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## Effectiveness of Breast Ultrasound for Breast Cancer Screening : A Systematic Review

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### ABSTRACT

Breast cancer is the most common cancer in Indonesia and has the highest mortality rate in women. Nowadays, the primary prevention is not clear yet to prevent the breast cancer. Secondary prevention with radiological modality is the only option to decrease the mortality of breast cancer. This study aims to identify ultrasound effectiveness and accuracy as a screening modality for early detection of breast cancer. Methods: A systematic review was analyzed using PRISMA without a meta-analysis method on articles published in 2014-2024. Articles searches were conducted using PubMed, Science Direct, and Google Scholar Database. Result: Based on the search results, seven eligible articles met the criteria for analysis. We found consistent evidence in 5 studies that breast cancer screening using ultrasound has high sensitivity (range sensitivity 68.9%-100%) and accuracy (range accuracy 0.687-0.999) compared to mammography alone. Breast ultrasound specificity is lower than mammography, ranging from 22% to 99.9%. The positive predictive value ranges from 4.3%-70%, and the negative predictive value of breast ultrasound ranges from 61.2%-100%. Conclusion: Breast Ultrasound can be an option as a breast cancer screening modality, especially in young women with dense breasts. It can be used in health facilities where mammography is unavailable.

**Keywords:** Ultrasound, Breast, Cancer.

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### INTRODUCTION

Breast cancer is a malignancy that originates from the epithelium of the ducts or lobules in breast tissue. Based on data from Globocan (The Global Cancer Observatory) in 2022, breast cancer is the most common cause of cancer in Indonesia. There are a total of 66271 (16.2%) new cases of breast cancer from 408661 total cancer patients. Breast cancer is also the cause of most cancer deaths in women, with a total of 22598 cases (Bray et al., 2024). The high case of death from breast cancer is due to the majority of patients who come already in an advanced stage. The cure rate for breast cancer reaches 80-90% if breast cancer can be found at stage I without invasion of cancer cells to the lymph nodes (Birnbaum et al., 2018)..

Until now, no primary prevention efforts have been found to prevent breast cancer. Secondary prevention is an effort that can be done by conducting breast screening examinations so that it can detect abnormalities in the breast due to breast cancer early. Some secondary prevention methods can be implemented, such as breast self-examination (SADARI), clinical breast examination (SADANIS), or supporting examinations such as mammography, breast ultrasound, or MRI. Based on data from the Indonesian health profile in 2021, with the SADANIS examination (clinical breast examination) in women 30-50 years old, 18150 breast lumps were found, and 3040 cases were suspected of breast cancer. The difference between the results of the SADANIS examination and the number of breast cancer cases in Indonesia is that the SADANIS examination can only detect breast cancer abnormalities that are > 2 cm in size, so breast abnormalities that are not palpable are often not detected. (Tiomaida Seviana, 2023).

A mammography examination is a recommended examination for breast cancer screening. However, this mammography examination is not evenly available in Indonesia, so breast cancer screening efforts have not been carried out optimally—the examination to detect other breast abnormalities using breast ultrasound. Ultrasound examination is a non-invasive method that uses high-frequency sound waves, which can produce a more detailed picture of tissue structures in the body. Breast ultrasound is a safe examination, can distinguish solid or cystic lesions in the breast, can be used in dense breasts, and can assist in guiding fine needle biopsies (Jacob et al., 2024).. Ultrasound examination equipment in Indonesia is currently evenly available and can be reached at first-level health facilities (Tiomaida Seviana, 2023).. The purpose of this literature review is to determine the effectiveness of using breast ultrasound for breast cancer screening that can be done in remote areas with limited access and to determine the shortcomings of breast ultrasound, in addition to knowing the comparison with other examination modalities. It is hoped that optimizing the use of ultrasound for breast cancer screening can increase the insight and knowledge of health workers so that they can find breast cancer as early as possible in Indonesia.

