review article

Ultrasound for Breast Cancer Detection Globally: A Systematic Review and Meta-Analysis

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abstract

PURPOSE Mammography is not always available or feasible. The purpose of this systematic review and meta-analysis is to assess the diagnostic performance of ultrasound as a primary tool for early detection of breast cancer.

MATERIALS AND METHODS For this systematic review and meta-analysis, we comprehensively searched PubMed and SCOPUS to identify articles from January 2000 to December 2018 that included data on the performance of ultrasound for detection of breast cancer. Studies evaluating portable, handheld ultrasound as an independent detection modality for breast cancer were included. Quality assessment and bias analysis were performed with the Quality Assessment of Diagnostic Accuracy Studies-2 tool. Sensitivity analyses and meta-regression were used to explore heterogeneity. The study protocol has been registered with the international prospective register of systematic reviews (PROSPERO identifier: CRD42019127752).

RESULTS Of the 526 identified studies, 26 were eligible for inclusion. Ultrasound had an overall pooled sensitivity and specificity of 80.1% (95% CI, 72.2% to 86.3%) and 88.4% (95% CI, 79.8% to 93.6%), respectively. When only low- and middle-income country data were considered, ultrasound maintained a diagnostic sensitivity of 89.2% and specificity of 99.1%. Meta-analysis of the included studies revealed heterogeneity. The high sensitivity of ultrasound for the detection of breast cancer was not statistically significantly different in subgroup analyses on the basis of mean age, risk, symptoms, study design, bias level, and study setting.

CONCLUSION Given the increasing burden of breast cancer and infeasibility of mammography in certain settings, we believe these results support the potential use of ultrasound as an effective primary detection tool for breast cancer, which may be beneficial in low-resource settings where mammography is unavailable.

INTRODUCTION

Breast cancer is the leading cause of cancer-related deaths among females worldwide. In 2018, 2.1 million new breast cancer cases and 626,679 deaths were reported.[1] Adequate access to detection of breast cancer with imaging is the first step in the diagnostic pathway to decrease mortality from this disease. Mammography, which has long been considered the gold standard for screening and early detection of breast cancer, is not always feasible, especially in limited-resource settings. This may be due to the high cost of purchasing and maintaining equipment as well as difficulty training and retaining skilled technologists and interpreting radiologists. Data from 2014 show that that per 1 million women between 50 and 69 years old, highly developed areas of the world have anywhere from 40 to 600 mammography units, whereas there is an average of 0 to 12 mammography units in most of sub-Saharan Africa and approximately 12 to 41 units in many developing areas in Asia.[2] In the United States, where 70% of women undergo mammography, the most recent estimates of the overall sensitivity and specificity of diagnostic digital mammography are 87.8% and 90.5%, respectively.[3,4] In low- and middle-income countries (LMICs), the reported sensitivity of mammography ranges from 63% to 95%; higher sensitivity is seen when examining palpable lumps, and lower sensitivity is seen in cases of dense breasts.[4]

Breast ultrasound, which is used in high-resource settings to supplement mammography in certain clinical scenarios, offers a potentially viable alternative for early breast cancer detection in some resource-limited areas because it is portable, lower cost than mammography, and versatile across a wider range of clinical applications. Breast ultrasound has been proven to be an exceptionally effective tool for imaging palpable abnormalities in the breast. It distinguishes

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Is portable ultrasound a viable breast cancer detection modality?

Knowledge Generated

A comprehensive literature review and meta-analysis revealed portable ultrasound to have an overall high sensitivity of 80.1% and specificity of 88.4% for detection of breast cancer in a variety of patient populations. When the available data from low-resource countries were considered, ultrasound maintained a diagnostic sensitivity of 89.25% and specificity of 99.1%.

Relevance

Portable ultrasound could serve as a global primary detection modality and triage method for breast lesions, particularly in low-resource areas where mammography is currently unavailable or infeasible.

cystic from solid masses and demonstrates those features of solid masses that would denote the mass as suspicious and warranting biopsy.[5-7] Ultrasound is a particularly useful diagnostic modality in dense breast tissue, often detecting breast cancers obscured on mammography.[8,9] Furthermore, if biopsy is required, ultrasound is the ideal imaging tool to guide subsequent procedures, further enhancing its utility in breast cancer diagnosis.[5-7]

The deployment of ultrasound as a diagnostic modality could be most helpful in LMICs, because they carry a disproportionate burden of disease. In 2012, 52.9% of the 1.7 million breast cancer cases were classified as global, and 62.1% of the breast cancer–related deaths occurred in LMICs.[10] Although breast cancer incidence is highest in high-income countries, mortality rates are lower in these locations as a result of advances in early detection, diagnosis, and treatment.[11,12] In 2018, the age-standardized incidence rate of breast cancer (per 100,000 women) in Northern America was 84.8, with a mortality rate (per 100,000 women) of 12.6, whereas for Western Africa the estimates were 37.3 and 17.8, respectively.[1] It is estimated that by 2020, 70% of all breast cancer cases worldwide will occur in LMICs, with a projected estimate to more than 1 million new cases per year in these areas.[5,13] These disproportionately high mortality-to-incidence ratios in LMICs are due to scarcity of available detection, diagnosis, and treatment of breast cancer.[14,15] It must also be acknowledged that data are severely lacking in LMICs, which can result even in an underestimation of the disease burden and barriers to care in these areas.[16] This situation is further exacerbated by insufficient patient education about breast health and the importance of early detection.[5,14] Identifying breast cancer at an early stage, before local, regional, or systemic spread, offers the potential for initiation of earlier, more effective treatment and is thus vital to improving outcomes in LMICs.[6]

Although the literature consistently reports increased breast cancer detection with use of supplementary screening ultrasound, few direct comparisons of mammography and ultrasound for average-risk patients have been reported.[3] The purpose of this systematic review and meta-analysis is to assess the potential of ultrasound, indicated by sufficiently high diagnostic performance against histologic confirmation and benchmarked against the highly accepted performance of mammography, for breast cancer detection, which could be particularly applicable in LMICs.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

We conducted a systematic literature review and meta-analysis following Cochrane Guidelines for Screening and Diagnostic tests and the Preferred Reporting Items for Systematic reviews and Meta-Analysis guidelines. We identified eligible studies in PubMed and Scopus (Amsterdam, the Netherlands) published between January 2000 and December 2018. The search was designed to identify all studies in which ultrasound was evaluated as a primary detection modality for breast cancer, both in a screening and diagnostic capacity. A comprehensive search strategy including free text and MeSH terms was developed in consultation with an experienced librarian specialist. Search terms included: “breast neoplasms,” “breast cancer,” “breast lesions,” “mammary ultrasound,” “breast ultrasound,” “breast diagnostic,” “mammography,” “low resource,” and “screening.” Titles and abstracts were screened to determine primary eligibility on the basis of the Preferred Reporting Items for Systematic reviews and Meta-Analysis algorithm (Fig 1). Reference lists of the retrieved publications were also screened for any additional relevant studies. If there were several publication reports for a specific study, the author was contacted to determine which study was most comprehensive for inclusion in this meta-analysis.

