Journal of Cardiovascular Disease Research

ISSN:0975 -3583,0976-2833 VOL 12, ISSUE 10, 2021

Original research article

Evaluation of the Utility of Screening Ultrasound (USG) in women with dense breasts: A systematic review

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Abstract

Background: Although mammography remains a cornerstone of breast cancer screening, its sensitivity is reduced in women with dense breasts, increasing the likelihood of undetected tumors and elevated interval cancer rates. To address these limitations, supplemental ultrasound (USG) has gained attention for its ability to identify mammographically occult lesions. However, questions remain regarding its diagnostic accuracy, false-positive rates, and cost-effectiveness as an adjunct to or substitute for mammography in this population.

Methods: A systematic search of the literature was done by searching PubMed and Google Scholar to identify studies comparing mammography alone with supplemental USG with mammography for breast cancer screening in women with dense breasts. Key outcomes included cancer detection rate, sensitivity, specificity, recall rate, false-positive rate, and cost considerations.

Results: Studies consistently showed that supplemental USG improves cancer detection in women with dense breasts compared to mammography alone. Pooled data demonstrated higher sensitivity (up to 96% when combined with mammography) but a modest decrease in specificity. While the addition of USG often led to an increase in recall rates and benign biopsies, it also identified mammographically occult cancers, potentially improving early detection. Some reports underscored the cost-effectiveness of USG-particularly in resource-limited settings-though others noted higher false-positive rates and increased demands on radiology services.

Conclusion: Screening USG appears to be a valuable adjunct for women with dense breasts, enhancing cancer detection beyond that achieved by mammography alone. Although false-positive results and associated healthcare costs remain concerns, emerging evidence supports integrating USG as part of a tailored screening approach for those with dense breast tissue. Future research should emphasize standardized protocols, longer-term outcomes (such as interval cancer rates and mortality), and refined patient selection criteria to optimize the balance between early detection benefits and potential harms.

Keywords: Breast density, ultrasonography, supplemental screening

Introduction

Breast cancer is the most common cancer affecting women globally [1]. Early detection through screening programs is the primary strategy for reducing mortality [2]. Mammography is the standard imaging method for breast cancer screening, and has been shown to reduce breast cancer mortality [2-4]. However, its effectiveness is significantly hampered by breast density [12, 4, 5, 6].

Dense breasts not only elevate breast cancer risk but also reduce the diagnostic accuracy of mammograms because dense tissue can obscure non-calcified breast cancers on mammograms [1, 4-7]. This obscuration leads to missed cancers, especially in women with dense breasts, where mammography sensitivity can drop as low as 30-48% [2]. Studies estimate that approximately 60% of women in their 40s have dense breasts [3]. Recognizing that mammography may be less accurate for Chinese women due to their typically small and dense breasts, the Chinese government has adopted ultrasound as the primary screening method in their 'Two Cancer Screening' campaign in 2009 [8].

Given the limitations of mammography in women with dense breasts, there is a growing interest in supplemental screening modalities. Breast ultrasound (USG) is a readily available and relatively inexpensive imaging technique that has shown potential in detecting cancers [6]. It can identify mammographically occult breast cancers, particularly in younger women or those with dense breasts [6, 8,

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[9]. Some studies have indicated that the combination of USG and mammography results in a significant increase in cancer detection rates compared to mammography alone [8, 9].

However, the value of supplemental USG screening must be balanced against the increased risk of biopsies and the additional workload it creates [6]. Studies have shown that while adding ultrasonography to mammography screening can increase cancer detection, it also substantially increases the number of false-positive findings [3]. Also, screening USG has high rates of false positives [10]. There are also questions about its cost-effectiveness and impact on patient outcomes [9].

Previous research has explored the efficacy of combined screening approaches. The Japan Strategic Anti-Cancer Randomized Trial (J-START) assessed the efficacy of adjunctive ultrasonography in screening for breast cancer in Japanese women aged 40-49 years [3]. The SomoInsight Study determined the improvement in breast cancer detection when automated breast US (ABUS) is used with screening mammography versus when screening mammography alone is used for asymptomatic women with dense breasts [11].

