI-guided breast biopsy. However, it is not widely used to biopsy lesions seen under ultrasound. All lesions that are seen under ultrasound are best biopsied under ultrasound guidance; the advantages are cost, patient comfort, procedure time, and no ionizing radiation. MRI-guided biopsy is expensive and time consuming, and is reserved for abnormalities that are identified only on MRI; a second look ultrasound is routinely performed for MRI-detected abnormalities in an attempt to substitute a preferred modality for guidance to MRI. The added sensitivity of using vacuum-assisted device is minimal and comes with significant added cost and a higher complication rate; in any case, it is not a sensible option in low resource settings. Postfire needle position verification is important and increases the yield of adequate samples during US-guided percutaneous breast biopsy. Postfire needle position is confirmed in an orthogonal plane [95]. The reported complication rate of VAB ranges from 0 to 9 % with a mean of 2.5 % [95]. The complication rate reported for core needle biopsy is as low as 0.2 % [95].

Lastly it is important to be aware of some abnormalities that are suggested based on morphological

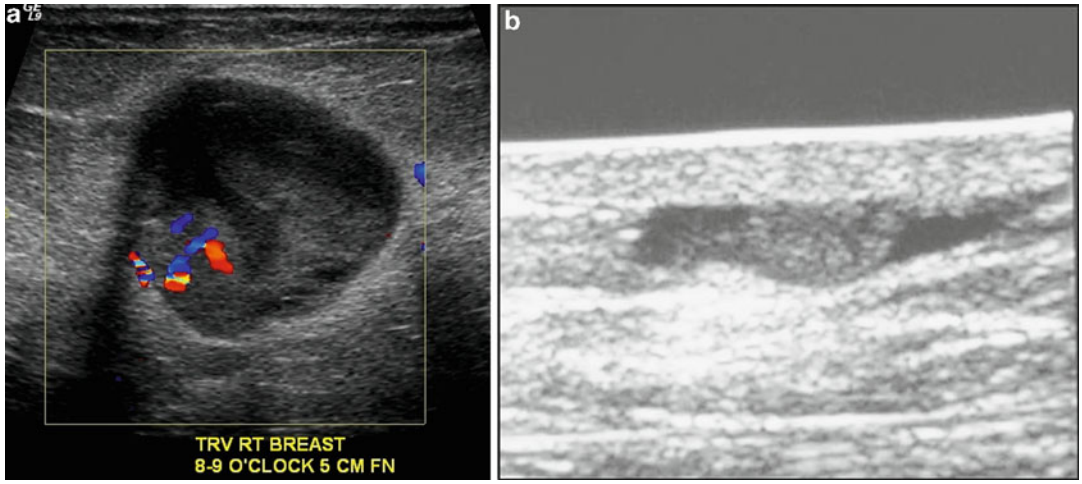

Fig. 4.7 Palpable abnormalities that are best excised surgically without percutaneous biopsy. (**a**) A cyst with a large irregular vascular mural nodule histologically proven at open surgical biopsy to be a low grade intracystic papillary cancer. (**b**) An intraductal mass histologically confirmed to be an intraductal papilloma with DCIS at open surgical biopsy. Patient presented with bloody nipple discharge

appearance that should prompt a recommendation for open surgical biopsy, bypassing core needle or fine needle aspiration biopsy (Fig. 4.7a, b). These include intraductal masses (Fig. 4.7b), intracystic masses (Fig. 4.7a) that require excision due to association of invasive cancer and a risk of underestimation of disease when sampled by needle techniques, and large tumors that may have to be excised for symptomatic relief and/or due to a risk of Phylloides tumor. In these circumstances, referral to a regional facility for surgical management is most appropriate.

