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PERSPECTIVE

The evidence and concerns about screening ultrasound for breast cancer

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The number of newly diagnosed breast cancer cases and related deaths is the highest among female malignancies in nearly all countries[1]. The estimated annual percentage change in mortality increased by an average of 0.29% to 0.75% per year from 1990 to 2019 in low- and middle-Social Demographic Index (SDI) countries. In contrast, the estimated annual percentage change in mortality decreased by an average of 1.52% per year in high SDI countries[2] due to early diagnosis and treatment. Most East Asian countries have not seen evidence of a reduction in breast cancer mortality[1].

The International Agency for Research on Cancer Working Group recommend mammography (MG) as the primary screening method. However, breast cancer screening using MG can be a challenge in places where MG units and trained professionals are unavailable. The shortage of machines and radiologists limits the implementation of MG-based breast cancer screening programs in some low-resource countries. Furthermore, the sensitivity of MG decreases from 86% in women with near-entire fatty breasts to 61% in women with extremely dense breasts[3]. Asian women typically have denser breasts. To address the problem of false-negative MG in East Asian countries, ultrasound has gained wide usage. Automated breast ultrasound (ABUS) standardizes the image acquisition procedure compared to hand-held ultrasound (HHUS). Therefore, ABUS is considered more objective, making ABUS a promising alternative to both HHUS and MG for breast cancer screening.

We reviewed the current status of breast cancer screening to identify the barriers to implementing breast cancer screening. We also summarized the evidence on using HHUS and ABUS for breast cancer screening to demonstrate the feasibility and scientific validity of performing HHUS- and ABUS-based breast cancer screening in Asian countries.

Evidence on using HHUS for breast cancer screening

HHUS as a supplementary method

The sensitivity of the test and participation rate are considered two main factors influencing the screening effect on breast cancer mortality. Several prior studies reported increased breast cancer detection when using HHUS as a supplementary method to MG among women with dense breasts or women at an elevated risk of developing breast cancer[4,5]. Common strategies for integrating HHUS into breast cancer screening include using HHUS for women with negative MG results and all women regardless of MG results. HHUS detected an additional 4.90 cancers per 1,000 screens, which was significantly more than tomosynthesis (2.83 cancers per 1,000 screens)[4]. Combining MG with HHUS, regardless of MG results, significantly increased cancer detection rates in high- and average-risk women. However, this approach is associated with elevated false-positive findings and recall rates. Instead of adding HHUS for all women with negative MG results, Dong et al. concluded that adjunctive HHUS should only be

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recommended for women who were classified as breast imaging reporting and data system (BI-RADS) 0–2 by MG but not for women classified as BI-RADS 3. Dong et al. also concluded that adjunctive HHUS should be recommended for women with BI-RADS 0–2, not only for women with dense breasts but also women with a history of benign breast disease (**Table 1**)[6].

The effects of MG plus HHUS in women with non-dense breasts are inconsistent across different studies. Nakamura et al. reported no significant difference in cancer detection and recall rate between women who underwent MG alone and women who underwent MG plus HHUS[7]. Nevertheless, Harada-Shoji et al. reported that MG plus HHUS had higher sensitivity in women with dense and non-dense breasts[8].

HHUS as the primary screening method

A pooled analysis of 11 joint screening studies indicated that HHUS, as a primary screening method, performed comparably to MG alone with respect to sensitivity, specificity, cancer detection rate, biopsy rate, and the proportion of node-negative cancers among screening-detected invasive cancers. However, HHUS had a higher detection rate for invasive cancers[9]. Moreover, compared to MG, HHUS alone detected more breast cancers across all age groups with the effect being more pronounced among women < 50 years of age (< 50 years: 77.4% *vs.* 50.6%, $P < 0.001$; > 50 years: 70.4% *vs.* 65.9%, $P < 0.001$)[10]. However, breast cancer detection rates with HHUS were also comparable to MG (52.3% *vs.* 53.2%) in high-risk Caucasian women, although HHUS detected more invasive and node-negative breast cancers than MG[11].

Several cross-sectional, observational, and prospective studies conducted in China reported that HHUS is a more sensitive method for breast cancer detection in Chinese women. Studies conducted in high- and average-risk Chinese women revealed that primary HHUS detected more breast cancers than MG, especially in women with dense breasts. A real-world study conducted in Beijing, China showed that HHUS for primary screening followed by MG for triage or combining both HHUS and MG had significantly higher sensitivity compared to HHUS alone or MG as primary screening followed by HHUS for triage in high-risk women (**Table 1**)[12].