## **METHOD**

The purpose of this study was to obtain information on the benefits and barriers of breast ultrasonography for breast cancer screening in women. This systematic review uses secondary data from research results in the form of scientific reports on the use of ultrasonography for breast cancer screening. This study uses the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) method without meta-analysis. Article searches were conducted using Pubmed, Google Scholar, and Science Direct databases. Article searches were conducted using keywords appropriate to the research topic: "Ultrasound," "Breast Cancer," AND "Screening," and using inclusion and exclusion criteria.

### **Inclusion Criteria:**

- a. Articles include quantitative studies
- b. The journal is not a systematic review or meta-analysis
- c. The results of the study noted the sensitivity and specificity of ultrasonography for breast cancer screening
- d. The study was conducted on women without complaints or with first-time breast complaints.
- e. Published in 2014 - 2024

### **Exclusion Criteria:**

- a. The journal is not in English or Indonesian
- b. Journal not fully accessible
- c. Journals are not original studies, such as article reviews, commentaries, or editorials.

Article selection using a PRISMA diagram to filter the selected articles. The selection of articles began by filtering titles and abstracts that matched the research topic. Furthermore, inclusion and exclusion criteria were used to make the research articles more suitable. The selected articles were then critically reviewed using a questionnaire from the Joanna Briggs Institute by the research study design. The articles were extracted by reviewing and briefly summarizing using tables. The table consisted of the author, year of publication, country, research title, research method, population, and results. Results were presented qualitatively in the form of meta-synthesis according to the measured outcomes, focusing on the accuracy of ultrasonography for breast cancer screening.

**RESULTS AND DISCUSSION**

From the systematic data search, 1524 articles were obtained and filtered based on titles and abstracts matching the topic. Of these articles, 1320 proceeded to the screening stage after removing duplicate articles. At the screening stage, the articles were excluded because they were close-access articles, were not original studies, and had yet to be published before 2014. At the eligibility stage, 699 articles were eliminated because they did not bring up relevant data, explained the use of ultrasound as additional support for mammography, there was no diagnostic data, and were a meta-analysis or systematic review study, so there were seven articles that would be reviewed in this study. Based on ten standardized questions, the seven selected articles were assessed for quality using the Critical Appraisal Checklist Tools from the Joanna Briggs Institute (JBI). The results showed that all articles had valid study results. Furthermore, data extraction was carried out from the seven selected articles to see the characteristics and results of the study.

