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RESEARCH ARTICLE

Breast Ultrasound Following a Positive Clinical Breast Examination: Does It Have a Role in Low- and Middle-Income Countries?

Vivien Tsu[1,2], John R. Scheel[3,4*], Amie Bishop[5], Marjorie Murray[1], Bernhard Weigl[6], Constance D. Lehman[7,8]

[1] PATH, Seattle, WA, USA
[2] University of Washington, School of Public Health, Department of Epidemiology, Seattle, WA, USA
[3] University of Washington School of Medicine, Department of Radiology, Seattle, WA, USA
[4] Seattle Cancer Care Alliance, Seattle, WA, USA
[5] Amie Bishop Consulting, LLC, Seattle, WA, USA
[6] Intellectual Ventures/Global Good, Bellevue, WA, USA
[7] Massachusetts General Hospital, Department of Radiology, Boston, MA, USA
[8] Harvard Medical School, Boston, MA, USA

***Corresponding author. Current address:** University of Washington, Seattle Cancer Care Alliance, 825 Eastlake Avenue East, G3-200 Seattle, WA 98109-1023; jrs4yg@uw.edu

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Abstract

Purpose: Breast cancer is the most common cancer among women worldwide, with an estimated 1.7 million new cases occurring in 2012. The majority of cases and deaths occur in low- and middle-income countries (LMICs), where population-based mammography screening is not available and countries must rely on clinical breast examination (CBE). Since ultrasound has the potential to reduce unnecessary biopsies by triaging women with palpable or focal breast findings at CBE, we searched for evidence in the literature on the effectiveness of ultrasound in detecting potential breast cancer following positive CBE findings.

Methods: We reviewed the literature from 2000 to 2014 for evidence on the performance of breast ultrasound, in the absence of mammography, used to evaluate women after a positive CBE. From the studies meeting our inclusion/exclusion criteria for our analysis, we extracted data on the study design, location, ultrasound transducer parameters, patient age, method for determining positive and negative cases, and number of malignancies detected/total number of women studied.

Results: We found 15 studies matching our inclusion/exclusion criteria, 9 from high-income countries and 6 from LMICs. Despite considerable variability in study design and patient populations, breast ultrasound consistently showed high sensitivity (median = 94 percent) and specificity (median = 80 percent) for detecting breast cancer and identifying normal and benign findings not requiring a biopsy. Clear patterns related to transducer frequency or income level were not discernible given the variations in patient populations and final diagnostic determinations.

Conclusion: Our systematic review suggests that breast ultrasound following a positive CBE may be a powerful diagnostic test to determine those who do or do not need biopsy. We encourage further research in breast ultrasound use after a positive CBE in LMICs to assess the accuracy of ultrasound in these settings and the feasibility of widespread implementation.

Introduction

BREAST cancer is the most common cancer among women, with an estimated 1.7 million new cases occurring in 2012 (1). More than half of cases and more than 60 percent of deaths now occur in low- and middle-income countries (LMICs) and these proportions are expected to increase. While the absolute number of deaths in industrialized countries will increase 23 percent by 2030, those in less developed countries will increase 55 percent (1). These grim figures demand renewed efforts to diagnose early stage breast cancer in LMICs when it is potentially curable.

The importance of early detection and

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treatment of breast cancer is well recognized (2,3) and is supported by the observed decrease in breast cancer deaths among women in high-resource regions undergoing screening mammography. However, there is disagreement on the relative contributions of population screening and adjuvant therapy to the decline in deaths (4,5). A study that developed seven independent statistical models to distinguish the effects of these two factors in the United States reported that the contribution of screening in these models ranged from 28 to 65 percent (6), indicating the difficulty of evaluating the differential impact of interventions. All major North American and European groups that make recommendations on breast cancer screening support routine mammography, starting at age 40 or 50 and performed every one or two years (7,8). Although the age of initiation and frequency of mammography exams for population screening has been the subject of much controversy (5,9,10), it remains the standard imaging technique for screening in developed countries.