The inclusion criteria were discussed between authors, and joint consensus was achieved. The studies eligible for inclusion in this systematic review and meta-analysis were peer-reviewed studies in human participants in which portable ultrasound was evaluated as a primary detection modality for breast cancer. The search was restricted to

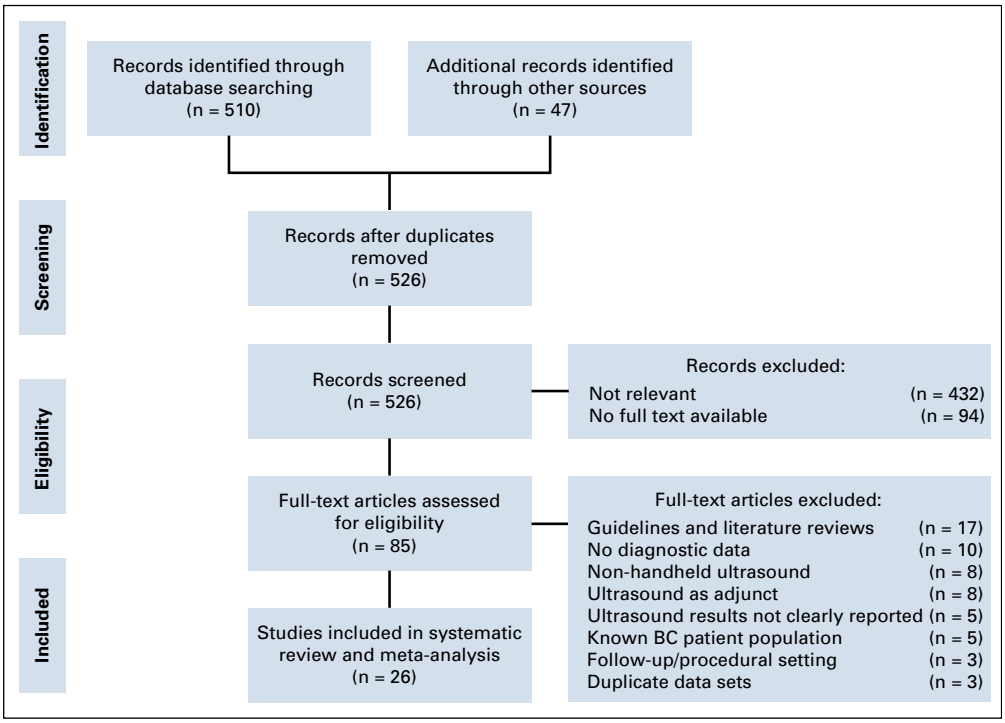

FIG 1. Flowchart of study selection. BC, breast cancer.

English language articles, and studies with portable ultrasound estimates were included. Prospective, retrospective, and cross-sectional studies published between January 2000 and December 2018 were included. The required reference standard was biopsy with histopathology results. Each manuscript was required to have extractable data to calculate true positives, false negatives, true negatives, and false positives so that sensitivity, specificity, positive predictive value, and negative predictive value (NPV) could be determined. Studies that compared mammography and ultrasound against verified histopathology were included, and data for both modalities were extracted. In comparative studies with other modalities, such as automated whole-breast ultrasound or magnetic resonance imaging, only handheld ultrasound estimates were extracted. Studies in populations with proven breast cancers were excluded, because they were deemed to bias diagnostic accuracy of the modality being evaluated. In addition, any study in which ultrasound was automated or examined only as a supplemental diagnostic modality, such as after mammography or magnetic resonance imaging screening, with only combined estimates recorded, were excluded. Studies in mammographically negative tissue with ultrasound diagnostic parameter values were included. When authors were unable to extract data for diagnostic parameter estimate calculations, primary authors of the considered article were contacted for clarification and raw data. In addition, duplicate articles were removed based on verified author, journal, title, and year of the study.

Data Extraction and Quality Assessment

One investigator (R.S.) extracted all study demographic data, including study type, study country, study setting, population, mean age, positive case definition, blinded image interpretation, and reference standard from each study. Two investigators (R.S. and D.S.) extracted data related to the number of ultrasound and mammography examinations, including quantification of true positives, true negatives, false positives, and false negatives. Two independent readers (R.S. and S.C.H.) performed the quality assessment and bias analysis with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.[17] Three domains were used to identify applicability concerns and risk for bias: patient selection, performance of index test, and standard of reference. Discrepancies were resolved by consensus review or a third reader (D.S.). Each study was given a final designation of low or high bias on the basis of these categories.

Data Analyses

Meta-analysis for assessing the diagnostic performance of ultrasound alone and also comparatively between ultrasound and mammography was conducted using STATA (version 15; STATA, College Station, TX). Extracted data for all included studies were pooled to yield summary estimates of sensitivity and specificity of ultrasound for detection of breast cancer. Heterogeneity was investigated with calculated Higgins I^2 values, with greater than 50% considered indicative of substantial heterogeneity among studies.[18] Forest plots were drawn to visually represent

overall diagnostic estimates and heterogeneity using the computing software R (version 3.5.2). Because significant variation was present among all studies, a Spearman correlation was performed between the sensitivity and false-positive rate (1 – specificity) to investigate the possibility of a threshold effect as the reason for the observed high heterogeneity. The result confirmed no positive correlation (Spearman rho, –0.1; *P* value = .4), so a bivariate random effects model was used to calculate pooled values for sensitivity, specificity, and diagnostic odds ratios (DORs) in contrast to using a summary receiver operating characteristic (ROC) model.[19-21] An ROC curve was constructed, and an area under the curve was calculated using Reviewing Manager (RevMan), version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014; Copenhagen, Denmark). Funnel plots of DORs were created, and the Deeks funnel plot asymmetry test was performed to evaluate for publication bias ,with *P* values $< .1$ considered statistically significant.[22,23] To account for presence of possibly missing studies, the trim and fill method was used to obtain the adjusted DORs for both ultrasound and mammography.[24]

To assess for possible improvement in ultrasound technology over the years, regression analysis of the DORs was performed and trended across publication years of the studies. Sensitivity analyses to assess for sources of heterogeneity were also performed by stratifying studies on the basis of covariates including study design, mean age, high-risk features, symptoms, tissue density, and bias level (on the basis of QUADAS-2). To evaluate for differences between the sensitivity and specificity of ultrasound and mammography for cancer detection in certain subgroups, a two-tailed test of proportion was used. DORs were linearly regressed against a covariate, and relative DORs (rDORs) were estimated to provide a comparison of diagnostic performance between different subgroups. *P* values $< .05$ were considered statistically significant.

