Focus | Breast Imaging

eISSN 2005-8330
https://doi.org/10.3348/kjr.2022.0099
Korean J Radiol 2022;23(6):574-580

Korean Journal of Radiology
KJR

Check for updates

Glandular Tissue Component on Breast Ultrasound in Dense Breasts: A New Imaging Biomarker for Breast Cancer Risk

Su Hyun Lee, Woo Kyung Moon

All authors: Department of Radiology, Seoul National University Hospital, Seoul, Korea

Take-home points

- Breast ultrasound can distinguish glandular and fibrous tissues in mammographically dense areas based on their echogenicity.
- The sonographic glandular tissue component (GTC), which reflects the degree of lobular involution, is an independent predictor of the risk of future breast cancer in women with dense breasts.
- Sonographic GTC information could identify the subset of women with dense breasts who are likely to benefit from supplementary screening.

INTRODUCTION

Breast density, which refers to the amount of radiopaque fibroglandular tissue (FGT) relative to radiolucent fatty tissue on mammography, is established as an imaging biomarker of breast cancer risk and is included in risk assessment models [1,2]. In dense breasts, the performance and resulting benefits of screening mammography are reduced, and additional screening tests, such as ultrasound (US) or MRI, are often recommended, along with the notification of breast density [3,4]. Supplemental screening increases cancer detection and reduces interval cancer, but results in substantial false-positive findings, recalls, patient anxiety, and costs [5-9]. Dense breasts are present in approximately half of screening-aged women [10,11] and do not always indicate at-risk tissue [12]. Therefore, women and healthcare professionals should discuss breast density and other risk factors (Table 1) [12,13]. The less-than-perfect association between mammographic breast density and future risk of breast cancer is explained by different types of breast tissue with different risk-modulating potentials that will appear equally dense on mammography [14]. A breast can be dense because it consists of predominantly duct and glandular components, which may contribute to a woman's risk; however, a breast may also be dense only due to tissue fibrosis, which will likely not affect the risk. The US can distinguish two very different tissue types in mammographic dense areas based on their echogenicity: nearly isoechoic glandular tissue and hyperechoic fibrous tissue (Fig. 1).

In the current edition of the Breast Imaging and Reporting Data System (BI-RADS), tissue composition in the US is defined as a homogeneous or heterogeneous background echotexture in terms of the balance between FGT and fat, similar to mammographic density [15]. However, the sonographic appearance of FGT varies between individuals and changes over time within the same individual [16,17]. With aging, the breast lobules involute physiologically, and the extent of the glandular component decreases. Studies evaluating the degree of lobular involution in background tissue using benign breast biopsy specimens have found an association between a

Received: February 14, 2022 **Revised:** April 4, 2022
Accepted: April 10, 2022
Corresponding author: Woo Kyung Moon, MD, PhD, Department of Radiology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
• E-mail: moonwk1963@gmail.com

Korean Journal of Radiology
KJR

higher degree of lobular involution and a reduced risk of breast cancer [18,19]. In a previous study, we proposed a method to classify the glandular tissue component (GTC) of FGT in breast US in 2017 [20]. The clinical practice of our institution and many other institutions in East Asia includes a description and classification of the GTC category in breast US reports, although it is not yet included in the BI-RADS. In line with the shift toward personalized medicine, it is increasingly important to discover image characteristics related to an individual predisposition to specific diseases [1,21]. If sonographic GTC can provide additional risk information beyond mammography, it has the potential to serve as an imaging biomarker for risk stratification and may be used to develop a personalized breast cancer screening algorithm.