Several studies have evaluated the performance of screening mammography plus screening ultrasonography compared with screening mammography alone in community practice [5]. Other studies have assessed adjunct screening with tomosynthesis or ultrasound in women with mammography-negative dense breasts [5, 12]. Few other studies have evaluated breast screening with ultrasound in women with mammography-negative dense breasts [12, 13].

Despite the existing literature, there remains a need for a comprehensive evaluation of the benefits and limitations of screening USG in women with dense breasts. Many previous studies included women at increased breast cancer risk due to factors other than breast density, limiting the generalizability to the general screening population of women with dense breasts [7].

Therefore, this systematic review aims to evaluate the utility of screening USG in women with dense breasts by assessing diagnostic accuracy, benefits, and limitations of screening USG, as well as its impact on cancer detection rates and patient outcomes.

Methods

Study Selection Process: The inclusion criteria for this systematic review were those studies that compared the effectiveness of supplemental USG with mammography compared to mammography alone in women with dense breasts for screening for breast cancer. Studies were included if they met the following criteria: they were published in English; included women with dense breasts undergoing breast cancer screening, where breast density was classified according to the Breast Imaging Reporting and Data System (BI-RADS) density categories. Studies reporting on sensitivity, specificity, cancer detection rate, false positive rate were included. Two independent reviewers assessed study quality and risk of bias. Discrepancies during study selection were resolved through discussion between reviewers.

Literature Search

Databases: A comprehensive literature search was conducted in PubMed and Google Scholar.

Search Strategy: The search strategies are as follows:

PubMed Search Strategy

("Ultrasonography"[Mesh] OR "Ultrasound Screening" OR "Breast Ultrasound" OR "Breast USG" OR "Screening Ultrasonography" OR "Adjunct Ultrasound").

And

("Breast Density"[Mesh] OR "Dense Breasts" OR "Mammographic Density" OR "Breast Tissue Density").

And

("Screening"[Mesh] OR "Early Detection" OR "Cancer Screening" OR "Mass Screening").

And

("Breast Cancer"[Mesh] OR "Breast Neoplasms" OR "Breast Tumors" OR "Breast Carcinoma")

Google Scholar Search Strategy

(intitle: "Ultrasound Screening" OR intitle: "Breast Ultrasound" OR intitle: "Screening Ultrasonography" OR intitle: "Adjunct Ultrasound")

And

(intitle: "Dense Breasts" OR intitle: "Breast Density" OR intitle: "Mammographic Density" OR intitle: "Breast Tissue Density").

And

(intitle: "Screening" OR intitle: "Early Detection" OR intitle: "Cancer Screening" OR intitle: "Mass Screening")

And

(intitle: "Breast Cancer" OR intitle: "Breast Neoplasms" OR intitle: "Breast Tumors" OR intitle: "Breast Carcinoma")

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And
(intitle: "Randomized Controlled Trial" OR intitle: "RCT" OR intitle: "Case-Control Study" OR intitle: "Case-Control Design").

Search Terms Rationale: This strategy combines Medical Subject Headings (MeSH) terms and keywords related to ultrasound screening, breast density, screening, and breast cancer to capture relevant studies. The Google Scholar search complements this by targeting titles containing key terms, specifically focusing on RCTs and case-control studies. The search strategy in Google Scholar is designed to identify study designs (RCTs and Case-Control Studies) that can provide higher levels of evidence regarding the effectiveness and utility of ultrasound screening in women with dense breasts. The search will encompass studies published from January 1990 January to 2020 December to capture the evolution of breast cancer screening techniques and technologies.