Greater than 50% of Chinese women have heterogeneous or extremely dense breasts, which is significantly higher that Caucasian counterparts. As a result, ultrasound is increasingly considered an effective alternative for personalized breast cancer screening in these geographic regions. More importantly, HHUS has the ability to detect more breast cancers at an early stage[11,13]. Countries that achieved a 2% annual reduction in breast cancer mortality rates diagnosed at least 60% of cases in stages I and II, which was aligned with one of the goals established by the Global Breast Cancer Initiative (GBCI) launched by the World Health Organization. Ohuchi found that 78% of breast cancer cases detected using HHUS alone were in clinical stages 0–I[13]. This highlights the potential of adopting HHUS screening to meet the GBCI objectives for breast cancer control.

ABUS evidence for breast cancer screening

HHUS is operator-dependent and lacks reproducibility, which limits use of HHUS in medical resource-constrained areas without professional radiologists or physicians. Unlike HHUS, ABUS is user-independent and separates image acquisition

Table 1 Summary of screening effectiveness of HHUS, ABUS, and MG

	HHUS	ABUS	MG
Sensitivity	Whether used alone or as an adjunctive method, HHUS is superior or at least comparable to MG, especially in women with dense breasts.	Whether used alone or as an adjunctive method, ABUS is superior or at least comparable to MG, especially in women with dense breasts in diagnostic studies.	With high sensitivity in women with non-dense breasts, but decreased sensitivity in women with dense breasts.
Specificity	With lower specificity compared to MG.	ABUS alone has lower or similar specificity compared to MG.	With high specificity.
Concerns	User-dependent with low reproducibility and high false-positive and recall rates.	Time-consuming with relatively high false-positive and recall rates.	Low sensitivity in women with dense breasts and requirement for infrastructure and personnel.

ABUS, automated breast ultrasound; HHUS, hand-held ultrasound; MG, mammography.

from interpretation, which enables additional comparison or analysis. These features are expected to facilitate the establishment of an imaging interpretation center, increasing the screening accuracy and standardizing the screening procedure with the expanding usage of ABUS in screening activities.

Studies evaluating ABUS screening performance have mostly been conducted among asymptomatic women. Like HHUS, adding ABUS to MG in women with dense breasts increased the invasive breast cancer detection rate in several prospective studies conducted in asymptomatic women. While no difference in tumor size was existed in cancers detected by ABUS and MG in the Gatta study[14], Kelly noted that joint screening with ABUS and MG doubled the breast cancer detection rate in women with dense breasts (3.60 to 7.20 per 1,000 screens). ABUS detected invasive breast cancers that were smaller in size. An observational screening study with a larger sample size reported similar results to Kelly, but with a smaller increase in cancer detection (5.40 to 7.30 per 1,000 screens)[15]. In a study involving Chinese asymptomatic women revealed that ABUS sensitivity alone was higher than MG with no loss in specificity. These differences were more pronounced in women with dense breasts but not statistically significant in women with non-dense breasts[16]. When used as a supplementary method for women with negative MG results and dense breasts, ABUS plus MG detected 99.1% of breast cancers in Chinese women (**Table 1**)[17].

Few studies have evaluated the effectiveness of ABUS in the screening settings. In a retrospective study, ABUS showed similar screening performance to previous screening results in clinical settings. Prospective studies evaluating ABUS as the primary screening method for breast cancer in screening settings in East Asian women have shown high sensitivity and specificity. Among Korean women, the sensitivity of ABUS alone was 83.3% and the specificity was 90.7%[18]. Among Chinese women aged 45–54 years with dense breasts, adding ABUS to MG detected an additional 0.83 cancers per 1,000 screens, significantly more than MG alone. However, no significant differences were observed in women aged 55–64 years or those with non-dense breasts[19].

Health system characteristics, including breast cancer early detection programs, breast cancer early detection guidelines, national cancer plans, breast cancer referral systems, and pathology services, are more developed in high-income countries (HICs) than low-income countries (LICs), which leads to disparities in breast cancer mortality between these countries. Nearly 68% of LICs lack breast cancer early detection programs or guidelines and 60% have no breast cancer referral systems[20]. Breast cancer screening and early diagnosis initiatives have been implemented at the provincial or institutional level in most Asian countries, some of which implement ultrasound and/or clinical breast examination (CBE) with MG-based screening programs. To address these gaps, pragmatic approaches to health system strengthening within a resource-stratified framework are essential to improve breast cancer care. Establishment of an imaging interpretation center and integration of artificial intelligence (AI) system into ABUS screening is expected to increase screening quality and extend coverage in areas without professionals.

Concerns with HHUS and ABUS use for breast cancer screening

High false-positive and recall rates are the main concerns regarding adjunct screening with ABUS or HHUS because further examination is required in women with positive screening results by MG or ultrasound. Implementing an integrated assessment system that combines MG with adjunctive ultrasound could potentially address this issue. In such a system, adjunctive ultrasound is utilized based on MG findings and the final category is decided by the assessment of combined MG and ultrasound to reduce unnecessary recalls. Chinese researchers proposed risk-based BI-RADS assessment criteria to improve the diagnostic efficiency of HHUS. Specifically, the Gail model was combined with BI-RADS categories to modify the final BI-RADS categories according to the individual risk level calculated using the Gail model. The combined sensitivity, specificity, positive predictive value, negative prediction value, and AUC were 95.6%, 91.3%, 85.0%, 97.6%, and 97.6%, respectively[21]. A risk prediction model could be incorporated with HHUS and ABUS in the future to increase screening accuracy and reduce unnecessary biopsies.