RESULTS

The literature search with PubMed and SCOPUS yielded 557 studies. After removal of duplicates, 526 studies remained and were screened. Four hundred forty-one studies were excluded based on irrelevance (432 studies) or unavailable full texts (nine studies). Eighty-five full-text articles were reviewed. Among these, 17 were guidelines or reviews of the literature, 10 lacked data for two by two diagnostic table calculations, eight focused on alternative ultrasound modalities, eight discussed ultrasound only as an adjunctive screening modality, five were about methods for reporting ultrasound findings, five were in patient populations with proven breast cancer, three were about the use of ultrasound in follow-up care or procedures, and three were derived from similar data sets. After excluding these ineligible studies, 26 studies were included in the final systematic review and meta-analysis (Fig 1).

The 26 included studies included a total of 76,026 ultrasound examinations and 29,178 mammography examinations (Data Supplement). Weigert et al[25] provided data from all 4 years of the study, but to avoid duplication of data, only the final year data were analyzed as patients carried over from the first year through the final year. Seventeen studies reported mean age younger than 50 years, and seven reported mean age older than 50 years. Of the included studies, two did not provide a mean age.[25,26] The selected studies were geographically diverse, representing a total of 17 countries. Five of the 26 studies took place in LMICs (Kosovo, Nigeria, Uganda, and India), as determined by the 2018 World Bank classification.[27-32] In our classification for this meta-analysis, high risk was defined as positive family history, BRCA mutation, elevated risk scores, or a combination of these, which six of the studies met.[33-38] Symptomatic was defined as nipple discharge, palpable lump, unspecified, or a combination thereof in eight included studies.[27-29,31,39-42] Eighteen studies were in asymptomatic women. Six of the 26 studies were given a dense tissue designation, because 50% or more of all included patients were reported to have dense breast tissue.[25,43-47] In terms of setting, 14 took place in the screening setting, nine studies in the diagnostic setting, and three in a combination of both settings. Six studies took place in mammographically negative population subsets.[25,44,45,47-49] In regard to study design, 15 were prospective and nine were retrospective. Two were cross-sectional in nature (Table 1).[30,38]

From the 26 studies reporting findings on the use of ultrasound as a detection modality for breast cancer, the pooled sensitivity, specificity, DOR, positive predictive value, and NPV (95% CI) were 80.1% (72.2% to 86.3%), 88.4% (79.5% to 93.6%), 30.7 (13.0 to 72.3), 0.86 (0.81 to 0.91), and 0.80 (0.75 to 0.85), respectively (Figs 2A and 2B; Data Supplement). Of the 15 studies that concurrently assessed the performance of ultrasound and mammography as compared with the gold standard of histopathology, sensitivity and specificity (95% CI) of ultrasound were 74.9% (63.9% to 84.5%) and 87.0% (73.7% to 94.1%), whereas for mammography estimates were 55.8% (44.9% to 66.3%) and 94.3% (86.3% to 97.7%), respectively (Figs 2C and 2D; Data Supplement). In the comparative studies, both the sensitivity and specificity of ultrasound was significantly higher ($P < .001$). Among these 15 studies, overall DOR (95% CI) of ultrasound was 20.0 (6.5 to 61.2), whereas for mammography it was 20.8 (7.9 to 55.0), with a comparative rDOR of 1.5 (0.2 to 5.0) that was not statistically significant (*P* value = .90). As illustrated by the ROC curves for the studies comparing ultrasound and mammography against histopathology in the same patients, the areas under the curves were statistically significantly higher for ultrasound (*P* value $< .001$), at 0.87 (0.84 to 0.90) and 0.77 (0.73 to 0.81; Fig 3).

TABLE 1. Summary of the Included Studies Assessing Diagnostic Performance of Ultrasound for Detecting Breast Cancer

Publication	Journal	Type of Study	Description of the Studied Population	Age Range, Years (mean)*	Positive Case Definition	Exclusions	Image Interpreter†	Reference Standard‡	Countries Represented	Setting of Examination	QUADAS-2 Bias
Bahl (2015)[39]	*AJR*	Retrospective	Pathologic nipple discharge	13-88 (48)	DCIS and invasive adenocarcinoma	None specified	Radiologist with 5 years of experience; same	Histopathology; 2 years follow-up	United States	Diagnostic	Low
Berg (2015)[43]	*Journal of National Cancer Institute*	Prospective	Dense breasts	25-91 (55*)	Invasive or IDC	None specified	Physician; same	Biopsy histopathology within 1 year of mammo screening; no cancer based on minimum clinical 1-year follow-up	United States, Argentina, Canada	Screening	Low
Choi (2014)[50]	*Asian Pacific Journal of Cancer Prevention*	Retrospective	Asymptomatic with benign findings	19-82 (47)	IDC and DCIS	Axillary lesions, mammographic abnormalities	N/A; Board-certified radiologist with 1-11 years experience	Histology; follow-up imaging (≥ 12 monhs)	Korea	Screening	Low
Devolli-Disha (2009)[27]	*Bosnian Journal of Basic Medical Sciences*	Prospective	Breast "symptoms"	30-77 (56)	IDC, ILC, mixed, tubular, medullary, mucinous	Younger than 30 years excluded from mammography	Radiologist; same	Histopathology (both)	Kosovo	Diagnostic	Low
Girardi (2012)[48]	*The Breast*	Prospective	Asymptomatic with negative mammography	33-84 (51.2)	IDC, ILC, DCIS	Symptomatic breast/ axillary findings, positive mammography	N/A: team of 5 radiologists with 6-34 years experience	Histopathology for surgery patients, FNAC and NCB for cases undergoing invasive assessment; at least 1 year follow-up	Italy	Screening	Low
Hou (2002)[35]	*Ultrasound in Medicine and Biology*	Prospective	Relatives of patients with breast cancer	36-75 (48.1)	Invasive cancer, DCIS, mucinous, medullary	Breast cancer history, known metastatic diseases	Two experienced physicians; same	Histopathology; unclear	Taiwan	Screening	Low
Houssami (2003)[40]	*AJR*	Retrospective	Symptomatic (breast diagnostic clinic)	27-55 (44.9)	IDC, ILC, tubular, medullary, DCIS	< 25 or > 55 years of age	Two radiologists with extensive experience, third radiologist arbitrator for disagreement; same	Histopathology; diagnostic assessment and not being registered as having breast cancer during a 2-year interval after attending the study center	Taiwan	Diagnostic	Low
Irurhe (2012)[28]	*Nigerian Quarterly Journal of Hospital Medicine*	Prospective	"Signs and symptoms" of breast lesions	18-59 (41.7)	Breast cancer (not specified)	Without signs and symptoms of breast lesion	N/A; attending radiology	Histopathology (both)	Nigeria	Diagnostic	Low