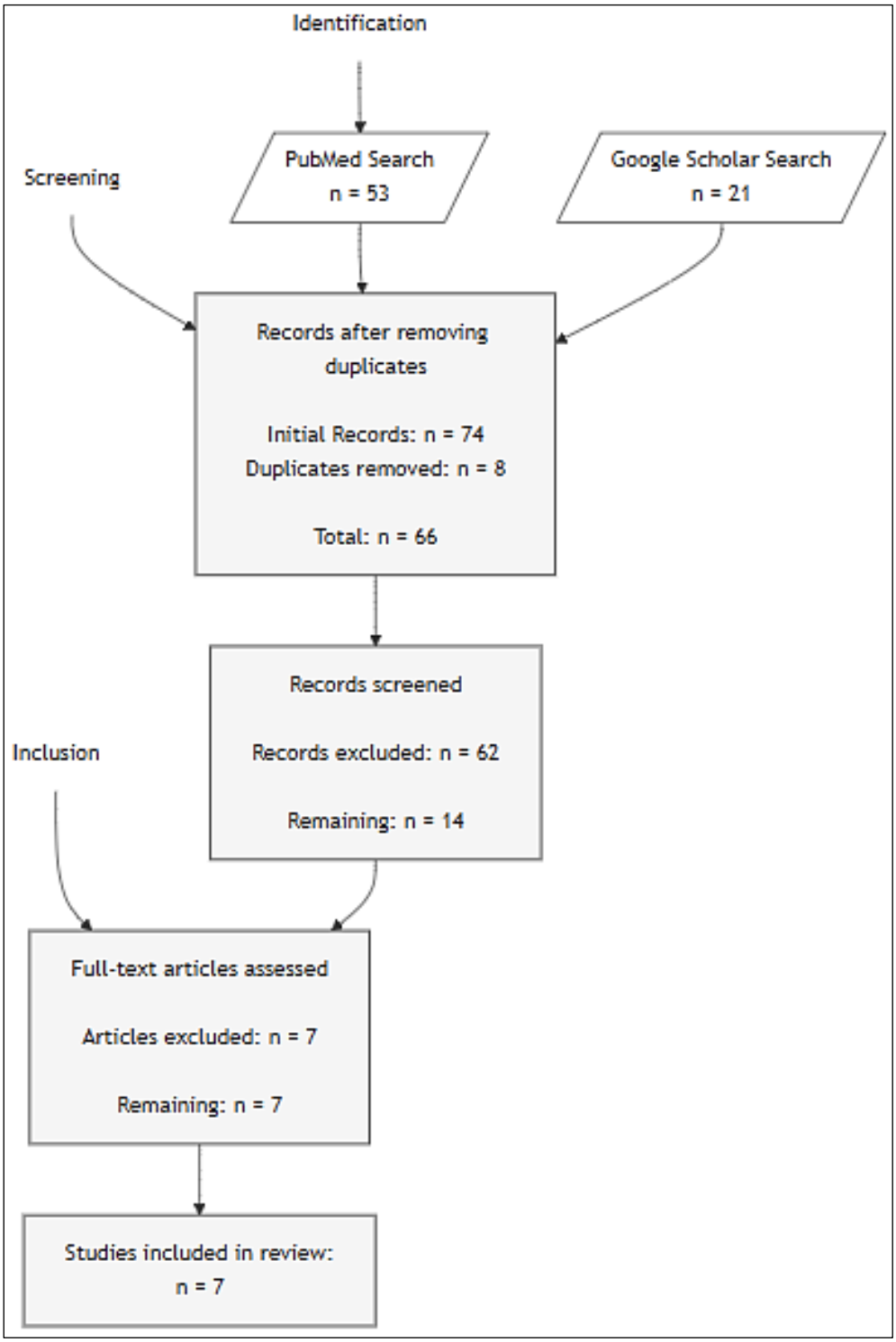

Fig 1: PRISMA flow diagram of the study selection process

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Results

Study Characteristics

Key characteristics of the included studies are summarized below:

Shen *et al*. (2015)

Study Design: Multi-center randomized trial.
Sample Size: 13,339 high-risk women.
Setting: 14 breast centers across China.
Interventions vs. Comparators: Mammography alone, ultrasound alone, or both methods.
Main Findings: Ultrasound detected more cancers than mammography in the combined group (100% vs 57.1% sensitivity, P=0.04). Ultrasound was more cost-effective [8].

Tagliafico *et al*. (2018)

Study Design: Prospective comparative trial (ASTOUND-2).
Setting: Italian breast screening services.
Interventions vs. Comparators: Tomosynthesis or ultrasound as adjunct screening modalities in women with mammography-negative dense breasts.
Main Findings: Adjunct imaging detects additional breast cancers not detected at mammography screening in women with dense breasts [12].