The debate taking place on screening mammography in industrialized countries is a luxury that most LMICs have not had. Population-based breast cancer screening using mammography has not been widely implemented in these regions because the infrastructure necessary to support screening programs, such as trained personnel, facilities, and equipment, is expensive to establish and maintain (11). In addition, the resources for providing effective educational and communication campaigns to encourage participation in screening have not been available.

An alternative to screening mammography for low-resource settings is clinical breast examination (CBE), a hands-on physical examination and visual assessment of the breasts by a healthcare professional, along with a careful medical history (12,13). There have been no published randomized clinical trials for CBE as a sole screening or early detection modality (14,15). Preliminary results have been reported from a randomized clinical trial in India evaluating whether CBE can reduce the incidence of advanced disease and mortality from breast cancer (16). However, conclusive results will only become available after completion of three rounds of screening and further follow-up.

The American Cancer Society recommends that women in their 20s and 30s have a CBE as part of a regular health exam by a health professional every three years and that, starting at age 40, women should have a CBE by a health professional every year (17). CBE has also been suggested both for population screening in LMICs (9,12,18) and for evaluating women presenting with breast symptoms such as lumps, pain, thickening, or nipple discharge (19). The International Agency for Research on Cancer states in its 2002 Handbook: “Clinical breast examination may be of particular importance in countries where there are insufficient resources for [screening] mammography and where disease is usually at an advanced stage at the time of diagnosis” (7). The World Health Organization notes that low-income areas have the option to implement early diagnosis programs based on awareness of early symptoms and referral for confirmed diagnosis and treatment (3).

Using CBE for screening raises the question of what the next steps should be after palpable masses or focal symptoms are identified. In well-resourced settings, a positive CBE is evaluated with breast imaging—mammography and/or ultrasound depending on the patient’s age—and biopsy is recommended for lesions suspicious for malignancy. Ultrasound is better able to differentiate solid from cystic masses than mammography (20-22), and it is generally acknowledged that ultrasound is an important tool in evaluating symptomatic women, especially women under age 40, whose breasts are typically denser than those of older women. Ultrasound is also widely used for triaging solid palpable masses that require a biopsy versus those that can safely be managed by imaging or clinical follow-up, thus reducing the number of unnecessary biopsies (23). For palpable breast masses, the American College of Radiology recommends ultrasound as the first imaging evaluation in women under age 30, ultrasound or mammography in women ages 30 to 39, and mammography followed by ultrasound (for most cases) in women ages 40 and older (24). Masses with distinct benign features on ultrasound (such as a simple cyst or lymph node) do not need further intervention, while masses with probable benign features on ultrasound can be followed clinically and with imaging. Masses with features suspicious for malignancy should undergo tissue sampling, with core needle biopsy (CNB) or fine needle aspiration (FNA) when available. The United Kingdom Association of Breast Surgery recommendations (25) are similar to those of the American College of Radiology.

Imaging with ultrasound of clinically suspicious palpable findings at CBE might be useful in LMICs, where mammography machines are not available and many hospitals may have ultrasound equipment appropriate for breast imaging. Ultrasound used in this way could alleviate the burden of evaluating symptomatic women, because CBE alone has poor diagnostic accuracy for separating benign from malignant lumps and thus requires more tissue sampling than is likely needed.

In view of the potential role that ultrasound could play in LMICs for triaging women with palpable or focal breast findings at CBE, either to biopsy or to follow up clinically or with imaging, we searched for evidence in the literature on the effectiveness of ultrasound in detecting potential breast cancer following positive CBE findings.

Materials and methods

We used PubMed, Google Scholar, and the Cochrane database to perform a systematic review of the literature regarding the performance of breast ultrasound in LMICs following a CBE-positive test. Our search criteria included English-language literature published within the period of 2000 through 2014, using the following terms: palpable AND (ultrasound OR sonography OR ultrasonography) AND (developing countries OR low-income countries). We excluded the following studies: population-based ultrasound screening of asymptomatic women; ultrasound examinations performed after mammography; ultrasound performance measures of palpable and non-palpable lesions if only reported combined; and ultrasound performance limited to “probably benign sonographic features.”

