Overcoming the limitations of screening mammography in Japan and Korea: a paradigm shift to personalized breast cancer screening based on ultrasonography

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Screening mammography programs have been implemented in numerous Western countries with the aim of reducing breast cancer mortality. However, despite over 20 years of population-based screening mammography, the mortality rates in Japan and Korea continue to rise. This may be due to the fact that screening mammography is not as effective for Japanese and Korean women, who often have dense breasts. This density decreases the sensitivity of mammography due to a masking effect. Therefore, the early detection of small invasive cancers requires more than just mammography, particularly for women in their 40s. This review discusses the limitations and challenges of screening mammography, as well as the keys to successful population-based breast cancer screening in Japan and Korea. This includes a focus on breast ultrasonography techniques, which are based on histopathologic anatomical knowledge, and personalized screening strategies that are based on risk assessments measured by glandular tissue components.

Keywords: Breast; Breast neoplasms; Screening; Ultrasonography; Glandular tissue component

Key points: Despite over 20 years of population-based screening mammography, the mortality rates in Japan and Korea continue to rise. Personalized breast cancer screening utilizing ultrasonography could be the most realistic solution.

Introduction

Screening mammography programs have been implemented in numerous Western countries with the aim of reducing breast cancer mortality [1–10]. Despite organizing population-based screening mammography for over two decades, Japan and Korea have not seen evidence of a decrease in breast cancer mortality [11,12]. For Japanese and Korean women, who tend to have dense breasts, the early detection of small invasive cancers necessitates more than just mammography. This is particularly true for women in their 40s, who have a high incidence of breast cancer [13,14]. A Japanese randomized controlled trial found that supplemental ultrasonography for breast cancer screening...
in women aged 40–49 years not only increased the sensitivity and detection rate of early invasive cancers, but also reduced the occurrence of interval cancers in the intervention group compared to the control group [15]. This review article seeks to outline the limitations of screening mammography and advocates for the use of screening ultrasonography. This technique, based on histopathologic anatomical knowledge, along with personalized screening based on risk assessment measured by glandular tissue components, could be a more effective approach.

Breast Cancer in Japan and Korea

Breast cancer is the type of cancer with the highest incidence, with 2.3 million new cases (representing 11.7% of all cancer cases worldwide) in men and women in 2020 [7]. It ranks as the fifth leading cause of cancer-related mortality, with 685,000 deaths. The incidence rates of breast cancer are rapidly increasing in East Asia, particularly in Japan and Korea, where historically the rates have been low. This surge is attributed to significant changes in lifestyle, dietary habits, reduced childbearing, increasing obesity, and physical inactivity [7].

For Japanese women, breast cancer is the malignancy with the highest incidence, with about 94,000 new cases per year in 2019. The lifetime probability of developing breast cancer is 1 out of 9 among women in Japan. It is projected to be the fourth leading cause of cancer-related deaths among Japanese women, with around 15,000 fatalities recorded in 2020. Furthermore, the mortality rate associated with breast cancer in Japan has been on the rise [11].

Similarly, in Korea, the incidence and mortality rates of breast cancer have been steadily rising and are projected to continue this upward trend in the future [12]. Notably, in 2018, 28,049 new cases of breast cancer were reported among Korean women, marking an increase of approximately 450% compared to 2000 [13].

Breast cancer tends to affect Japanese and Korean women at an earlier age compared to their Western counterparts, with the highest incidence of the disease observed among women in their 40s [13,14].

The region-specific incidence and mortality age-standardized rates for female breast cancer in 2020 are presented in Fig. 1 [16].

Breast Cancer Screening in Japan and Korea

The Japan Breast Cancer Screening Program, initiated in 2000, offers biennial screenings to women aged 50 and above, utilizing medio-lateral oblique one-view mammograms [14]. Since 2004, the program has expanded to include women in their 40s, employing two-view mammograms. This unique program combines recommended screening mammography with a clinical breast examination (CBE), although CBE has not been recommended since 2016. While the Japan Breast Cancer Screening Program does not impose an upper age limit, as of 2021, it actively encourages Japanese women aged between 40 and 69 to participate in breast cancer screening. Most Japanese women receive financial support from local governments or their employers to undergo breast cancer screening. In Japan, both double reading and comparison reading are recommended practices.

In Korea, the National Cancer Screening Program has advocated for biannual screening mammograms for women aged 40 and above since 1999. A single reading is considered sufficient in Korea [17]. In 2005, the target demographic for complimentary screening services expanded to include not only recipients of Medical Aid, but also beneficiaries of National Health Insurance in the lower half of the income spectrum. The remaining half of the population can also

Fig. 1. Age-standardized region-specific incidence and mortality rates per 100,000 for female breast cancer cases in 2020 in Eastern Asia, Northern America, Northern Europe, and Australia/New Zealand. The chart shows that the breast cancer mortality-incidence rate in Eastern Asia is the highest among four areas worldwide. Reference: Sung et al. [16].
access these screening services, but they are required to cover 10% of the total cost [18].