Corsetti *et al*.: (2008)

Study Design: Evaluation of ultrasound in women with dense breasts and negative mammography reports.
Main Findings: Presents data on incremental detection and false-positive findings, and estimates the cost of adjunct screening USG [13].

Lee *et al*. (2019)

Study Design: Observational cohort study using Breast Cancer Surveillance Consortium (BCSC) registries.
Sample Size: Data on screening mammography with vs without same-day breast ultrasonography from January 1, 2000, to December 31, 2013 [5].
Setting: Community practice.
Interventions vs. Comparators: Screening mammography plus same-day screening ultrasonography compared with screening mammography alone.
Main Findings: Significantly higher short-interval follow-up and biopsy recommendation rates with screening mammography plus same-day ultrasonography compared with mammography alone. No significant increase in cancer detection or decrease in interval cancer rates was observed [5].

Ohuchi *et al*. (2016)

Study Design: Randomized controlled trial (J-START).
Sample Size: Asymptomatic women aged 40-49 years.
Setting: 42 study sites in 23 prefectures in Japan.
Interventions vs. Comparators: Mammography and ultrasonography (intervention group) or mammography alone (control group).
Main Findings: Investigated the efficacy of adjunctive ultrasonography [3].

Melnikow *et al*. (2016)

Study Design: Systematic review.
Data Sources: MEDLINE, PubMed, EMBASE, and Cochrane database from January 2000 to July 2015.
Study Selection: Studies reporting BI-RADS density reproducibility or supplemental screening results for women with dense breasts.
Data Extraction: Quality assessment and abstraction of 24 studies from 7 countries; 6 studies were good-quality.
Main Findings: The sensitivity of ultrasonography for women with negative mammography results ranged from 80% to 83%; specificity, from 86% to 94%; and positive predictive value (PPV), from 3% to 8% [7].

Yuan *et al*. (2020)

Study Design: Systematic review and meta-analysis.
Data Sources: Medline, Cochrane, EMBASE and Google Scholar databases (January 1, 1980 to April 10, 2019).
Study Selection: Studies of women with dense breasts screened by mammography and/or ultrasound (USG).

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Main Findings: The pooled sensitivity values of mammogram alone and mammogram with USG in patients were 74% and 96%, while specificity of the two methods was 93% and 87%, respectively. Breast cancer screening by supplemental USG among women with dense breasts shows added detection sensitivity compared with mammogram alone [9].

Table 1: Characteristics of included studies

Title of Study	Location	Study Design	Sample Size	Intervention	Comparator	Key Findings
A multi-centre randomised trial comparing ultrasound vs mammography for screening breast cancer in high-risk Chinese women. S Shen *et al.*	China	Multi-center randomized trial	13,339 women	Ultrasound alone, mammography alone, the combined methods	Mammography alone, Ultrasound alone	Ultrasound detected more cancers than mammography in the combined group (100% vs 57.1% sensitivity, P=0.04). Ultrasound was more cost-effective.
A prospective comparative trial of adjunct screening with tomosynthesis or ultrasound in women with mammography-negative dense breasts (ASTOUND-2). A.S. Tagliafico *et al.*	Italy	Prospective comparative trial	5300 women	Tomosynthesis or ultrasound as adjunct	Mammography-negative dense breasts	Adjunct imaging detects additional breast cancers not detected at mammography screening in women with dense breasts.
Breast screening with ultrasound in women with mammography-negative dense breasts: evidence on incremental cancer detection and false positives. Corsettia *et al.*	Italy	Observational Cohort	26,047 women	Ultrasound	Mammography-negative dense breasts	Presents data on incremental detection and false-positive findings and estimates the cost of adjunct screening USG.
Performance of Screening Ultrasonography as an Adjunct to Screening Mammography in Women. LEE JM *et al.*	United States	Observational cohort study	3386 women	Screening mammography plus ultrasonography	Screening mammography alone	Significantly higher short-interval follow-up and biopsy recommendation rates with screening mammography plus ultrasonography compared with mammography alone. No significant increase in cancer detection.
Sensitivity and specificity of mammography and adjunctive ultrasonography for breast cancer screening in women aged 40-49 years (J-START): a randomised controlled trial Ohuchi	Japan	Randomized controlled trial	76,196 women	Mammography and ultrasonography	Mammography alone	Investigated the efficacy of adjunctive ultrasonography.
Supplemental Breast Cancer Screening in Women with Dense Breasts. Melnikow *et al.*	Multiple	Systematic review	24 studies	Hand-held ultrasonography (HHUS), automated whole-breast ultrasonography (ABUS), breast magnetic resonance imaging (MRI)	Mammography	Sensitivity of ultrasonography for women with negative mammography results ranged from 80% to 83%; specificity, from 86% to 94%; and positive predictive value (PPV), from 3% to 8%.
Supplemental breast cancer-screening ultrasonography in women with mammographically dense breasts: a systematic review and meta-analysis. Yuan *et al.*	Multiple	Systematic review and meta-analysis	21 studies	Mammography with adjunctive ultrasonography or additional ultrasonography following a negative mammography	Only screening mammography or no comparative group	Breast cancer screening by supplemental US among women with dense breasts shows added detection sensitivity compared with mammogram alone.