After the primary searches, we searched the bibliographies of relevant papers and contacted experts in the field for further recommendations appropriate for our inclusion/exclusion criteria described above. Papers published prior to 2000 were included from the latter searches if they met the other inclusion criteria; two papers were added on this basis. While our interest was primarily the use of ultrasound in LMICs, we included selected studies from high-income countries if they met our other inclusion/exclusion criteria because of the scarcity of studies in LMICs, and for comparison purposes. From those studies meeting our inclusion/exclusion criteria for our analysis we extracted data on the study design, study location, ultrasound transducer parameters, patient population (age), the method for determining positive and negative cases (fine needle aspiration, core needle biopsy and surgical biopsy), and the number of malignancies detected/total number of women studied. We also extracted ultrasound performance measures, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Results

This review covers a targeted group of studies that specifically report the performance of breast ultrasound, in the absence of or independent of mammography findings, following a positive CBE. Initial searches resulted in several hundred papers, which were assessed for relevance to our question. Our review of these reduced to 15 the number of papers that reported at least sensitivity of breast ultrasound for detection of malignancy after palpable masses or focal symptoms were found at CBE.

Two studies were from low-income countries and four were from lower middle–income countries: these are presented in Table 1. The remaining nine papers reported studies in upper-middle or high-income countries and are presented in Table 2. We included two studies that evaluated performance on pre-selected sonographically solid lesions because of our interest in the ability of ultrasound to differentiate malignant from nonmalignant palpable lumps. Four of the six LMIC studies, and four of the nine upper-income studies, were prospective, while the remainder were retrospective. All were performed at single institutions.

Patient populations

The 15 selected studies assessed breast ultrasound performance in different patient populations with different breast cancer prevalence. Three studies restricted participants to narrow age ranges (under 30 years (26); under 35 years (27); 30-39 years (28)). Some chose to investigate all women who had palpable findings and imaging during a given time period (26,28), one study reviewed a sample of women with symptoms and imaging who had confirmed cancer and an age-matched sample confirmed as nonmalignant (29). Studies from Taiwan (30) and India (31) pre-selected only cases identified as solid lesions on ultrasound, to see if ultrasound could further differentiate benign and malignant solid lumps. These are more restricted populations than the one our review initially set out to analyze, which included all palpable lesions, whether solid or cystic.

Equipment used for ultrasound

Most transducers used in studies from lower-income countries (Table 1) had a frequency of 7.5 MHz, with one study using a 12 MHz probe for some cases. In the higher-income studies, frequencies of the probes ranged from 6 to 14 MHz but were usually higher than in the lower-income country studies. One study in lower-income countries and two studies in the higher-income group did not report on the transducer frequency used (32-34).

Definition of ultrasound detection of malignancy

Ultrasound detection of malignancy in the selected studies was based on either the American College of Radiology Breast Imaging Reporting and Database System (BI-RADS) Atlas (4th edition) (35), which characterizes lesions using a specific lexicon and assigns them to a category based on a level of suspicion for malignancy; or on descriptors similar to those of BI-RADS, such as shape, margins, echogenicity, and ratios of dimensions.

In most studies, the gold standard for assessing ultrasound performance was histopathology based on either CNB or surgical excision; however, two studies of women under the age of 40 in the United States used 24 months of clinical and tumor registry follow-up for the majority of those with benign findings at ultrasound, and histopathology for those suspected of having a malignancy (26,28). One study used only FNA and cytology as the reference standard (31), while the rest used some combination of FNA, CNB, or surgical biopsy. Intervention methods for tissue sampling are given for each study in the tables below. Sensitivity, specificity, and other performance measures were reported for detecting cancer; some papers also reported performance for differentiating cysts from solid masses, but we report only performance in detecting

Table I. Performance of breast ultrasound in symptomatic women in low and lower-middle–income countries[a]