Table 1. Risk Factors for Breast Cancer

Risk Factor*	Relative Risk
Genetic mutations	
BRCA1 or 2	8–20
PALB2	4–6
ATM/CHEK2	2–4
Family history†	
3 first degree relatives	2.0–7.5
2 first degree relatives	2.4–3.6
1 first degree relative	1.7–1.9
1 second degree relative	1.2–1.5
Therapeutic radiation to the chest (at < 30 years)	7–17
Personal history of breast lesions	
Proliferative lesions without atypia	1.5–2
Atypical ductal hyperplasia	4–5
Atypical lobular hyperplasia	3–4
Lobular carcinoma in situ	4–10
Treated breast cancer‡	1.2–5.0
Hormonal factors	
Late parity or nulliparity	1.2–1.7
Early menarche or late menopause	1.2–1.3
Combined hormone replacement therapy	1.2–1.5
Postmenopausal obesity	1.2–1.9
High breast density	1.5–2.1

*Data are in part from Singletary 2003 [13], †Refers to the breast or ovarian cancer but without known susceptibility mutation. Risk varies with age of the affected relative(s), ‡The risk of second breast cancer varies with age at diagnosis.

Herein, we briefly describe the classification, influencing factors, and histology of sonographic GTC and discuss the association between sonographic GTC and future risk of breast cancer in women with dense breasts. We also discuss the clinical applicability of sonographic GTC as imaging biomarkers for risk stratification and direction for future work.

Sonographic GTC: Classification, Influencing Factors, and Histology

Similarly to MRI, US with sectional imaging capabilities can provide information on the distribution and amount of FGT and fat in the breast. After scanning the entire breast with the handheld or automated US, the GTC relative to the fibrous tissue in the FGT can be qualitatively assessed in terms of the proportion of isoechoic areas to hyperechoic areas and classified as minimal, mild, moderate, or marked (Fig. 2). When the distribution of GTC in the breast was not uniform, the dominant pattern observed in at least two quadrants was determined to be GTC. If the left and right breasts do not have an apparent equal GTC, the breast with the highest GTC should be used. The GTC could be dichotomized as “low” or “high” according to a GTC that

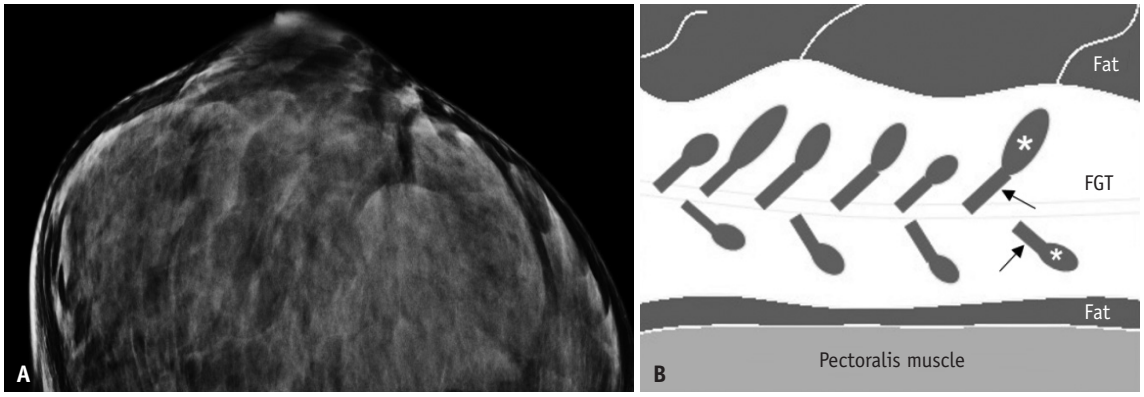

Fig. 1. Sonographic appearance of dense breasts.
A. Craniocaudal mammography shows extremely dense FGT. Glandular and fibrous tissues are equally dense, so the two types of tissue are indistinguishable on mammography. **B.** Sonographic breast anatomy shows glandular tissue within FGT as gray (isoechoic to fat) and fibrous tissue as white (hyperechoic to fat). The glandular tissue consists of lobules (asterisks) and terminal ducts (arrows), more anteriorly and less posteriorly, increasing volume during lactation, and involuted with aging. FGT = fibroglandular tissue