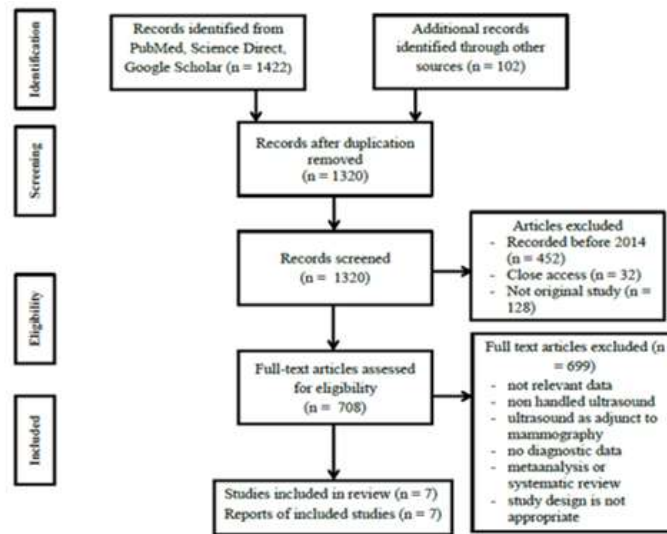


Figure 1. Prism Flow Diagram

Table 1. Results of Data Extraction from Literature

Author	Research Title	Methods	Population	Results
(Wang et al., 2022)	Comparison of ultrasound and mammography for early diagnosis of breast cancer among Chinese women with suspected breast lesions: A prospective trial	Prospective Trial	Two thousand seven hundred thirty-seven participants aged 35-70 years had suspected breast cancer lesions on physical examination.	a. Ultrasound sensitivity was 95.7% (95% CI 94.6-96.5), while specificity was 42.9% (95% CI 39.7-46.2) $p < 0.001$ . b. Accuracy (AUC) of ultrasonography was 0.768 (95% CI .752-0.784), higher than mammography 0.713 (95% CI 0.696-0.729) $p < 0.001$ c. Age, body mass index, and breast density do not affect the sensitivity and accuracy of ultrasound examination.
(Omidiji et al., 2017)	Breast Cancer screening in a resource-poor country ultrasound vs mammography	Cross-sectional comparative descriptive study	Three hundred women aged 30-60 years who came for breast cancer screening.	d. The sensitivity of ultrasonography was 100% compared to mammography 85.7%. e. The specificity of ultrasonography (22%) is

Author	Research Title	Methods	Population	Results
				lower than mammography (55.4%) f. Ultrasound accuracy 0.84 g. Positive predictive value 33.3%, negative predictive value 100%)
(Berg et al., 2016)	Ultrasound as the primary screening test for breast cancer: Analysis from ACRIN 6666	Prospective Trial	Two thousand eight hundred nine participants from the United States, Canada, and Argentina. Two thousand six hundred sixty-two participants had three annual examinations (7473 examinations) with ultrasound and mammography.	a. Sensitivity of ultrasonography 52.3% (95% CI 43.2-61.3) vs 53.2% (95% CI 44.1 - 62.2) on mammographic examination b. ultrasound specificity 86.3% (95% CI 86.1-8.8) c. Cancer detection by ultrasonography was 91.4% with invasive type. d. Recall rate 20.9% (95%CI 19.4-22.5), biopsy rate 8.8% (95%CI 7.7-9.9), positive predictive value 4.3% (95%CI 2.9-9.4) e. Cancer detection by ultrasonography shows similar results, and most cancers seen through ultrasonography are invasive and node-negative.
(Sun et al., 2022)	The Clinical Application of Combined Ultrasound, Mammography, and Tumor Markers in Screening Breast Cancer among High-Risk Women	Cross-sectional study	Thirty-eight thousand two hundred forty-one women aged 30-70 years were surveyed using a breast cancer high-risk factor questionnaire. Ten thousand eight hundred twenty-one subjects were randomly screened using ultrasonography, mammography, and tumor marker CA 153.	a. The sensitivity and specificity of ultrasonography (70% and 91.51%) were higher than mammography (66.67% and 90.63%) and tumor marker CA 153 (44.44% and 89.61%). b. Positive and negative predictive value (60.86% and 94.17%) c. Combination screening results in higher accuracy of screening results than single screening.
(Shen et al., 2015)	A multi-center randomized trial comparing ultrasound vs. mammography for breast cancer screening in high-risk Chinese women	Multicentre randomized trial	Thirteen thousand three hundred thirty-nine high-risk women aged 30-65 were randomized to screening, ultrasonography, or a combination of	a. Ultrasonography sensitivity is 100% (95% CI 73.2-100.0) higher than mammography 57.1% (95% CI 29.6-81.2) <i>P value</i> 0.04 b. The specificity of ultrasonography and mammography were not significantly different, 99.9% (95%CI 99.8-100.0)