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Risk of Bias Assessment

Selection Bias: Some studies may have selection bias due to the non-random selection of participants [9]. For instance, women receiving mammography plus USG were more likely to have dense breasts or a family history of breast cancer [5].

Performance Bias: In some studies, the physical exam was done after a mammography and/or ultrasound exam, and the physician was not masked to the results of the mammography or USG [8]. This may introduce performance bias.

Detection Bias: Studies that lacked clear descriptions of follow-up may have detection bias [7].

Attrition Bias: Arising from incomplete outcome data [9].

Reporting Bias: Some studies may have reporting bias due to the selective reporting of results.

Overall Risk of Bias: The overall risk of bias varied across studies. Some studies were rated as good quality, while others were rated as fair or intermediate [7, 9].

Table 2: Risk of Bias Assessment of the included studies

Study	Risk of Bias Assessment Tool Used	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk of Bias
A multi-centre randomised trial comparing ultrasound vs mammography for screening breast cancer in high-risk Chinese women (S. Shen *et al*.)	Cochrane Risk of Bias 2	High-risk women were recruited using a questionnaire-based risk-assessment model, which could introduce selection bias. Exclusion criteria included pregnancy, lactation, known metastatic cancer, signs or symptoms of breast disease, presence of breast implants, breast surgery within prior 12 months, and those who had a mammography or ultrasound exam within the past 12 months.	Physical exam was done after imaging, and the physician was not masked to imaging results.	Participants with positive screening results underwent biopsy for definitive diagnosis. The BI-RADS lexicon was used to organize the interpretation and reporting of both screening modalities.	Follow-up involved various methods (telephone, mail, E-mails, or face-to-face interviews) for those not returning for screening.	Study registered at clinicaltrials.gov.	moderate overall risk of bias
A prospective comparative trial of adjunct screening with tomosynthesis or ultrasound in women with mammography-negative dense breasts (A. Tagliafico *et al*.)	Newcastle-Ottawa Scale	Not specified	Independently interpreted tomosynthesis and ultrasound.	Outcomes were ascertained from excision histopathology or completed assessment.	Not specified.	Not specified	moderate risk of bias
Breast screening with ultrasound in women with mammography-negative dense breasts: Evidence on incremental cancer detection and false positives, and associated cost (V. Corsetti *et al*.)	Newcastle-Ottawa Scale	Acceptable considering women in the highest breast density categories are at increased risk and more likely to have interval cancer.	Not specified	Not specified	Not specified	None declared.	risk of bias is moderate
Performance of Screening Ultrasonography as an Adjunct to	Newcastle-Ottawa Scale	Potential selection bias due to differences in characteristics	Most women with screening ultrasonography-detected	Recall rate was based on the end-of-day BI-RADS	Matching was performed separately for	Analyses adjusted for characteristics included in the propensity score	overall risk of bias is moderate