https://doi.org/10.3348/kjr.2022.0099

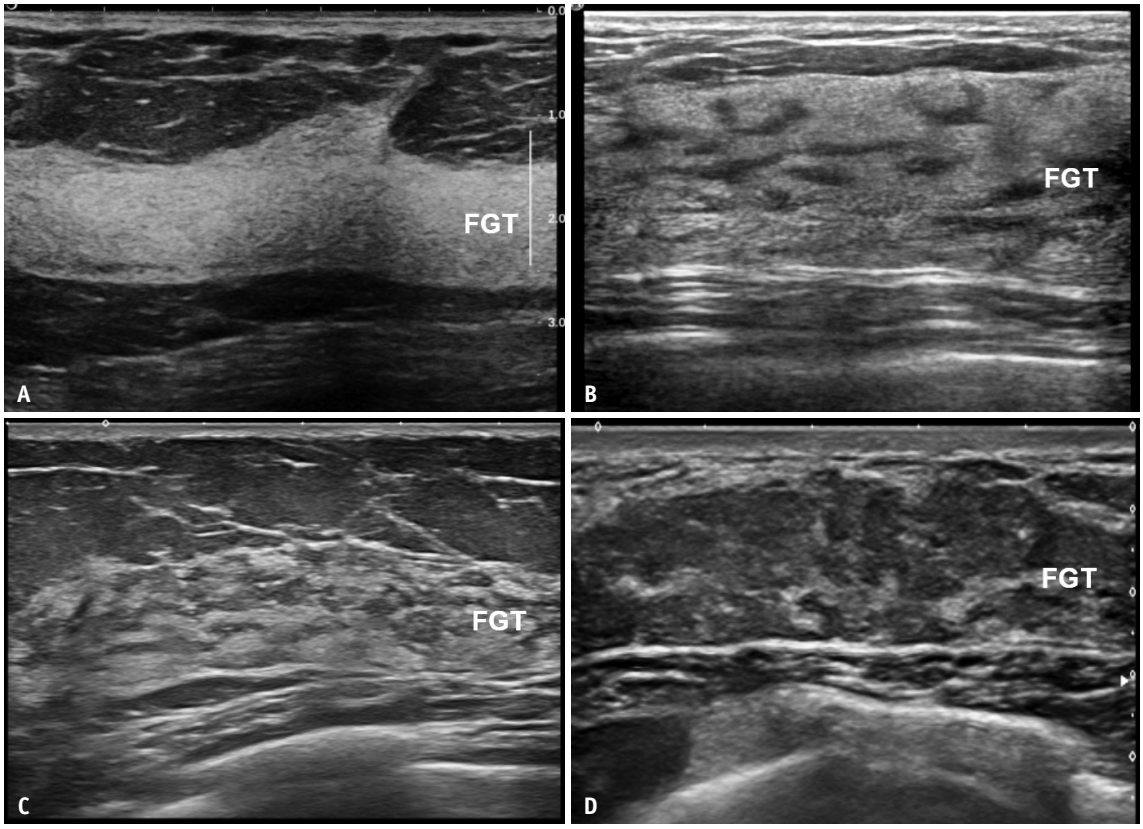

Fig. 2. Images of the transverse ultrasound in four women show varying GTCs in FGT. GTC is qualitatively classified into four categories: **(A)** minimal, **(B)** mild, **(C)** moderate, and **(D)** marked. GTC could be dichotomized as "low" for minimal **(A)** or mild **(B)** GTC or "high" for moderate **(C)** or marked **(D)** GTC. GTC = glandular tissue component, FGT = fibroglandular tissue

represents 50% of the breast FGT. Notably, fat lobules in the FGT, which are distinct from glandular tissue, were not counted in the GTC assessment. In a prospective study involving 11 radiologists, the interobserver agreement for the classification of GTC was moderate in 38 women (age range, 25–72 years) with dense and nondense breasts on mammography [20]. The mean κ value was 0.45 for the four-category classification and 0.48 for the dichotomous classification, which was comparable to or lower than that for mammographic assessment of breast density and was similar to or higher than that for US background echotexture of background parenchymal enhancement (BPE) on MRI [22-24].