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TABLE 1. Summary of the Included Studies Assessing Diagnostic Performance of Ultrasound for Detecting Breast Cancer (Continued)

Publication	Journal	Type of Study	Description of the Studied Population	Age Range, Years (mean)*	Positive Case Definition	Exclusions	Image Interpreter†	Reference Standard‡	Countries Represented	Setting of Examination	QUADAS-2 Bias
Jeh (2016)[51]	*Acta Radiologica*	Prospective	Asymptomatic or palpable lump	20-80 (48)	IDC, ILC, mixed ductal- mucinous, mucinous, DCIS	Nonbiopsied lesions	N/A; three radiologists with > 6 years of experience in breast imaging	Histopathology (both)	Republic of Korea	Screening and diagnostic	Low
Kolb (2002)[44]	*Radiology*	Prospective	Dense breasts	Range not given (54.7)	Invasive cancers, DCIS	Nondense breasts	N/A; one radiologist specializing in "breast cancer detection"	Histopathology; 6 month,1 year, 2 year follow-up	United States	Screening	Low
Kuhl (2005)[33]	*JCO*	Prospective	Clinically asymptomatic with high familial risk	27-59 (41.7)	Invasive cancer, DCIS	Patients with symptoms	Radiologist with substantial expertise; same	Histology; 6 month/ 1 year follow-up	Germany	Screening	Low
Lehman (2007)[36]	*Radiology*	Prospective	BRCA1/BRCA2 carriers or at least 20% probability of carrying BRCA1/ BRCA2 mutation	25-72 (46)	Invasive cancer, DCIS	MRI known contraindication, palpable or actionable lesion, biopsy in study breast or adjuvant chemotherapy/ radiation within 6 months of study entry, first- or second-degree relative with BRCA1/BRCA2, untreated malignancy, metastatic malignancy within past 5 years, psychiatric condition preventing informed consent	Certified radiologist (1 of 15 total); same	Histopathology; no additional follow-up	United States	Screening	Low
Lehman (2012)[42]	*AJR*	Retrospective	"Focal" breast signs or symptoms	30-39 (35)	Invasive carcinoma, DCIS	Diagnostic imaging mammographic finding, nipple inversion or discharge as sole reason of evaluation, follow-up known malignancy	N/A; one of seven subspecialized radiologists	Histopathology; 24 months follow-up	United States	Diagnostic	Low
Leong (2012)[45]	*Annals Academy of Medicine, Singapore*	Prospective	Asymptomatic with negative, dense mammograms	30-64 (45.1)	IDC and DCIS	Lost to follow-up	N/A; sonographer and verified radiologist with 3-15 years experience	Histopathology; mammography at 1-2 years follow-up	Singapore	Screening	Low

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TABLE 1. Summary of the Included Studies Assessing Diagnostic Performance of Ultrasound for Detecting Breast Cancer (Continued)

Publication	Journal	Type of Study	Description of the Studied Population	Age Range, Years (mean)*	Positive Case Definition	Exclusions	Image Interpreter†	Reference Standard‡	Countries Represented	Setting of Examination	QUADAS-2 Bias
Matovu (2016)[29]	*The Journal of Global Radiology*	Prospective	Self-detected lumps	17-70 (33)	Breast cancer (type unspecified)	< 18 years, pregnant, or acutely ill	N/A; American board-certified radiologist reviewed	Histopathology; follow-up 1 year after examination	Uganda	Diagnostic	High
Moon (2014)[49]	*European Journal of Ultrasound*	Prospective	Asymptomatic Korean women	40-87 (53.8)	Invasive carcinoma, DCIS	Follow-up mammography after breast cancer surgery, diagnostic mammography, age < 40 years, no follow-up for at least 12 months, screening mammography because of a family history, previous biopsy of high risk, no additional evaluation after BI-RADS category 0 on screening mammography, other malignancies, interstitial mammoplasty	One of seven dedicated breast imaging radiologist with 1-15 years' experience; same	Histopathology; follow-up over a period of at least 12 months	Korea (Seoul)	Screening	Low
Omidiji (2017)[30]	*Ghana Medical Journal*	Cross sectional	Screening campaign attendees in tertiary hospital in Lagos state	30-60 (41.0)	IDC, DCIS	Symptoms (mastalgia, nipple discharge or lump), previous breast excisions/ biopsies, history of trauma, never breastfed, pregnant/ lactating	Trained radiologists; same	Histopathology; unclear	Nigeria	Screening	High
Shao (2013)[41]	*Journal of X-Ray Science and Technology*	Retrospective	Suspected breast cancer (pain, lumps, discharge)	26-85 (53.2)	IDC, DCIS, mucinous adenocarcinoma, ILC, neuroendocrine carcinoma	Ulcerations or wounds of breast, breast radiotherapy or chemotherapy past 6 months	Consensus by 3 experienced radiologists with 6-12 years experience; same with 7-13 years experience	Histopathology; normal findings on serial breast imaging over follow-up period of at least 2 years	China (Shanghai)	Diagnostic	High

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TABLE 1. Summary of the Included Studies Assessing Diagnostic Performance of Ultrasound for Detecting Breast Cancer (Continued)

Publication	Journal	Type of Study	Description of the Studied Population	Age Range, Years (mean)*	Positive Case Definition	Exclusions	Image Interpreter†	Reference Standard‡	Countries Represented	Setting of Examination	QUADAS-2 Bias
Shen (2015)[34]	*BJC*	Prospective (RCT)	Chinese women with high risk characteristics	30-65 (46.4)	IDC, DCIS	PUMCH younger than 30 years, pregnancy, lactation, known metastatic cancer, signs and symptoms of breast disease, breast implants, breast surgery/ mammography/ ultrasound examination past 12 months	Experienced radiologists from each center with standardized training	Histopathology; clinical follow-up at 1 year	China (Beijing)	Screening	Low
Sim (2004)[37]	*Annals Academy of Medicine, Singapore*	Retrospective	Familial risk	25-58 (42.4)	Invasive carcinoma, DCIS	Inadequate follow-up, lack of histopathologic correlation	Radiologist; same	Histopathology; negative imaging results for next 2 years after initial imaging	Netherlands	Screening	High
Singh (2008)[31]	*JK Science*	Prospective	Palpable breast masses	20-49 (41.0)	Breast carcinoma	Without lumps	N/A; expert sonologist in department of radio diagnosis	Fine needle aspiration cytology or histopathology (both)	India	Diagnostic	Low
Tan (2014)[26]	*Medical Journal of Malaysia*	Retrospective	Asymptomatic and symptomatic Malaysian women	< 40 to > 60 (< 50)	Breast carcinoma	None specified	Radiologist in training decided on need for ultrasound, images reviewed by radiologist; same	Histopathology (both)	Malaysia	Screening and diagnostic	Low
Uchida (2008)[46]	*Breast Cancer*	Prospective	Asymptomatic Japanese women	Range not given (54.9)	DCIS, IDC	None specified	Two mammogram examiners; specialized technicians	Histology (both)	Japan	Screening	High
Warner (2001)[38]	*JCO*	Cross sectional	Proven BRCA1/ BRCA2 mutations or strong family history breast or ovarian cancer	26-59 (43.4)	DCIS, invasive cancers	Pregnant or lactating, metallic foreign objects in body, history of bilateral breast cancer, known metastatic disease	Not specified; experienced physician	Histology; follow-up time within 1 year of screening	Canada	Screening	Low