Study/design	Location (Economic Level[a])	Transducer Frequency	Mean Age (range)	Method for Diagnosis[b]	Number malignant/ Total Cases	Ultrasound Performance[c] (in %)
Ngotho 2013(27) Prospective	Kenya (Low Income)	7.5-12 MHz	25.5 (18–34)	FNA, CNB	6/58	Sensitivity: 100 Specificity: 94.2 NPV: 100 PPV: 66.7
Gonzaga 2010(36) Prospective	Uganda (Low Income)	7.0 MHz	N/A (40%: 30–39 20%: 20–29)	CNB, SBx	7/80	Sensitivity: 57.1
Irurhe 2012(37) Prospective	Nigeria (Lower-middle Income)	7.5 MHz	42 (18–59)	FNA, CNB	13/100	Sensitivity: 100 Specificity: 96.6 NPV: 100 PPV: 81.3
Devolli-Disha 2009(39) Prospective	Kosovo (Lower-middle Income)	7.5 MHz	56 (30–77)	SBx	259/546	Sensitivity: 72.6 Specificity 88.5
Singh 2008(33) Retrospective	India (Lower-middle Income)	Not Stated	41 N/A	FNA, CNB, SBx	20/100	Sensitivity: 65.0
Pande 2003(31) Prospective	India (Lower-middle Income)	7.5 MHz	41 (17-80)	FNA	19/36[d]	Sensitivity: 95.0 Specificity: 94.1 NPV: 93.8 PPV: 96.0

[a] Defined by the World Bank list of economies (51)

[b] FNA = fine needle aspiration; CNB = core needle biopsy; SBx = Surgical biopsy

[c] NPV = Negative Predictive Value; PPV = Positive Predictive Value

[d] Included only cases with positive findings on ultrasounds (e.g. masses and cysts)

Table II. Performance of breast ultrasound in symptomatic women in upper-middle and high-income countries[a]

Study/design	Location (Economic Level[a])	Transducer Frequency	Mean Age (range)	Method For Diagnosis[b]	Number malignant/ Total	Ultrasound Performance[c] (in %)
Li 2014(38) Retrospective	China (Upper-Middle Income)	7-14 MHz	Not Stated	CNB, SBx	2294/5296	Sensitivity: 97.9 Specificity: 49.7
Akbari 2012(32) Prospective	Iran (Upper-Middle Income)	Not Stated	Not Stated (30–79)	FNA, CNB, SBx	95/164	Sensitivity: 69.5 Specificity: 49.3 NPV: 65.3 PPV: 54.0
Zhu 2008(40) Prospective	China (Upper-Middle Income)	6-13 MHz	46 (17– 83)	SBx	69/139	Sensitivity: 94.2 Specificity: 87.1
Lehman 2012(28)	USA (High Income)	12 MHz	35 (30–39)	CNB, SBX, 2-year follow-up	23/1208	Sensitivity: 95.7 Specificity: 89.2 NPV: 99.9 PPV: 13.2
Loving 2010(26) Retrospective	USA (High Income)	12 MHz	24 (12–29)	FNA, CNB, SBx, 2-year follow-up	3/1091	Sensitivity: 100 Specificity: 80.5 NPV: 100 PPV: 1.9
Chen 2004(30) Prospective	Taiwan (High Income)	7.5-10.0 MHz	Not Stated (14–83)	CNB, SBx	391/1203 solid masses[d]	Sensitivity: 79.3 Specificity: 89.3 NPV: 90.0 PPV: 78.1
Houssami 2003(29) Retrospective	Australia (High Income)	7.5-11.5 MHz	Not Stated (25-55)	FNA, SBx, 2-year follow-up	240/473	Sensitivity: 81.7 Specificity: 88.0
Moss 1999(34) Prospective	United Kingdom (High Income)	Not Stated	Not Stated	SBx	256/456	Sensitivity: 88.9 Specificity: 77.9
Yang 1996(41)	Hong Kong (High Income)	5-10 MHz	37 (13–85)	FNA, SBx	67/408	Sensitivity: 97.0 Specificity: 96.88 NPV: 99.4 PPV: 85.3

[a] Defined by the World Bank list of economies (51)
[b] F NA = fine needle aspiration; CNB = core needle biopsy; SBx = Surgical biopsy
[c] NPV = Negative Predictive Value; PPV = Positive Predictive Value
[d] Included only cases with positive findings on ultrasounds (e.g. masses and cysts)

malignancy. Eight studies did not specify the histological types of malignancies diagnosed (27,31-34,36-38) while the remaining seven gave histological definitions of malignancies (26,28-30,39-41); none of the latter excluded ductal carcinoma in situ.