The time-consuming nature of ABUS poses a concern when adopting ABUS for mass screening. Brunetti et al. compared the image acquisition and interpretation times of ABUS to HHUS. Brunetti et al. reported that the average time to perform and read images was 5 min for HHUS and 17 min for ABUS. Furthermore, approximately 60% of the time was spent on ABUS execution and the remaining 40% was spent on image interpretation. However, the ABUS examination time decreased as technologists became more familiar with the technique. Previously, manufacturers recommended three-view

scanning for all women, while four-view scanning was suggested for women with large breasts. Breast coverage was satisfactory in 94.1% and 91.9% of women with small breasts with two- and three-view scanning, respectively. In addition, there was no difference in sensitivity and specificity between two- and three view-scanning[22]. Scanning and reading times varied depending on the number of views. Therefore, selecting two-view scanning for population-based breast cancer screening might be a feasible and time-saving strategy for most Asian women who have small breasts (**Table 1**).

Studies evaluating screening performance of ABUS were mostly conducted among asymptomatic women in studies with small sample sizes or in retrospective screening studies. The lack of large-scale prospective randomized clinical trials evaluating the effectiveness of ABUS alone in screening settings limited the robustness of the evidence and hindered definitive conclusions regarding the clinical utility and impact on breast cancer outcomes. Moreover, the long-term screening effect of HHUS or ABUS on breast cancer mortality remains unclear due to insufficient follow-up in previous studies. The five-year survival rate of ultrasound-detected breast cancer was reported to be nearly 98% with a median follow-up of 7 years in Korea[23]. Instead of extending the follow-up period of existing studies, modeling studies could be used to estimate the impact of ultrasound screening on breast cancer mortality.

Adapting a screening strategy based on risk

Risk-based screening has grown significantly in recent years because population-based screening may not be the most efficient use of resources. Numerous observational and modeling studies have shown that personalized screening is cost-effective. Breast density-stratified screening, which involves changing screening intervals rather than adding supplemental methods, has been proven cost-effective for women at average risk of breast cancer. Incorporating supplemental screening based on the risk of masking due to high breast density requires additional resources and could reduce cost-effectiveness. In contrast, identifying high-risk women for adjusted screening approaches and adopting fewer intensive strategies for women at lower risk has proven to be cost-effective[24]. The main factors included in the risk prediction models are age, breast density, family history, and previous biopsies, with some models also incorporating genetic information. However, the net health benefit depends on the particular risk-stratification strategy and more studies are warranted to assess newer risk-stratification technologies, especially those specialized for the Asian population.

Apart from mammographic breast density, which is calculated as the proportion of dense breast tissue (including glandular and stromal), limited or absent lobular involution has been independently associated with a higher risk of developing breast cancer. The glandular tissue component, which reflects the extent of lobular involution, can be distinguished by HHUS and ABUS and has been reported to be independently associated with breast cancer risk[25]. Therefore, using HHUS- and ABUS-adjusted breast density measurement might improve breast cancer risk prediction.

Future perspectives

Several key areas require further exploration to optimize the integration of HHUS and ABUS into national screening programs. First, large-scale prospective randomized clinical trials are needed to evaluate the long-term effectiveness of HHUS and ABUS in reducing breast cancer mortality. Modeling studies could complement these trials to estimate the impact on population health outcomes.

Second, the integration of AI into HHUS and ABUS interpretation holds great potential to enhance diagnostic accuracy, reduce reading times, and minimize false-positives. AI-assisted imaging interpretation centers could help expand access in geographic regions with limited radiologic expertise. Caution should be exercised when integrating AI into screening activities with a strong emphasis on rigorous evaluation and careful consideration of the role of these emerging technologies.

Third, personalized, risk-based screening approaches should be further developed and validated for the Asian population. Incorporating HHUS- and ABUS-adjusted breast density measurement may improve breast cancer risk prediction and screening efficiency. Cost-effectiveness analyses should also guide the implementation of tailored screening strategies to ensure resource-efficient deployment in different healthcare settings.

Finally, pragmatic approaches to health system strengthening are crucial, especially in resource-limited settings. Establishing sustainable screening programs, enhancing training for healthcare professionals, and improving infrastructure for imaging interpretation will be vital steps toward closing the gap in breast cancer outcomes between high- and low-resource

regions. By addressing these challenges, ABUS could have a transformative role in achieving the GBCI goals and ultimately reducing breast cancer mortality worldwide.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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