There was a moderately positive correlation between GTC and breast density ($\rho = 0.55$, $p < 0.001$), indicating that women with higher breast density had higher GTC [20]. Furthermore, there was a significant difference in the mean GTC according to the mammographic density category ($p < 0.001$) in premenopausal and postmenopausal women. Women with high levels of GTC were also more likely to be younger (age < 50 years), non-obese (body mass index < 25), premenopausal, and nulliparous. In our experience, exogenous hormone therapy or endocrine therapy for breast cancer can affect sonographic GTC, but the menstrual cycle has little effect on sonographic GTC.

The sonographic GTC is correlated with the histological amount of glandular tissue and represents the most terminal duct lobular unit in the FGT, which is the primary anatomic source of breast cancer and its precursors [15-17]. In women with benign breast biopsy results, sonographic GTC was inversely associated with lobular involution in normal background tissue [25]. In other words, women with high GTCs more often had no or mild lobular involution, while women with low GTC had moderate or complete lobular involution. Therefore, a high GTC, reflecting a large number of residual lobules, may represent FGT at risk for breast cancer.

Association Between Sonographic GTC and Future Breast Cancer

An association between high GTC and an increased risk of developing breast cancer was recently documented in

https://doi.org/10.3348/kjr.2022.0099

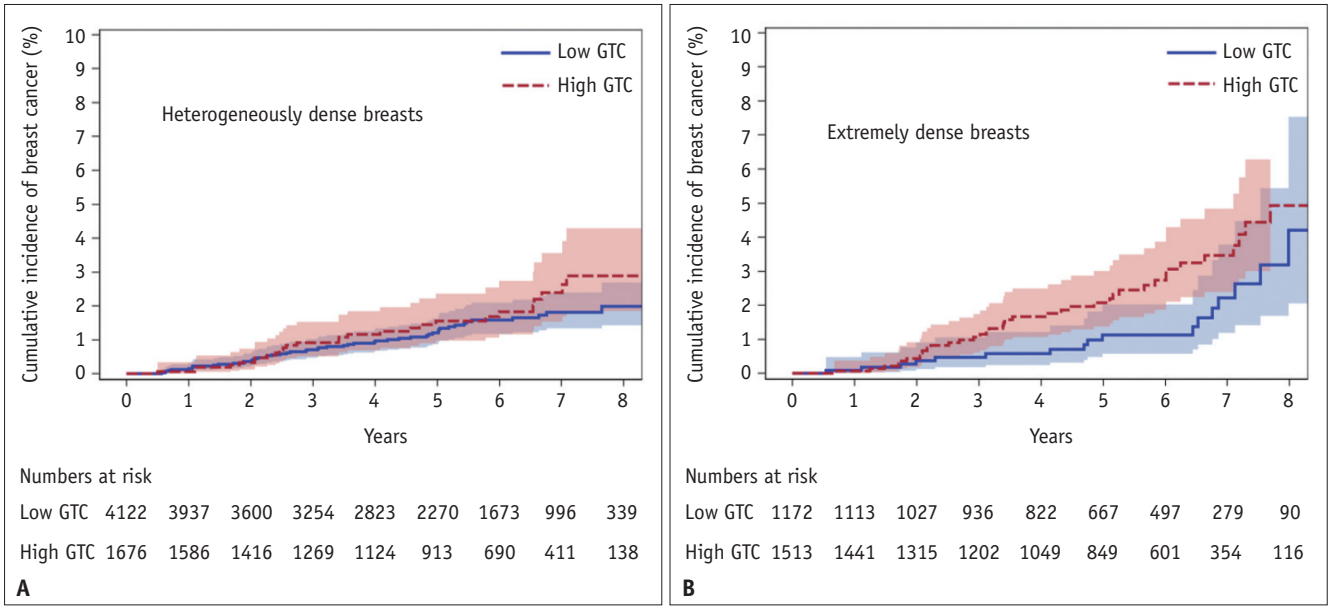

Fig. 3. Kaplan–Meier curves show the cumulative incidence of breast cancer according to the low versus high baseline GTC as assessed using breast ultrasound in 5798 women with heterogeneously dense breasts (A) and 2685 women with extremely dense breasts (B). GTC = glandular tissue component