Performance of ultrasound

In general, studies using more powerful transducers reported higher sensitivities: of eight studies using probes with frequencies of at least 10 MHz, sensitivities ranged from 79.3 to 100 percent, with a median of 96 percent. In the four studies using probes with frequencies of 7 or 7.5 MHz, the range was from 57.1 to 100 percent, with a median of 84 percent. Of note, two small studies using probes with frequency of 7.5 MHz obtained sensitivities of 95 and 100 percent, in lower middle–income countries.

The number of cases reported in studies from LMICs was smaller than those reported from higher income countries, ranging from 36 to 546 cases with a median of 90. Sensitivities in all six studies ranged from 57.1 to 100 percent, with a median value of 84 percent, while median specificity was 94.2 percent (Table 1). In the two studies that included only solid lumps, sensitivity and specificity were 79.3 percent and 89.3 percent, respectively, for the Taiwanese study and 95 percent and 94.1 percent, respectively, for the small study from India.

In aggregate, studies from upper-middle and high-income countries showed that ultrasound detected 3,201 cancers (range 3–2,246) among the 3,438 cases included in the studies. Overall, the median sensitivity was 94.2 percent (range 69–100), median specificity was 87.1 percent (range 49–97), median PPV was 54.0 percent (range 2–85), and median NPV was 99.4 (range 65–100). Four studies reviewed more than 1,000 cases each (26,28,30,38), reporting sensitivities of 79.3 to 100 percent, with a median value of 96.8 percent (Table 2).

In two large studies conducted in the United States, sensitivity of ultrasound for detecting malignancy in women ages 30 to 39 was 95.7 percent and specificity was 89.2 percent (28), while for women younger than 30 years of age the numbers were 100 percent and 80.5

percent, respectively (26). In both studies, most of the women with benign findings at ultrasound did not have histological examination of the tissue, but instead were followed by imaging surveillance and tumor registries for at least 24 months. Because the study populations were not preselected for women who had biopsies, the number of malignant cases present was much lower than for studies that intentionally reviewed cases known retrospectively to have been malignant. Another retrospective study in a high-income setting chose to evaluate ultrasound performance on equal numbers of cases with and without malignant diagnoses, reporting a sensitivity of 81.7 percent and specificity of 88.0 percent (29).

Discussion

No randomized clinical trials have been conducted to evaluate the efficacy of breast ultrasound for detection of malignancy in symptomatic women; however, our review identified a number of prospective and retrospective analyses on ultrasound performance for palpable findings following a CBE. Sensitivity varied considerably across the studies, but in 10 of the 15 studies sensitivity was at least 80 percent and median specificity was 88 percent. The sensitivity, specificity, and NPV of ultrasound were generally high, while PPV was often low. The sensitivities observed in high-income countries were generally higher than in LMICs, and the specificities observed in LMICs were generally higher than in high-income countries; however, despite the wide range of performance in LMICs, it is clear that it is possible to achieve good sensitivity even with modest resources. The composition of the patient populations in LMICs may include more women with larger masses, since they are more likely to represent prevalent rather than incident disease, but this is difficult to distinguish from these studies. Sensitivity may also be overestimated in LMICs if screen-negative women were not followed, since this may lead to under-ascertainment of false negatives. Nevertheless, the reported performance of breast ultrasound following a positive CBE was generally favorable across all studies and warrants further evaluation.