Author	Research Title	Methods	Population	Results
			ultrasonography and mammography.	vs 100% (95%CI 99.9-100.0) <i>P value</i> 0.51 c. Positive predictive value of ultrasonography 70% (95%CI 45.7-87.2) <i>P value</i> 0.87 d. Diagnostic accuracy (AUC) of ultrasonography was superior 0.999 (95%CI 0.999-1.000) compared to mammography 0.766 (95%CI 0.591-0.941) <i>P value</i> 0.01
(Cortesi et al., 2019)	Breast ultrasonography in the screening protocol for women at hereditary-familial risk of breast cancer: Has the time come to rethink the role of breast ultrasonography in different risk categories?	Single-center, prospective, nonrandomized comparison study	2313 women without complaints with different risk factors (136 mutation carries, 1749 high risk, 428 moderate risk)	a. Sensitivity of ultrasonography 29.4%, mammography 55%, MRI 93.7% ( <i>p-value</i> <0.001) b. There was no significant difference in the sensitivity of ultrasonography for high-risk and intermediate-risk women (33.6% vs. 24.5%).
(Ghameian N, Tehrani N, 2021)	Accuracy of mammography and ultrasonography and their BI-RAD in the detection of breast malignancy	Cross-sectional study	Women who presented for screening or biopsy from 2016-2018 in Babul, Northern Iran. Two hundred ten patients underwent core needle biopsy and were assessed.	a. The sensitivity and specificity of ultrasonography were 68.9% (95%CI 59.1-77.5) and 48.6% (95%CI 39.9-58.5). Accuracy (AUC) 0.587 (95%CI 51.8-65.4) b. The positive and negative predictive values of ultrasonography were 57% (95%CI 51.5-62.4) and 61.2% (95%CI 52.8-69), respectively. c. The combination of mammography and ultrasonography results in higher accuracy than the use of ultrasonography or mammography alone.

Research conducted by Yingjiau Wang et al. in the first article explained that ultrasound examination is more accurate for detecting breast cancer in breast lesions than mammography examination. However, the specificity was lower for ultrasound examination than mammography (42.9% vs 62.3  $p < 0.001$ ). Ultrasound sensitivity and accuracy also did not change with age, body mass index, or breast density ( $p < 0.05$ ). However, the specificity of ultrasonography decreased with increasing body mass index to 29.1% (95% CI 22.9-36.1  $p < 0.001$ ) (Wang et al., 2022).

The second article by Olubukola A.T Omidiji et al. aimed to compare mammography and ultrasonography as breast cancer screening tools in women in Nigeria. Ultrasound had high sensitivity

(100%), low specificity (22%), low positive predictive value (33.3%), and high accuracy in detecting breast cancer (84%). Ultrasonography is superior in using ultrasound images suggestive of breast cancer, such as mass (100%), spiculation (50%), microlobulation (10%), architectural distortion, and axillary lymphadenopathy (20%) (Omidiji et al., 2017)..

The third article by Wendie A Berg et al. aims to compare the use of ultrasonography for breast cancer screening and compare it with mammography in the same patients. The study was conducted on 2809 United States, Canada, and Argentina participants. Cancer detection yielded comparable results with ultrasonography and mammography (52.3% vs. 53.2%), with ultrasonography more frequently detecting invasive cancers (53/58, 91.4%, median size 12 mm, range = 2- 44 mm). The cancer detection rate in the first year was 9/1000 (95% CI = 6.1-13.4) and 7.1/1000 (95% CI = 5.2-9.1) in the second and third years, which was similar for mammography (7.5/1000 and 8.1/1000). Screening in 4814 participants in the first showed a higher recall rate than mammography (20.9% vs. 11.5%) and a higher biopsy rate (8.8% vs. 2.4%) (Berg et al., 2016).

The fourth article by Lin Sun et al, aimed to compare the difference between single examination and combination examination to provide better benefits in breast cancer screening. From 10821 women aged 30-70 years with high-risk factors were randomly divided into several groups: the ultrasonography group, mammography group, CA 153 group, and the group with combined examinations. The sensitivity and specificity of ultrasonography (70% and 91.51%) were higher than mammography (66.67% and 90.63%) and tumor marker CA 153 (44.44% and 89.61%). Ultrasonography accuracy was 0.881. Positive predictive value 60.86, and negative predictive value 94.7% (Sun et al., 2022).