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Screening Mammography (J.M. Lee *et al.*)		between women receiving mammography plus ultrasonography vs. mammography alone. Propensity score matching was used to address this. 25.7% of women receiving mammography plus ultrasonography did not have dense breasts.	abnormalities received same-day additional imaging, and a single screening report was issued regardless of whether imaging included only screening or both screening and diagnostic views.	assessment after any additional workup.	each subgroup needed for each performance measure.	model to account for potential residual confounding.	
Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan Strategic Anti-cancer Randomized Trial (Ohuchi *et al.*)	Cochrane Risk of Bias 2	Not specified	Findings of mammography, ultrasonography, and clinical examination were independently assessed.	Further assessments deemed necessary if scores of 3 or higher were assigned.	Analyses were done by intention to treat.	Not specified.	The risk of bias is assessed as moderate, potentially leaning towards low
Supplemental breast cancer-screening ultrasonography in women with dense breasts: a systematic review and meta-analysis (W.-H. Yuan *et al.*)	AMSTAR 2	Not specified	Not specified	Not specified.	Not specified.	Publication bias analysis by funnel plot was not performed due to the limited number of studies included (<10 studies).	Moderate, potentially bordering on low
Supplemental Screening for Breast Cancer in Women with Dense Breasts (Melnikow *et al.*)	AMSTAR 2	Limited to fair or good-quality randomized, controlled trials, cohort studies, or diagnostic accuracy studies with reference standards applied to all participants. Studies focusing primarily on women at high risk for breast cancer were analyzed separately when possible.	Not specified	Sensitivity, specificity, PPVs, NPVs, and available clinical outcomes were examined. Recall was defined as the need for any additional diagnostic testing after supplemental screening, including imaging and biopsy.	Not specified.	Not specified	Moderate, potentially bordering on low

Narrative Synthesis

The effectiveness of mammography with supplemental USG compared to mammography alone in women with dense breasts is as follows:

Cancer Detection Rate: Supplemental USG generally improves the cancer detection rate in women with dense breasts [9]. In the study by Shen *et al.* (2015), ultrasound detected more cancers than mammography in the combined group [8].

Sensitivity and Specificity: Supplemental USG increases sensitivity but may slightly decrease specificity [9]. The pooled sensitivity values of mammogram alone and mammogram with USG in patients were 74% and 96%, while specificity of the two methods were 93% and 87%, respectively [9].

Recall Rates: Adjunctive USG may lead to increased recall rates due to more findings requiring further investigation [5]. However, Lee *et al.* found that mammography plus ultrasonography screening was associated with fewer end-of-day assessments for additional imaging [5].

False Positivity: There is a potential increase in false-positive findings with the use of adjunctive USG,

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leading to unnecessary biopsies [9]. Lee *et al*. found that the false-positive biopsy rates were significantly higher with mammography plus ultrasonography [5].

Cost-Effectiveness: The cost-effectiveness of supplemental USG needs to be carefully considered [8, 9].

Trade-offs: The increase in cancer detection must be weighed against the drawbacks of increased false positives and potential unnecessary interventions [5].

Table 3: Outcome and narrative synthesis of the included studies

Study Title with Author Name	Modalities Compared	Population	Cancer Detection Rate (per 1000 women screened)	Recall Rate (%)	Key Outcomes
A multi-centre randomised trial comparing ultrasound vs mammography for screening breast cancer in high-risk Chinese women (S. Shen *et al*.)	Mammography vs. Ultrasound vs. Combined	High-risk Chinese women	Mammography: 0.72 Ultrasound: 1.51 Combined: 2.02	Not specified	Ultrasound is superior to mammography for breast cancer screening in high-risk Chinese women; ultrasound is the least costly screening modality.
Performance of Screening Ultrasonography as an Adjunct to Screening Mammography (J.M. Lee *et al*.)	Mammography + Ultrasonography vs. Mammography Alone	Women across the spectrum of breast cancer risk	Mammography + Ultrasonography: 5.4 Mammography Alone: 5.5	Mammography + Ultrasonography: 9.9 Mammography Alone: 17.6	No significant increase in cancer detection; significantly higher false-positive biopsy rates with supplemental ultrasonography.
Supplemental breast cancer-screening ultrasonography in women with dense breasts: a systematic review and meta-analysis (W.-H. Yuan *et al*.)	Mammography Alone vs. Mammography + Ultrasonography; Follow-up USG after negative mammography	Women with dense breasts	Not specified (Pooled sensitivity and specificity reported)	Not specified	Addition of US to mammography improves sensitivity for detection of breast cancer, but slightly decreases specificity. Follow-up US has good diagnostic sensitivity and specificity.
Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan Strategic Anti-cancer Randomized Trial (Ohuchi *et al*.)	Mammography and ultrasonography (intervention group) or mammography alone (control group)	asymptomatic women aged 40–49 years	Mammography arm 3.3, mammography plus ultrasonography arm (3.9)	Not specified	Mammography with adjunctive ultrasonography was associated with a significantly higher detection rate of breast cancer than mammography alone