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TABLE 1. Summary of the Included Studies Assessing Diagnostic Performance of Ultrasound for Detecting Breast Cancer (Continued)

Publication	Journal	Type of Study	Description of the Studied Population	Age Range, Years (mean)*	Positive Case Definition	Exclusions	Image Interpreter†	Reference Standard‡	Countries Represented	Setting of Examination	QUADAS-2 Bias
Weigert (2017)[25]	*Breast Journal*	Retrospective	Dense breasts	45-77 (not given)	Malignancies and high-risk lesions including ADH and LCIS	Abnormal mammogram or breast density < 50%	Radiologists in practice from 10 to 35 years, certified ultrasound technologists	Histopathology; 6 months follow-up	United States	Screening	High
Youk (2011)[47]	*European Radiology*	Retrospective	Dense breasts	21-74 (47.5)	Malignancies (not including high-risk lesions)	No surgical biopsy or at least 2-year follow-up ultrasound for nonmalignant core needle or fine needle result	One of nine radiologists with fellowship training or extensive clinical experience of 4-8 years in breast imaging; same	Histopathology; at least 2 years follow-up	Korea (Seoul)	Screening and diagnostic	Low

Abbreviations: ADH, atypical ductal hyperplasia; AJR, *American Journal of Roentgenology*; BI-RADS, Breast Imaging Reporting and Data System; BJC, *British Journal of Cancer*; DCIS, ductal carcinoma in situ; FNAC, fine-needle aspiration cytology; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; JCO, *Journal of Clinical Oncology*; mammo, mammography; MRI, magnetic resonance imaging; NCB, needle core biopsy; PUMCH, Peking Union Medical College Hospital; RCT, randomized controlled trial.

*Median when mean not available.

†Mammogram; ultrasound.

‡Positive cases; negative cases.

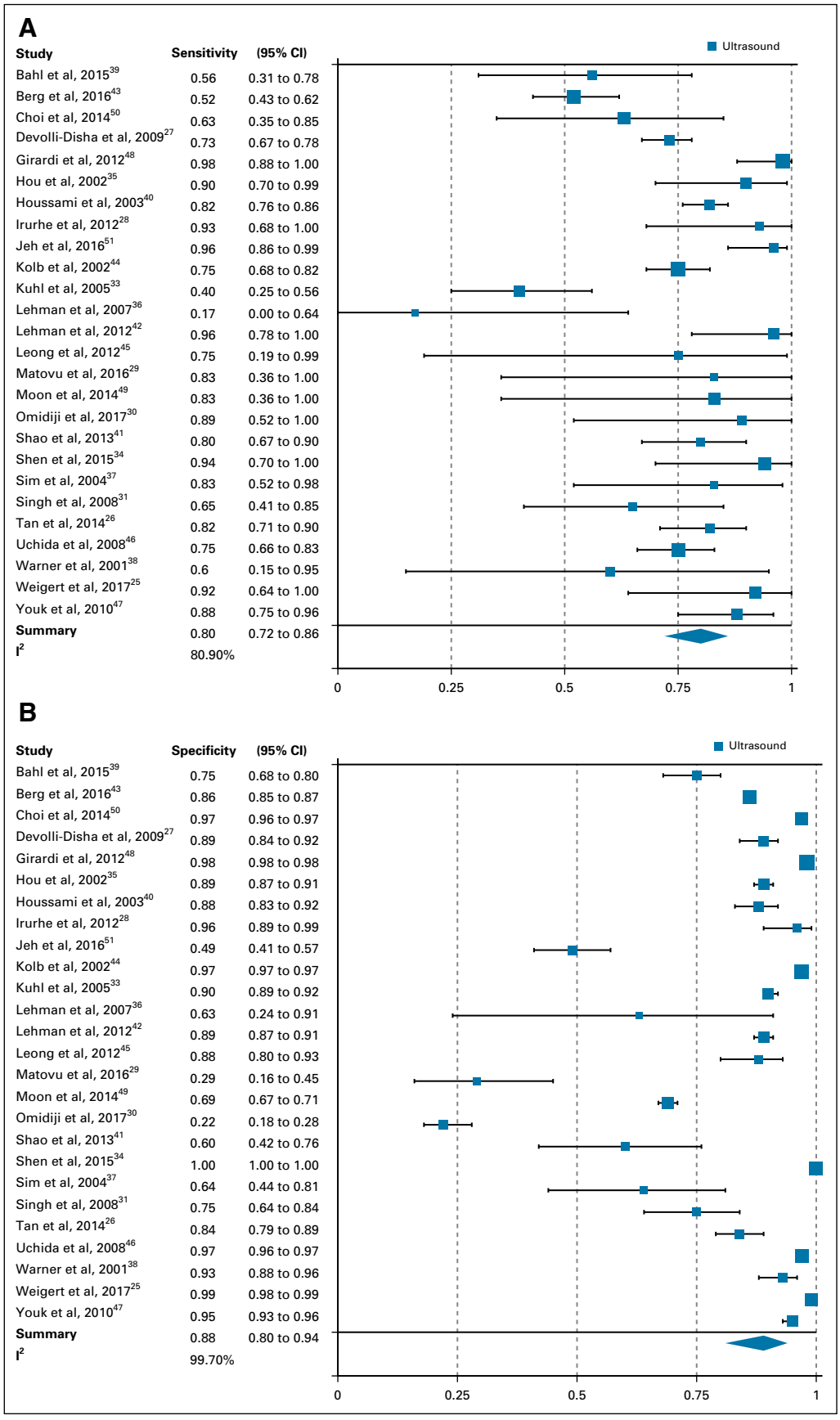

FIG 2. (A) Sensitivity of ultrasound overall. (B) Specificity of ultrasound overall. (C) Comparative sensitivity of ultrasound and mammography. (D) Comparative specificity of ultrasound and mammography. I^2, Higgins I^2 index.