The fifth article by S Shen et al. aims to compare the performance of ultrasound and mammography for breast cancer screening in women with high-risk factors for breast cancer. Thirteen thousand three hundred thirty-nine patients with high-risk factors for breast cancer were obtained and then randomized into mammography, ultrasound, and combination groups. In the ultrasound group, ultrasound sensitivity was 100% (95% CI 73.2-100), specificity was 99.9% (96% CI 99.8-100.0), positive predictive value was 70% (95% CI 45.7-87.2), and diagnostic accuracy (AUC) was 0.999 (95% CI 0.999-1.000) (Shen et al., 2015).

The sixth article by L Cortesi et al. aims to evaluate ultrasound screening to detect breast cancer in women with a family history of breast cancer, using mammography and clinical breast examination after six months. The sensitivity of ultrasonography was 29.4%, mammography 55%, and MRI 93.7% (p-value <0.001). The sensitivity of the combination of ultrasound and mammography examination was 100% at high risk and 80.4% at moderate risk (Cortesi et al., 2019).

The seventh article by Naser Ghanaian et al. aims to assess the accuracy of ultrasonography and mammography and the BI-RADS classification based on findings in the diagnosis of breast cancer, as well as help for screening and early diagnosis of masses in the breast. Of the 210 patients examined, 106 masses were found to be malignant. The results showed that the sensitivity and specificity of ultrasonography were 68.9% (95% CI 59.1-77.5) and 48.6% (95% CI 39.9-58.5). Accuracy (AUC) 0.587 (95% CI 51.8-65.4). The sensitivity of mammography and ultrasonography was not significantly different in this study. (72.6% vs 68.9% and 43.9% vs 48.6%, respectively) (Ghameian N, Tehrani N, 2021).

### **Advantages of Ultrasound for Breast Cancer Screening**

Breast ultrasound examination is a relatively safe method that does not use ionizing radiation. In contrast, mammography examinations use X-ray radiation, so there is concern that radiation effects may occur with repeated use of mammography in young women and pregnant women. Ultrasound is relatively safe because it uses high-frequency sound waves that can be used in pregnant women and repeated routine screening. It is easily accessible to the public. In addition, an ultrasound examination is also convenient to perform as no compression of the breast causes discomfort during the examination,

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and the examination can be viewed in real time. The cost of an ultrasound examination is among the least expensive of the examination modalities for breast cancer screening (Berg et al., 2016). Images on breast ultrasonography that lead to malignancy, such as hypoechoic images with irregular shapes, indistinct boundaries (spiculated, microlobulated, angular), there are posterior acoustic shadows, there are microcalcifications inside or outside the mass, vertical orientation where the height is longer than the width of the mass, and distortions in the architecture around soft tissue (Candelaria R, Hwang L. Bouchard R, 2013).

Breast ultrasound examination can be performed on dense breast tissue, whereas in mammography examination, the accuracy value will be reduced and can cause false adverse conditions during examination. Research conducted by Yingjiao Wang et al. explained that the sensitivity value of ultrasound is significantly higher than mammography (95.7% in ultrasound and 78.9% in mammography). The sensitivity and specificity values of breast ultrasound also did not differ significantly with age, body mass index, and breast density ( $p < 0.05$  in all subgroups of age, body mass index, and breast density). This study also described different sensitivity values of mammography when used in dense breasts (ACR BIRADS c and d), which were 87.4% in low-density breasts (ACR BIRADS a and b) and 78.2% in denser breasts (ACR BIRADS c and d). Similar results were also described by Emine Devolli et al.; ultrasound examination is superior to use in women aged  $<40$  years, with a sensitivity of 82.9%, compared to mammography, with a sensitivity of 34.3%. In addition, ultrasound examination has a higher sensitivity value in dense breasts (BI-RADS d), 68.8%, compared to mammography examination, with a sensitivity of 0% (Laçi et al., 2023)..