Discussion

Cancer Detection Rate: Shen *et al*. reported that the cancer detection rate was 0.72/1000 in the mammography group, 1.51/1000 in the ultrasound group, and 2.02/1000 in the combined group in a multicentre randomised control trial comparing USG versus mammography in high-risk women [8]. A meta-analysis indicated that the combined sensitivity of mammography with USG for breast cancer detection was significantly higher than that of mammography alone (96% vs. 74%) [9]. Another study, however, found comparable cancer detection rates between mammography plus ultrasonography and mammography alone (5.4 vs 5.5 per 1000 screens) [5]. A study in Japan reported a cancer detection rate of 3.3 per 1000 screens in the mammography arm and 3.9 per 1000 screens in the mammography plus ultrasonography arm [5]. For women with dense breasts, the cancer detection rate with mammography alone was 1.8 per 1000 screens, increasing to 2.4 per 1000 screens with added ultrasonography [5]. A systematic review noted that supplemental US screening increases the cancer detection rate [9].

Recall Rates: One study reported that recall rates with DBT ranged from 7% to 11%, compared to 9% to 17% with digital mammography alone [7]. The addition of ultrasonography to mammography screening approximately doubled recommendations for further assessment [5].

Sensitivity and Specificity: In one of the studies, ultrasound was more sensitive than mammography (100% vs 57.1%, P=0.04) with better diagnostic accuracy (0.999 vs 0.766, P=0.01). There was no

ISSN:0975 -3583,0976-2833 VOL 12, ISSUE 10, 2021

difference between mammography and ultrasound in specificity (100 vs 99.9%, P=0.51) [8]. A meta-analysis showed that the pooled sensitivity for mammography alone was 74% and for mammography plus USG was 96%. The pooled specificity for mammography alone was 93% and for mammography plus USG was 87% [9]. Another analysis found that mammography plus USG had higher sensitivity and lower specificity than mammography alone (sensitivity: 1.00 vs. 0.72, RR= 0.683, P < 0.05; specificity: 0.75 vs. 0.87, RR= 1.09, P value insignificant) [9].

False Positivity: The false-positive biopsy rates were significantly higher with screening mammography plus same-day ultrasonography compared with mammography alone (52.0 vs 22.2 per 1000 screens) [5]. Supplemental USG screening was associated with an increase in the false-positive rate [9].

Cost-Effectiveness and accessibility: Ultrasound was the least costly screening modality for breast cancer, costing only 17.4% of mammography or 36.5% of combination screening and is easily accessible as discussed in one study [8].

Trade-offs: While supplemental US increases cancer detection sensitivity, it slightly decreases diagnostic specificity for breast cancer [9]. There is a potential increase in false-positive results with supplemental ultrasonography screening [9].

Limitations

The systematic review has limitations including variations in study designs, heterogeneity of populations, and equipment used, which can affect the generalizability of findings. Also, there is a lack of long-term follow-up data on outcomes like interval cancer rates and mortality. In many studies women at increased breast cancer risk due to risk factors other than breast density is also included, limiting the generalizability to the general screening population of women with dense breasts [7]. These limitations show the need for further research, especially in trials with longer follow-up and standardized methodologies.

Conclusions

In conclusion, this systematic review suggests that supplemental USG along with mammogram, offers a superior alternative to mammogram alone for breast cancer screening in women with dense breasts due to improved cancer detection. However, further research is needed, including trials with longer-term follow-up, to fully understand the impact of supplemental USG with mammogram on long-term clinical outcomes and to address the limitations identified in this review.

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