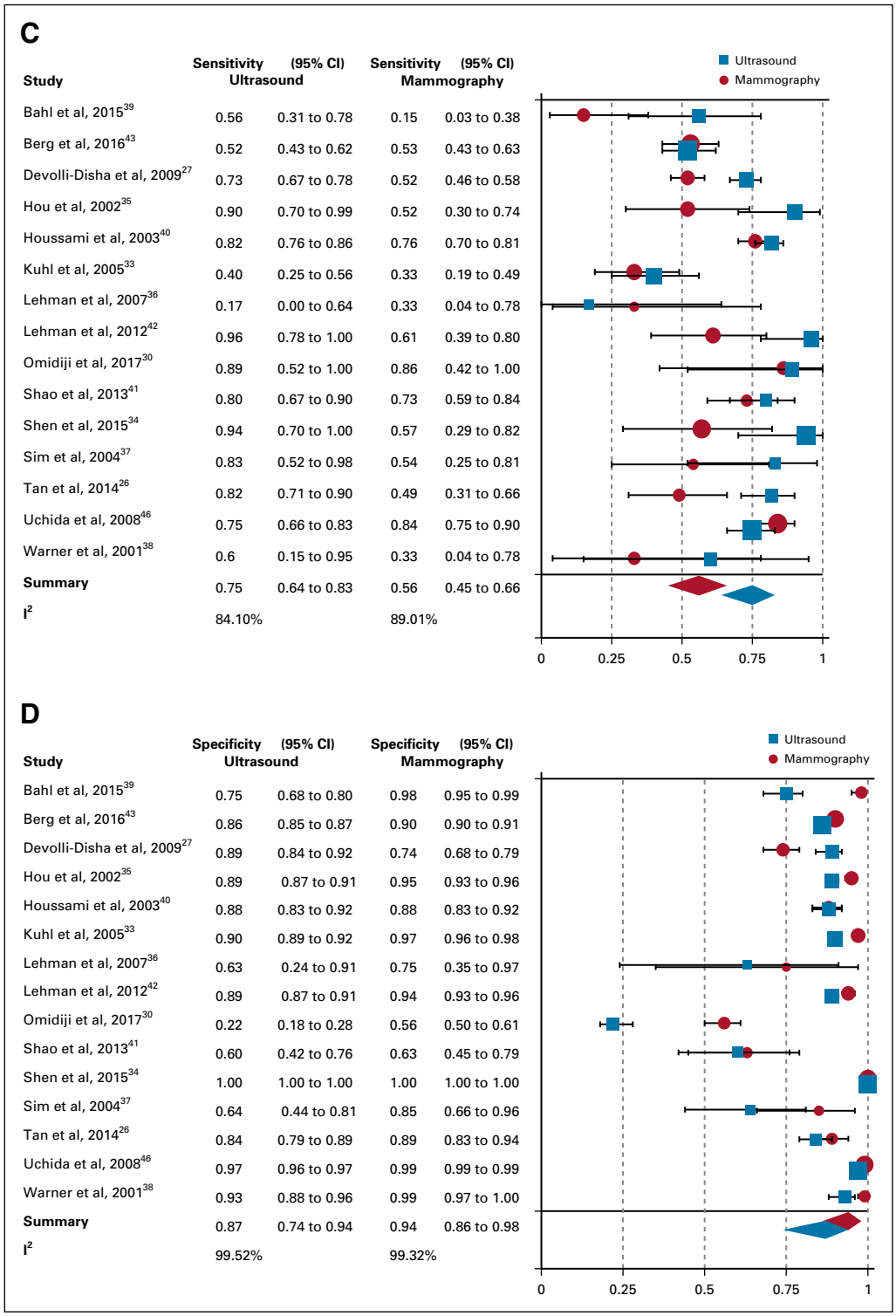

FIG 2. (Continued).

Visual funnel plot assessment revealed no evidence of publication bias (Data Supplement). In addition, the slopes of the Deeks funnel plot asymmetry tests for ultrasound alone and ultrasound versus mammography did not support any presence of publication bias. Using the trim and fill method, adjusted DORs (95% CI) were 30.0 (16.5 to 54.5) and 19.2 (7.9 to 46.6) for overall ultrasound and mammography, respectively. Comparing these values with the original calculated DORs (ultrasound: 20.0 [6.5 to 61.2] and mammography: 20.8 [7.9 to 55.0]), we observed no

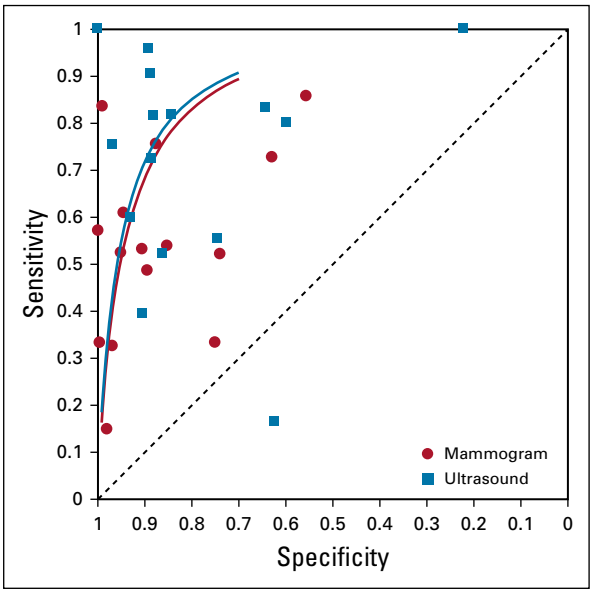

FIG 3. Summary receiver operating curves, fifteen studies comparing ultrasound and mammography.

statistically significant difference, and thus we concluded our results were not biased by publication bias. On the basis of the QUADAS-2 assessment, there were no concerns regarding applicability to clinical practice in any of the included studies (Data Supplement). Regarding internal validity, 20 of the studies (76.9%) had a low risk of bias, and six (23.1%) had a high risk of bias. The most common reason for risk of high bias was inconsistent blinding of the radiologists to final pathology results. The second most common risk factor for bias was observed in the flow and timing assessment; specifically, not all patients received the same reference standard.

The set of studies was heterogeneous for overall pooled ultrasound sensitivity ($I^2 = 80.9\%$) and specificity estimates ($I^2 = 99.7\%$). Potential sources of heterogeneity were investigated using meta-regression, with covariates of mean age younger than or older than 50 years, country of study (LMIC *v* high-income country), risk category (high *v* low), presence of symptoms, breast tissue density (high *v* low), study design (retrospective *v* prospective), bias level (QUADAS-2), and study setting (screening *v* diagnostic). The performance of ultrasound for detection of breast cancer did not significantly statistically differ (*P* value cutoff = .05) by these covariates (Table 2). In the five studies from LMICs, ultrasound maintained a high pooled diagnostic sensitivity of 89.2% and specificity of 99.1%. For comparison, the pooled estimates from studies performed in high-income country populations were 80.3% and 91.0% for sensitivity and specificity, respectively. None of the LMIC studies included patients in the previously defined high-risk category, but four of the five studies were in symptomatic patients with palpable lumps. Among comparative studies of portable ultrasound and mammography, there was no statistically significant difference in terms of rDOR when these data were stratified by age, risk, and presence of symptoms (Table 3). However, subanalyses by age, risk, and symptom categories yielded a significantly higher sensitivity and specificity for ultrasound as compared with mammography (*P* values $< .001$; Table 3).