Of the five literatures analyzed, it was found that the sensitivity and accuracy of ultrasound examination to detect breast cancer were superior to mammography examination (sensitivity range 68.9%-100% and accuracy range 0.687-0.999). The cancer detection rate on ultrasound examination shows the same results as mammography examination for breast cancer screening (9/1000 vs 7.5/1000).7 In Hailong Chen's study assessing the comparison of imaging modalities to detect tumor size  $< 2$  cm in breast cancer explained that the sensitivity value of ultrasound to detect tumor size  $< 1$  cm is 85.1%, and 92.1% to detect tumor size  $> 1.1 - 2$  cm. Ultrasound has the advantage of detecting small breast cancers and is independent of breast density (Chen et al., 2021).

From research articles on young and high-risk populations, it was found that the use of ultrasonography is effective in finding breast cancer with superior sensitivity than mammography. Breast ultrasound is also good at distinguishing cystic and solid masses, which are difficult to distinguish on mammography. The use of ultrasound is also helpful as an additional breast cancer screening examination in women with negative mammography results. This was explained in a study by Veronica Girardi of 22131 asymptomatic women, where there were 1.85/1000 women who developed breast cancer using ultrasound examination despite previous negative mammography examination results. This study also explained the high detection of breast cancer in negative mammography as evidenced by a history of previous breast cancer (5.59/1000), younger women (1.95/1000), and dense breasts (2.21/1000). (Buchberger et al., 2018).

### **Obstacles to Ultrasound Examination**

Ultrasound examination is highly dependent on the operator's skill and experience. The ability of the radiologist to perform the ultrasound examination can affect the quality and accuracy of the results. To overcome this obstacle, standardized training and practices are needed to provide consistent and accurate results in each health facility (Jacob et al., 2024); (Candelaria R, Hwang L. Bouchard R, 2013).

Ultrasound examination has limitations for detecting microcalcifications. Microcalcifications are tiny calcium deposits that can be an early sign of breast cancer. Ductal carcinoma in situ (DCIS) currently accounts for 15-20% of all breast cancers and can generally be detected by the presence of microcalcifications with screening mammography in asymptomatic women. In Marion E Scoggin's

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study of 691 patients with DCIS, 362 (52%) DCIS lesions were detected by ultrasonography: 276 (76%) masses and 86 (24%) other lesions (microcalcifications, architectural distortion, and ductal abnormalities). Calcifications by ultrasound examination were usually present within masses and concealed breast tissue and were associated with architectural distortion and intraductal location. Although ultrasonography is not the standard for detecting microcalcifications, with the use of high-frequency transducers, microcalcifications can be evaluated (Scoggins et al., 2015).

The specificity of ultrasonographic examination is low compared to mammographic examination. The specificity of ultrasonography is further decreased in obese women due to increased breast thickness as well as fat, which reduces the quality of the images produced. This low specificity may increase the false positive rate of the examination, increasing patient anxiety and unnecessary biopsy requests. The false positive rate is higher in ultrasonography (8.9%) than in mammography examination (5.6%). However, the false positive rate can decrease to 4.4% if ultrasonography is combined with mammography (Berg et al., 2016); (Parmar et al., 2022).

## CONCLUSION

One of the efforts to reduce the mortality rate of breast cancer is by screening women so that the cure of breast cancer increases if breast cancer is found as early as possible. Breast cancer screening using ultrasonography has advantages and limitations. The advantages of ultrasonography include low-cost examination, readily available and affordable by the community; results can be seen in real-time, comfortable and safe to use because it does not use ionizing radiation so that repeated examinations can be done according to indications; superior to use in young women aged <40 years compared to mammography, not affected by breast density, has a higher sensitivity than mammography, can detect minor breast abnormalities <1 cm compared to mammography examination, and can detect breast cancer in women with negative mammography examination results. The barriers to ultrasound examination for breast cancer screening include operator-dependent examination, limited detection of microcalcifications compared to mammography, low specificity, and higher false positive rate compared to mammography. Ultrasound examination can be an option as a breast cancer screening tool, especially in young women with dense breasts. It can be used in health facilities where mammography is not available.

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