Summary

In the face of increasing incidence and mortality from breast cancer, implementation of health care interventions aimed at early diagnosis are critical to reduce the disparity in mortality rates that currently exist between developed and developing countries. Screening mammography has proven benefits as shown in multiple clinical trials in reducing mortality from breast cancer. An organized screening mammography program, however, is not a feasible or cost-effective strategy in developing countries for many reasons, most importantly because of the prohibitive cost and the resources needed to set up such a program (Table 4.1). A well-organized screening mammography program requires the manpower resources of physicians skilled in reading mammography, technologists competent in obtaining satisfactory images, patient tolerance of a somewhat uncomfortable exam, relatively costly initial equipment costs, and maintenance costs for equipment. Regulatory body oversight to ensure quality in the performance and interpretation of screening studies are additional challenges in low- to mid-resource countries that are simultaneously facing competing health care priorities such as malnutrition and communicable diseases. A set up for opportunistic screening mammography with availability of diagnostic mammography, diagnostic sonography, and image-guided percutaneous biopsy including stereotactic biopsy for abnormalities such as microcalcifications or other findings that are only visible at mammography may be an option in urban areas of mid resource countries.

The aim of a breast cancer screening program will be to find a high percentage of the cancers that exist in the target population and finding these cancers while keeping false positives as low as possible. The goal should also be to find small and preferably node negative cancers (Fig. 4.8a–c),

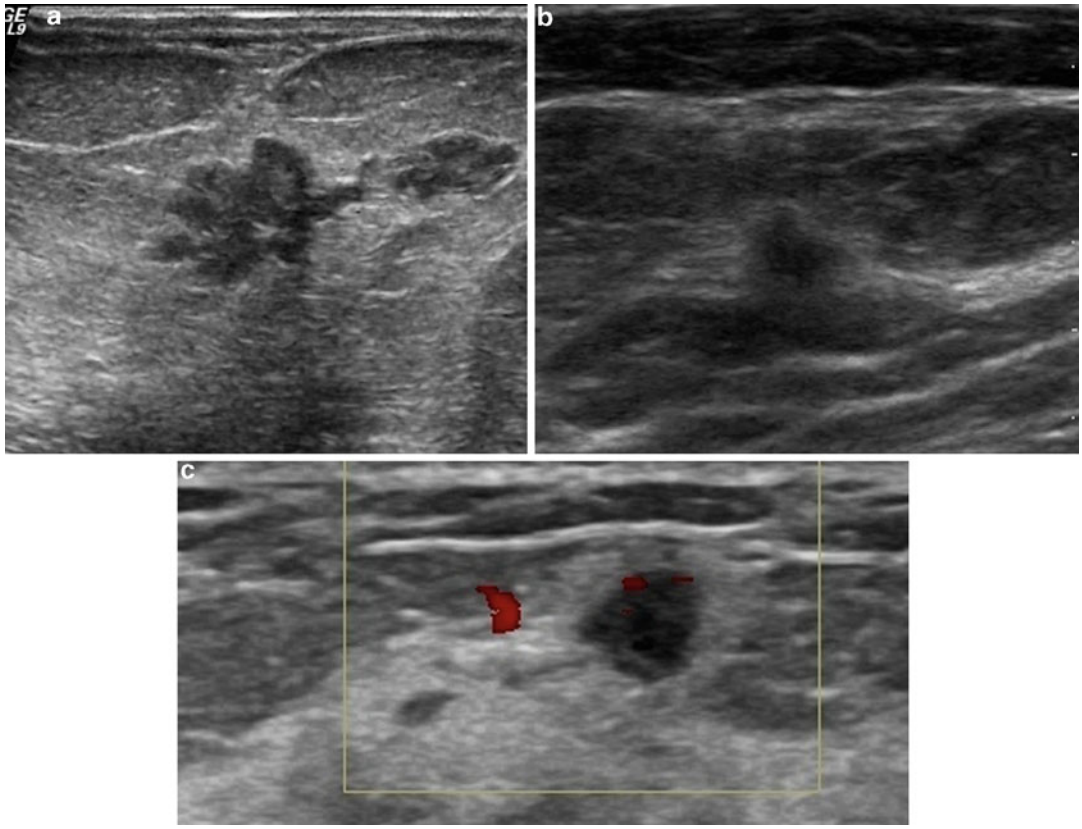

Fig. 4.8 Examples of small node negative early stage palpable breast cancers identified on ultrasound. (**a**) Intraductal mass seen on ultrasound of a palpable mass histologically proven to be DCIS. (**b**) Small irregular mass with malignant sonographic features histologically confirmed to be an invasive ductal cancer. (**c**) Small spiculated mass with malignant features confirmed to be an invasive cancer by a US-guided core needle biopsy