The most comprehensive guidelines on early detection, diagnosis, and treatment of breast cancer in LMICs come from the Breast Health Global Initiative, an international program cofounded in 2002 by the Fred Hutchinson Cancer Research Center and Susan G. Komen for the Cure (42). The Breast Health Global Initiative has held five global summits to address various aspects of breast cancer in LMICs. In a report on the 2002 summit, researchers noted that in cases with a finding of a palpable mass, ultrasound could be used to distinguish cysts from solid masses and provides "an estimation of the likelihood of malignancy in a solid mass" (43). In subsequent publications, a tiered system was defined to stratify national health resources into four levels—basic, limited, enhanced, and maximal (44,45)—with recommendations at each level to match the economic capacities of countries. At the "basic" resource level, clinical history and CBE may be the only detection modalities available, while at the "limited" level, countries are encouraged to perform outreach and education promoting CBE for age groups at higher risk, and to use diagnostic ultrasound (with mammography, if available) for women with positive findings at CBE.

Many of the reports emphasized the need for high-quality equipment, careful operator training, and availability of trained radiologists for accurate interpretation. Classifying solid masses as malignant or benign typically requires skilled radiologists (30); however, training non-physician sonographers for some aspects of breast imaging could build human capacity in LMICs. Successful training of midwives in Zambia and Uganda for conducting limited screening ultrasound exams for obstetric use (46,47) demonstrates the potential for this approach. Other researchers in Uganda have pointed out that ultrasound equipment is tenfold more available in sub-Saharan Africa than are mammography machines, which are twice as expensive and dedicated to only one type of procedure (48).

Although traditional ultrasound devices are widely available in LMICs (49), transducers of appropriate frequency may need to be sourced, or existing transducers modified for breast evaluation. According to the American College of Radiology, "breast ultrasound should be performed with a high-resolution real-time linear array scanner operating at a center frequency of at least 10 MHz and preferably higher" (50). Our analysis found that many studies used suboptimal equipment, although that was probably the best available transducer. While we did note higher sensitivities in studies using higher frequency transducers, these studies varied in other ways, which may have confounded the results.

Exciting advances continue to be made in developing less expensive, more portable, and more rugged ultrasound units with power options including battery and solar power(52-55). Although many of these systems have been developed for non-breast applications, continued advances in breast imaging applications, including higher frequency transducer development, will support expansion of breast ultrasound into more remote areas.

This review revealed several limitations in the available data that constrain our ability to assess the performance of ultrasound in LMICs. The small number of studies from LMICs, and the variations in study populations and methods for determination of final outcome (biopsy type, with or without follow-up), are particular challenges. For example, in the two studies that included only patients with solid lumps, one might have expected a lower level of ultrasound performance, since researchers agree that ultrasound is good at distinguishing solid from cystic lesions but less effective at differentiating benign from malignant solid lesions (56); however, that was true in only one study. Another inconsistency was whether the number of cases reported included the number of lesions or number of patients. Few of the studies in lower-income settings had at least two-year follow-up of negative cases, so we should be cautious in interpreting negative predictive values.

Despite the shortage of advanced technologies for breast cancer screening, diagnosis, and treatment in many LMICs, more can and must be done with existing resources to improve access to services. Addressing the burden of breast cancer requires educating women and their healthcare providers so they can recognize and act on symptoms of breast cancer, such as palpable lumps or focal pain (9). Providers must be able to refer women with suspicious findings on CBE and ultrasound to appropriate pathology services (FNA or CNB) to confirm diagnoses. Additional research is also needed to determine the feasibility of and strategies for bringing treatment interventions such as surgery, hormone receptor testing, and chemotherapy within reach of women confirmed to have cancer. It is early and appropriate treatment, and not simply early detection and diagnosis, that save lives.

Conclusion

Overall, despite considerable variability in study design and patient populations, results of reviewed studies in high-resource areas and a limited number of LMICs consistently show the value of breast ultrasound in evaluating women with a positive CBE. These findings, despite their limitations, are encouraging. Our search found only a handful of studies reporting performance in low-resource countries, and we encourage more studies to assess the accuracy of ultrasound in these settings and the feasibility of widespread implementation. ❐

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Conflict of interest

The authors report no conflict of interest.

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