DISCUSSION

Although mammography is widely accepted as the gold standard for early breast cancer detection, it is not widely available globally. In contrast, ultrasound is accessible, versatile, and cost effective. To our knowledge, our systematic review and meta-analysis of 26 studies with a total of 76,058 patients is the most comprehensive analysis of the sensitivity of ultrasound as a primary modality for breast cancer detection. Our meta-analysis showed that ultrasound had an overall pooled sensitivity and specificity (95% CI) of 80.1% (72.2% to 86.3%) and 88.4% (79.8% to 93.6%), respectively, for the detection of breast cancer. In addition, this high sensitivity and specificity did not differ based on subgroup analyses. Our findings add to a growing body of literature describing ultrasound's detection capacity for breast cancer. It is known that ultrasound is effective for the detection of small, invasive, node-negative cancers in dense breast tissue, where the sensitivity of mammography drops from 85% to 47.8% to 64.4%.[52,53] In addition, numerous studies report high sensitivity and NPV up to 100% when ultrasound is used for cancer detection at the site of focal breast symptoms.[42,54] However, there is limited information on the value of ultrasound as an early detection tool in primarily asymptomatic women. Our study evaluated the diagnostic potential of breast ultrasound, in a variety of patient populations, as a primary detection modality to provide supportive data for implementation in settings where mammography is unavailable.

As a detection modality, ultrasound has particular potential to affect early detection rates in areas that lack access to mammography. When LMIC-only data were considered, ultrasound maintained a diagnostic pooled sensitivity of 89.2% and pooled specificity of 99.1%. However, it is important to note that this high sensitivity and specificity may partly be due to the small number of studies in these countries and lack of diagnostic data of other modalities in these settings. The 15 included studies comparing mammography and ultrasound against the gold standard of histopathology further indicated that ultrasound has statistically significantly increased sensitivity and specificity in the studied populations. Because of the current approved uses of ultrasound, the comparative studies were predominantly in populations where mammography is known to perform on par with or more poorly than ultrasound, namely in women with dense breasts, with symptoms, and those at high risk for breast cancer. In areas where access to breast care is limited by resource constraints and mammography is generally not available, these population subsets are much more common. For example, Asian

TABLE 2. Sensitivity Analyses of the Diagnostic Performance of Ultrasound for Detecting Breast Cancer

Including Studies With	No. of Studies (No. of women examined)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Heterogeneity, %		DOR (95% CI)	rDOR (95% CI)	*P*
				Sensitivity	Specificity			
Mean Age*								
< 50 years	17 (17,569)	80.28 (69.63 to 88.35)	85.81 (71.70 to 93.52)	83.37	99.46	24.62 (8.02 to 75.65)	1.632 (0.208 to 12.820)	.627
> 50 years	7 (54,874)	77.03 (63.69 to 86.50)	90.97 (79.72 to 96.27)	84.57	99.84	33.79 (8.94 to 127.77)		
Country								
LMIC	6 (1,102)	74.95 (65.03 to 82.81)	68.87 (33.82 to 90.55)	89.20	99.06	6.62 (1.55 to 28.24)	0.279 (0.028 to 2.759)	.262
UIC	20 (74,956)	80.27 (70.62 to 87.31)	91.04 (83.91 to 95.19)	77.43	99.72	41.30 (15.97 to 106.85)		
Risk								
Low risk	20 (66,497)	81.71 (74.43 to 87.28)	86.79 (77.11 to 92.75)	77.43	99.72	29.35 (12.99 to 66.30)	0.857 .857 (0.094 to 7.846)	.887
High risk (positive family history/BRCA mutation, risk scores)	6 (9,561)	71.07 (39.80 to 90.13)	92.54 (69.12 to 98.57)	86.72	99.14	30.49 (2.13 to 436.25)		
Symptoms								
Not present	18 (65,770)	80.47 (96.28 to 88.27)	91.03 (81.45 to 95.91)	84.21	99.75	41.80 (13.72 to 127.39)	0.401 (0.058 to 2.776)	.339
Present (nipple discharge, palpable lump, and not specified)	8 (2,815)	77.70 (68.58 to 84.75)	70.90 (64.65 to 89.62)	70.99	95.96	13.84 (4.82 to 39.76)		
Tissue density†								
Dense	6 (41,035)	73.29 (57.30 to 84.88)	95.30 (91.08 to 97.57)	85.57	99.68	55.62 (15.75 to 196.38)	2.956 (0.365 to 23.951)	.296
Not dense	20 (35,023)	81 22 (71.32 to 88.26)	85.01 (72.18 to 92.53)	81.99	99.70	24.52 (8.65 to 69.50)		
Study design‡								
Prospective	15 (64,689)	79.29 (65.35 to 88.60)	89.91 (77.92 to 97.75)	64.88	99.72	34.12 (9.12 to 127.75)	0.965 (0.131 to 7.135)	.971
Retrospective	9 (10,879)	81.92 (77.59 to 85.59)	88.96 (78.51 to 94.67)	72.81	96.72	36.55 (14.20 to 94.06)		
Bias level (QUADAS to 2)								
Low	20 (63,190)	79.44 (68.78 to 87.14	90.87 (84.10 to 94.93)	86.44	99.59	38.46 (14.55 to 101.68)	0.479 (0.054 to 4.208)	.491
High	6 (12,868)	80.33 (72.60 to 86.30)	75.28 (36.01 to 94.28)	50.46	99.83	12.44 (2.44 to 63.41)		
Study setting§								
Screening	14 (71,117)	76.20 (61.04 to 86.74)	93.11(83.48 to 97.30)	82.84	99.81	43.23 (10.32 to 181.12)	0.341 (0.043 to 2.737)	.295
Diagnostic	9 (2,855)	77.96 (69.60 to 84.53)	78.57 (64.35 to 88.17)	68.71	95.64	12.97 (5.05 to 33.33)		

Abbreviations: DOR, diagnostic odds ratio; LMIC, low- or middle-income country; QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2; rDOR, relative diagnostic odds ratio; UIC, upper-income country.

*Two studies not included because no mean age provided.

†≥ 50% of all included patients with classified "dense" breast tissue.

‡Two studies not included because cross-sectional design.

§Three studies not included because setting mixed or unclear.