The policies and practices of screening mammography in Japan, Korea, the USA, and the UK are presented in Table 1.

In many developed Western nations, mortality rates have been on a downward trend since the early 1990s. This decline is largely attributed to the introduction of early breast cancer detection programs, particularly screening mammography, in the 1980s [1]. Both Japan and Korea have been conducting population-based screening mammography programs for over two decades. However, as previously noted, the mortality rates in these two countries continue to rise.

The reduction in breast cancer mortality is closely linked to both the benefits of screening mammography and advancements in breast cancer treatment [19]. Japan and Korea are countries with substantial resources and advanced development. In these nations, due to their robust healthcare infrastructures and insurance systems, many women diagnosed with breast cancer can quickly access cutting-edge chemotherapy and hormone therapy. Consequently, Japanese and Korean women with breast cancer undeniably benefit from these advances in treatment.

When considering the link between reduced breast cancer mortality rates and advancements in screening mammography and breast cancer treatment, it becomes apparent that the continued increase in breast cancer mortality rates in Japan and Korea may be due to insufficient utilization of screening mammography.

### Issues of Screening Mammography in Japan and Korea

There are established causal relationships between the primary parameters of population-based screening mammography—sensitivity and participation rate—and the outcomes of breast cancer [20]. Therefore, the reduction in breast cancer mortality is contingent upon the sensitivity and participation rate of screening mammography. Breast radiologists can improve the performance of this imaging technique; however, the participation rate in screening mammography is a more complex issue.

In the Japan Strategic Anti-cancer Randomized Trial (J-START) study, the sensitivity of mammography alone was found to be 47.4% in truly asymptomatic Japanese women in their 40s [21]. Screening mammography sensitivity for women aged 45–49 years in Korea ranged from 54% to 67% [22], a figure lower than that for older women within the same country. The sensitivity rate in the general female population in Korea was 86.5%, a rate comparable to that of Western women, due to a high recall rate of 19.1% [18].

Concerning sensitivity values, it appears that women in their 40s from Japan and Korea derive minimal true benefit from screening mammography due to the masking effect caused by their dense breasts.

### Issues Associated with Dense Breasts and Mammography

Dense breasts have two critical issues regarding mammography: low mammographic sensitivity due to the masking effect and an elevated risk of breast cancer [23]. The masking effect, in particular, poses a significant challenge. This effect implies that cancer detection via mammogram can be hindered by the superimposition of overlapping radiopaque dense breast tissues on an underlying malignancy. This complication arises when a three-dimensional breast is imaged on a two-dimensional plane (Fig. 2).

Japanese women are 15 times more likely to exhibit high breast density than their Australian counterparts. It is estimated that about 89.9% of Japanese women between the ages of 40 and 49 have heterogeneous and extremely dense breasts, in contrast to 38.5% of Australian women in the same age range [24]. Similarly, the percentage of women with dense breast tissue detected during mammography is higher among Korean women than among Western women [25]. In both Japan and Korea, the age-specific incidence of breast cancer reaches its peak during the 40s [13,14], as opposed to the peak in the 60s observed among Western women. This suggests that Japanese and Korean women in their 40s face a dual challenge: a higher incidence of breast cancer and denser breast tissue, which results in less effective screening mammography.

### Biological Underpinnings of Breast Density

Breast density reflects the presence of fibroglandular tissues, which include duct lobular units, fibrous tissues, and fat-containing stroma. The involution of duct lobular units, including terminal duct lobular units (TDLUs), is a histological marker of breast cancer risk.
is currently no global consensus advocating for the use of these supplemental breast cancer screening techniques in such women [14,34].

In Asian countries, ultrasonography has been suggested as a potential supplementary method for breast cancer screening, given the low sensitivity of mammography due to a masking effect [14,15,21,35,36]. Breast ultrasonography is the most cost-effective, convenient, readily accessible, and radiation-free method in breast imaging, and it eliminates the need for breast compression. Moreover, a meta-analysis has demonstrated that supplemental ultrasonography screening among women with dense breasts can increase the cancer detection rate by approximately 40% compared to mammography alone [37]. The J-START, the first large-scale, randomized controlled trial of supplemental breast screening ultrasonography for women aged 40–49 years, evaluated the effectiveness of screening mammography with additional ultrasonography. The results showed that supplemental ultrasonography not only increased the sensitivity and detection rate of early invasive cancers, but also reduced the occurrence of interval cancers in the intervention group compared to the control group [15,36]. While mortality rates are the most significant parameters for assessing the effectiveness of supplemental breast ultrasonography screening, the preliminary results from the J-START are crucial in guiding women with dense breasts in their choice of personalized breast cancer screening. Considering the higher incidence of breast cancer among women in their 40s in Japan and Korea, any reduction in mortality is likely due to the high sensitivity of supplemental breast cancer screening ultrasonography among women with dense breasts.