women who underwent breast US supplemental screening [25]. In a cohort study of 8483 Korean women (mean age, 49 years) with dense breasts on mammography, 137 (1.6%) developed breast cancer, with a median follow-up of 5.3 years (interquartile range, 3.3–7.0 years). The baseline sonographic GTC distribution was minimal in 11%, mild in 51%, moderate in 28%, and marked in 10% of patients, with a low GTC of 62% and a high GTC of 38% when dichotomized. Women with breast cancer had higher rates of high baseline GTC than those without breast cancer (49% and 37%, respectively; $p = 0.006$). At follow-up, the incidence of breast cancer was higher in women with high baseline GTC than in those with low baseline GTC ($p = 0.007$) (Fig. 3). In the multivariate analysis, baseline GTC was the only factor associated with breast cancer risk (hazard ratio [HR], 1.49; 95% confidence interval [CI], 1.05–2.11; $p = 0.026$) after adjusting for other risk factors (age, menopause, family history of breast cancer, history of benign biopsy, and breast density) as covariables. Additionally, GTC remained predictive of cancer when repeated measures were included in the analysis. These findings suggest that sonographic GTC is a robust imaging biomarker of breast cancer risk that is independent of the many established factors used in standard risk models.

In the subgroup analysis, a high baseline GTC was associated with an increased risk of breast cancer among women aged 50–59 years (HR, 1.86; 95% CI, 1.05–3.27; $p = 0.033$), postmenopausal women (HR, 1.97; 95% CI, 1.15–3.28; $p = 0.014$), women with a history of benign breast biopsy (HR, 2.59; 95% CI, 1.19–5.61; $p = 0.016$), women without a family history of breast cancer (HR, 1.74; 95% CI, 1.19–2.53; $p < 0.001$), and women with extremely dense breast tissues (HR, 1.80; 95% CI, 1.01–3.19; $p = 0.045$) [25]. Accordingly, sonographic GTC is likely to be more predictive of subsequent breast cancer in postmenopausal women with a history of benign breast biopsy than in premenopausal women without a history of benign breast biopsy. This finding is likely due to the different causes of high GTC in women with dense breasts. High GTC can be caused by hormonal stimulation in premenopausal women, reflecting a physiological situation that will resolve with cessation of exposure. Meanwhile, a high GTC can also reflect true changes in structural and proliferative tissue, often including atypical hyperplasia. Therefore, such a sonographic GTC may indicate a substantially increased risk of subsequent breast cancer beyond hormonal stimulation of glandular tissue. These results suggest that sonographic GTC can be combined with other established breast cancer risk factors to improve risk stratification. However, the significance of GTC in high-risk women is unclear, as the study population in our study was mostly average-risk women.

Clinical Applicability of Sonographic GTC

Breast US is the most widely used low-cost imaging

https://doi.org/10.3348/kjr.2022.0099

modality, in conjunction with mammography, for the screening, diagnosis, treatment, monitoring, and surveillance of breast cancer. Unlike other breast imaging methods, US does not pose a radiation hazard and does not require an injection of a contrast agent; therefore, it is suitable for repeated evaluation [4]. Breast density information can also be obtained from breast US [26]. Therefore, breast cancer risk prediction using breast US can easily be applied to a large population of women.