TABLE 3. Performance of Mammography Versus Ultrasound: Sensitivity Analysis of 15 Studies With Direct Comparisons

Including Studies With	No. of studies (No. women examined)	Sensitivity, % (95% CI)	*P*	Specificity, % (95% CI)	*P*	DOR (95% CI)	rDOR (95% CI)	*P*
Age								
> 50 years								
Mammography	4 (17,191)	65.90 (50.60 to 78.48)	< .001	89.41 (65.65 to 97.39)	< .001	16.32 (2.30 to 115.59)	0.962 (0.039 to 23.951)	.977
Ultrasound	4 (17,191)	70.39 (59.51 to 79.36)		87.78 (71.95 to 95.27)		17.08 (5.64 to 51.71)		
< 50 years								
Mammography	11 (11,987)	50.57 (37.70 to 63.36)	< .001	95.58 (87.13 to 98.57)	< .001	22.10 (7.50 to 65.09)	0.956 (0.135 to 8.077)	.964
Ultrasound	11 (12,103)	77.39 (61.17 to 88.15)		86.72 (67.84 to 95.29)		22.35 (4.74 to 105.37)		
Risk*								
Low								
Mammography	9 (19,611)	61.93 (47.22 to 74.73)	< .001	89.70 (78.04 to 95.52)	< .001	14.16 (5.33 to 37.60)	1.151 (0.269 to 4.933)	.840
Ultrasound	9 (19,733)	73.64 (67.50 to 83.82)		81.67 (66.45 to 90.93)		14.62 (6.10 to 335.05)		
High								
Mammography	6 (9,567)	43.10 (32.59 to 54.28)	< .001	97.86 (88.36 to 99.63)	< .001	34.65 (4.88 to 245.85)	1.142 (0.022 to 59.979)	.942
Ultrasound	6 (9,561)	71.07 (39.80 to 90.13)		92.54 (69.12 to 98.57)		30.49 (2.13 to 436.25)		
Symptoms*								
Present								
Mammography	4 (2,106)	48.49 (27.84 to 69.67)	< .001	88.99 (67.36 to 96.94)	< .001	7.61 (3.12 to 18.51)	0.529 (0.057 to 4.899	.510
Ultrasound	4 (2.090)	77.62 (61.37 to 88.33)		81.40 (69.64 to 89.31)		15.18 (4.77 to 48.26)		
Absent								
Mammography	11 (29,966)	61.11 (49.68 to 71.45)	< .001	93.35 (81.23 to 97.85)	< .001	22.06 (6.46 to 75.29)	0.763 (0.094 to 6.172)	.789
Ultrasound	11 (27,204)	73.42 (58.89 to 84.19)		88.82 (71.59 to 96.16)		21.94 (5.03 to 95.65)		

Abbreviations: DOR, diagnostic odds ratio; rDOR, relative diagnostic odds ratio.

*Qualifications for risk and symptoms as defined in Table 2.

women tend to have dense breast tissue and a younger peak age of breast cancer incidence, making ultrasound a potentially more accurate breast cancer detection modality in this population.[34] In addition, women presenting with late-stage disease and symptoms are known to represent the largest proportion of the women presenting for breast cancer concerns in LMICs or low-resource regions of high-income countries.[55,56]

Because patients in LMICs often present with locally advanced disease and have a younger average age at diagnosis, there is impetus for using ultrasound as the first imaging modality in these areas.[11] The findings from this study on the diagnostic utility of ultrasound may therefore be most viable in these settings. Guidelines specific for detection of breast cancer in the LMIC setting further support the use of ultrasound. The Breast Health Global Initiative advocates for the introduction of diagnostic ultrasound at the resource-limited level, given that it is more widely available than mammography in these countries and extremely useful in women with palpable lesions.[57] For example, in Uganda, where organized breast health programs are widely absent, only four mammography units exist for a population of 6 to 7 million women.[58] Ultrasound could enable greater access to breast cancer detection in Uganda, where the alternative is a complete lack of breast imaging in the absence of mammography.

The studies included in this meta-analysis were highly heterogeneous. We hypothesized that the heterogeneity could be caused by variability in study definitions from geographically diverse locations and populations. Thus, we performed meta-regression to further investigate the source of heterogeneity within the studies. In addition, we completed subset analyses with variables that capture these differences, including participant mean age, country, risk category, symptom presence, tissue density, study bias level (QUADAS-2), and study setting. This evaluation yielded no significant difference between categories as an explanation for the heterogeneity. We further investigated the heterogeneity by confirming no threshold effect with a Spearman correlation coefficient. As a result of these additional analyses, we find that the heterogeneity is related to diversity of studies and likely has limited impact on our results and conclusions.

Strengths of this study include use of broad, comprehensive search terms and multiple databases to capture all potentially relevant studies. Uniquely, this study evaluates the performance of ultrasound alone and compares mammography and ultrasound estimates for cancer detection, whereas most of the literature reviews ultrasound as a supplemental detection technique.[53] This work adds to the growing body of evidence identifying regions and populations where breast ultrasound would be an effective, available early detection tool. This could facilitate a path to earlier detection of breast cancer for the 50% of women globally who currently have no access to breast imaging. However, as evidenced in this study, direct data from LMICs is sparse, so estimates from high-income countries are more heavily weighted in the pooled analyses. In addition, some included studies are subject to verification bias, because only patients with suspicious imaging findings received the gold standard of histopathology, which could lead to overestimation of sensitivity. Although there are other methods to determine the ground truth, such as a 2-year cancer-free interval for benign-appearing lesions, not all of the manuscripts reviewed provided this level of detail. To limit potential bias, papers with study populations that included only patients with previously diagnosed breast cancer were excluded, because these studies in higher-risk women would potentially yield a higher accuracy of breast ultrasound.

It is evident that additional research is needed to investigate the full potential of breast ultrasound for early breast cancer detection where mammography is infeasible. It is possible that the use of portable ultrasound could assist in development of a breast cancer care program that could ultimately include mammography or partner with programs that include mammography. More recent studies focus on comparing portable ultrasound to automated whole-breast ultrasound instead of comparing estimates to mammography.[50,51] Ideally, future research would include direct comparisons of mammography and ultrasound in population-based settings and focus on asymptomatic women for early detection, yet this would require large populations and would be costly. In addition, false positives are persistently a concern with all breast imaging modalities, and more research is needed to define the best practices in resource-limited settings to avoid unnecessary use of resources, which ultimately does not change patient outcomes. Technical capacity and training programs for handheld, portable breast ultrasound are additional important considerations when using an ultrasound-based detection program. There is evidence this can be achieved on a small scale and could be scalable.[59]

In conclusion, on the basis of the existing literature, our review demonstrates ultrasound has the potential to yield high sensitivity and specificity for breast cancer detection. Ultrasound is widely available, easy to maintain, economical, durable, and easily portable. Given the increasing global burden of breast cancer and lack of access to timely detection with imaging, ultrasound may be an effective primary detection tool and triage method for breast lesions, particularly in low-resource settings where mammography is not available.

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