Ultrasonography has some drawbacks such as high operator

**Paradigm Shift to Personalized Ultrasound-Based Breast Cancer Screening**

As previously noted, screening mammography appears to offer limited benefits to Japanese and Korean women in their 40s. Therefore, the focus should now shift toward developing more effective screening methods. Several supplemental breast cancer screening techniques, such as ultrasonography, digital breast tomosynthesis, and breast magnetic resonance imaging, have been suggested to improve the sensitivity and early detection rates of breast cancer in women with dense breasts. However, there

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**Fig. 2. Triple-negative breast cancer measuring 20×11 mm in the left breast of a 40-year-old woman.**

A. There are no mammographic abnormalities in the fibroglandular tissues due to the masking effect.

B. A transverse gray-scale breast ultrasonography image shows a hypoechoic mass (arrow) with relatively smooth margins at 12 o’clock.
dependency, time consumption, lack of reproducibility and standardization that results in high false positive rates. Therefore, quality assurance and control are particularly important because they help minimize screening-associated harms [38]. In addition, women should be informed of the possibility of a false alarm and recall decline with incidence screening via breast ultrasonography screening [39].

Breast Ultrasonography Technique Based on Histopathologic Anatomical Knowledge

On ultrasonography, fibroglandular tissue appears as a combination of isoechoic and white areas (Figs. 3, 4) [27,28]. Duct lobular units, including TDLUs, and the surrounding stroma (periductal/lobule) are represented as isoechoic dendritic structures within this tissue. Mammary fibrous tissues and edematous stroma are shown as white areas within the fibroglandular tissue. The isoechoic dendritic patterns within the fibroglandular tissue are fundamental and crucial histopathologic anatomical structures in breast ultrasonography. This is because they can illuminate duct lobular units, including TDLUs, within the fibroglandular tissue. Even if the entire duct lobular units, including TDLUs, are atrophic, parts of their basic structure can often be seen as some isoechoic dendritic structures on ultrasonography. By focusing on the three-dimensional continuity and regularity of the normal isoechoic dendritic pattern, it becomes easier to identify isoechoic abnormal lesions, such as non-mass lesions, and subtle distortions [27,28,40]. Familiarity with the isoechoic dendritic patterns on ultrasonography is a critical factor in successfully detecting subtle abnormal lesions, such as ductal carcinoma in situ (DCIS) (Fig. 3).

Stavros noted the presence of periductal stromal fibroelastic tissues around the distal ducts, which can be seen as isoechoic bands on ultrasonography [41]. In contrast, Izumori et al. reported that the periductal stroma is not only present in the distal ducts, but also in all duct lobular units, including TDLUs [27,28]. The extralobular stroma, a normal component of the breast’s histopathologic anatomical structure, can be categorized into two types based on the location and quantity of fibrous connective tissues, stromal matrix, and fat [27,28]. These two types are the periductal/lobule stroma and the edematous stroma, both of which exhibit age-related changes and variations.

Two viewpoints are necessary to understand the normal histopathologic anatomical structure of the breast. The first involves understanding the isoechoic dendritic patterns found in fibroglandular tissue, while the second pertains to the distribution of fat lobes and mammary glands throughout the entire breast. Gaining insight into the normal histopathologic anatomical structure of the breast via ultrasonography will equip us with the ability to detect subtle isoechoic malignant lesions, such as DCIS (Fig. 3) [27,28,42]. Utilizing a breast ultrasonography technique grounded

Fig. 3. Ultrasonography technique based on histopathologic anatomical knowledge. An ultrasonographic image shows a non-mass lesion (dotted lines) at the edge of the breast with irregularities of the isoechoic dendritic pattern and disrupted duct tapering. Normally, duct and lobule patterns tapering off at the edge of the breast are noted. The results of the pathological examination confirmed ductal carcinoma in situ (DCIS). It should be noted that it is easy to detect DCIS appearing as a small mass (triangle) without a breast ultrasonography technique based on histopathologic anatomical knowledge.
in histopathologic anatomical knowledge will not only decrease the duration of the examination but also enhance the precision of the breast ultrasonography diagnosis.