although, without use of high quality mammography and skilled mammography physicians, this may be a difficult goal; downstaging cancers from the now prevalent Stage 3 and Stage 4 to a Stage 1B to Stage 2 cancers may be feasible. This by itself is expected to make a significant difference in mortality and morbidity.

For the majority of women in developing countries, particularly those residing in rural areas, and for programs that are government funded, a modified triple assessment approach as outlined (Fig. 4.9) consisting of a high quality CBE by health care workers who have received formal training in performing breast examination; this is most practical. Such a screening examination in women aged 40–64 years performed on an annual basis is recommended. In those with a palpable abnormality, a focused breast ultrasound should be performed. Diagnostic mammography is not a feasible method of evaluating a palpable abnormality in low resource settings for many reasons described earlier. Substituting ultrasound has several advantages including less cost, better triaging of palpable abnormalities to determine the need for tissue sampling, and a superior method of guidance for biopsy of solid palpable masses. Core needle biopsy of such masses during a single visit ensures better patient compliance. Ultrasound is helpful in significantly reducing the need to biopsy of a significant number of benign abnormalities that account for palpable lumps. Judicious use of ultrasound has a potential to have an acceptable positive biopsy rate. Comprehensive training of physicians and health care workers performing

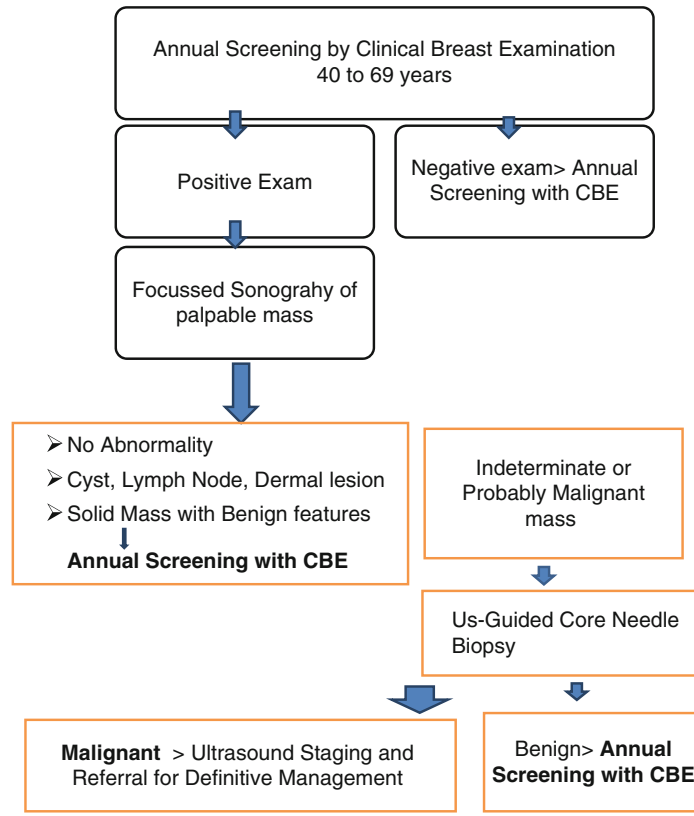

Fig. 4.9 Algorithm of proposed breast cancer screening strategy

this ultrasound and providing telemedicine support as needed will be key to the success of this modified triple assessment approach. Such an approach will, however, have to be validated through rigorous large observational studies; RCTs, although ideal to prove benefit of mortality reduction, may not be feasible. RCTs have been traditionally considered the gold standard; observational studies have also been shown to perform well in testing efficacy of a certain intervention in a population [96].

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