**Sonographic Assessment of the GTC**

The sonographic GTC of the breast can be evaluated using either handheld or automated breast ultrasonography [29]. It is categorized as minimal, mild, moderate, or marked, depending on the percentage of isoechoic or hypoechoic areas within the fibroglandular tissues (Fig. 4). The GTC can be dichotomized as either "low" or "high," based on a GTC that represents 50% of the breast’s fibroglandular tissues. It is worth noting that GTCs may not be consistent across all breast quadrants. In such instances, the dominant pattern observed in at least two quadrants or the area with the thickest fibroglandular tissues is identified as the GTC. An important point to remember is that fat lobules, despite their distinctness from glandular tissues, are not included in the GTC evaluation, even if they appear as isoechoic areas.

In a retrospective cohort study of 8,483 Korean women (mean age, 49 years) with dense breasts on mammography, the baseline sonographic GTC was found to be minimal in 11% of patients, mild in 51%, moderate in 28%, and marked in 10%. When dichotomized, a low GTC was observed in 62% of patients, while a high GTC was seen in 38% [29]. Over a follow-up period of up to eight years (interquartile range, 3.3 to 7.0 years), 137 cases of breast cancer (1.6%) were recorded. After adjusting for other risk factors such as menopausal status, biopsy-confirmed benign breast disease,
family history of breast cancer, and mammographic density, a high GTC was associated with a higher risk of cancer (hazard ratio, 1.5; P=0.026) than a low GTC (Fig. 5). The results of this study suggest that sonographic GTC data can be used to stratify breast cancer risk and identify those women with dense breasts who are most likely to develop breast cancer and would therefore benefit from supplemental screening ultrasonography. For example, an average-risk woman with dense breasts and a high GTC, as determined by diagnostic ultrasonography, might consider supplemental screening ultrasonography. Conversely, average-risk women with dense breasts who have a low GTC, in conjunction with other risk factors, may demonstrate a reduced risk when undergoing screening ultrasonography. These women may not need annual screenings, and the screening interval could be extended to every 2–3 years. By combining information on sonographic GTC and mammographic breast density, we can better identify women who may benefit from supplemental screening. This could potentially enhance the risk-to-benefit ratio of screening ultrasonography [30].

The GTC can potentially affect the effectiveness of screening ultrasonography. A retrospective study found that a high GTC was linked to a significantly higher rate of abnormal interpretations than a low GTC (20.1% vs. 8.5%, P<0.001) during supplemental screening breast ultrasonography [43]. It is crucial to differentiate between the various echo patterns of normal GTC and non-mass findings in order to decrease false positives and reduce the need for short-term follow-up in screening ultrasonography [44].

**Future Directions of Breast Screening Ultrasonography in Japan and Korea**

Breast screening ultrasonography is the most practical supplementary method for population-based screening programs in Japan and Korea, given its capacity to handle high-volume screening. However, this technique is heavily reliant on the operator, necessitating real-time adjustments of gain, dynamic range, contrast, field depth, and the positioning of both the examiner and patient. Quality control is particularly crucial in a screening setting. As such, there is a need for guidelines on quality assurance and quality control for screening ultrasonography. The J-START has developed quality assurance guidelines [38], which include quality control for supplementary ultrasonography systems, educational and training programs, and interpretation criteria [45,46]. Furthermore, a comprehensive assessment system for intensive breast cancer screening using mammography and supplementary ultrasonography has been established in Japan [47].

Regarding sonographic GTC assessment, it is necessary to conduct an international study that includes women from various races and ethnicities to confirm the significant risk of breast cancer. Recently, such a study was initiated to validate the substantial risk discrimination for dense breasts among women of diverse races.
and ethnicities (ClinicalTrials.gov registration no. NCT05460975). This international study should also investigate potential differences in sono­graphic GTC assessment, including interobserver variability, based on race and ethnicity. Lastly, standardization is essential. Therefore, a sonographic GTC assessment system should be incorporated into the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) breast ultrasonography lexicon, along with non-mass lesions [40,48].

Conclusion

The sensitivity of breast cancer screening is vital to its success in reducing breast cancer mortality. Women in Japan and Korea typically have such dense breast tissue that they require more than just mammography. A personalized breast cancer screening approach using ultrasonography presents the most realistic solution to the low sensitivity of mammography screening among these women, particularly those in their 40s. Alongside quality control programs for breast cancer screening ultrasonography, we have suggested a technique based on histopathologic anatomical knowledge and the GTC concept. This technique aims to enhance screening performance and identify women most susceptible to breast cancer. Therefore, breast screening ultrasonography should be the cornerstone of a next-generation population-based breast cancer screening program in Japan and Korea.

Author Contributions

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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