Information obtained with sonographic GTC could be helpful in better defining the risk of breast cancer and tailoring supplementary screening in women with dense breasts. For example, if an average-risk women undergoes diagnostic US and shows dense breasts and a high GTC, she may be reassessed to determine whether her absolute risk is sufficiently high to warrant supplemental screening. Alternatively, average-risk women with dense breasts who undergo screening US may demonstrate a reduced risk if low GTC is considered along with other risk factors; these women may no longer require annual US screening, and the screening interval can be adjusted to 2–3 years. When GTC is combined with breast density, we can focus on women who need and can benefit from supplemental screening. The possibility of a risk-adapted screening strategy for BPE has also been reported [27], but it applies to a much smaller population of women who undergo MRI. Personalized screening in women with dense breasts should move toward selecting a more suitable and preferred screening method through discussions between clinicians and women undergoing screening.

Directions for Future Work

There are several challenges to overcome for the clinical use of GTC as imaging biomarkers. First, an association between high levels of GTC and an increased risk of breast cancer was demonstrated only in a retrospective single-center study of Korean women [25]. Therefore, our results may not be generalizable to other populations. A prospective, multicenter, international study that includes women of various races and ethnicities to validate whether sonographic GTC is associated with the risk of breast cancer and can provide additional risk information beyond mammography. Second, it is necessary to determine whether GTC affects US sensitivity. Sonographic detection of small and subtle lesions may be difficult in breasts with high GTC; however, no related research results have been reported. Additionally, it is worth studying whether high or low GTC is associated with certain types of breast cancer and treatment responses. Third, standardization of GTC assessment is also an important issue, considering that US is highly dependent on the examiner for image acquisition and interpretation. The large field of view (FOV) of automated US scans may be more suitable for GTC classification than the small FOV of a handheld US technique [15,28]. Finally, as with breast density or BPE, the need for quantitative measurement of GTC using a computer is increasing [29]. Radiomics or machine learning methods to analyze FGT appearance in breast imaging are promising for developing more personalized risk prediction models [30].

CONCLUSION

We proposed a method to classify the GTC of FGT in breast US and found that the sonographic GTC reflecting the degree of lobular involution was an independent predictor of future breast cancer risk in women with dense breasts. Sonographic GTC can be used to stratify the risk of breast cancer and identify the subset of women with dense breasts who are at the highest risk of breast cancer and are likely to benefit from supplemental screening. More validation is needed for the clinical application of GTCs as imaging biomarkers of breast cancer risk.

Key words

Dense breast; Breast cancer; Screening; Risk factors; Ultrasonography; Glandular tissue component

Availability of Data and Material

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

ORCID iDs

Su Hyun Lee
https://orcid.org/0000-0002-0171-8060
Woo Kyung Moon
https://orcid.org/0000-0001-8931-3772

Funding Statement

None

https://doi.org/10.3348/kjr.2022.0099

Korean Journal of Radiology
KJR

REFERENCES

1. Weaver O, Leung JWT. Biomarkers and imaging of breast cancer. *AJR Am J Roentgenol* 2018;210:271-278
2. Boyd NF, Guo H, Martin LJ, Sun L, Stone J, Fishell E, et al. Mammographic density and the risk and detection of breast cancer. *N Engl J Med* 2007;356:227-236
3. Butler RS, Hooley RJ. Screening breast ultrasound: update after 10 years of breast density notification laws. *AJR Am J Roentgenol* 2020;214:1424-1435
4. Berg WA, Rafferty EA, Friedewald SM, Hruska CB, Rahbar H. Screening algorithms in dense breasts: AJR expert panel narrative review. *AJR Am J Roentgenol* 2021;216:275-294
5. Ohuchi N, Suzuki A, Sobue T, Kawai M, Yamamoto S, Zheng YF, et al. Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan Strategic Anti-cancer Randomized Trial (J-START): a randomised controlled trial. *Lancet* 2016;387:341-348
6. Comstock CE, Gatsonis C, Newstead GM, Snyder BS, Gareen IF, Bergin JT, et al. Comparison of abbreviated breast MRI vs digital breast tomosynthesis for breast cancer detection among women with dense breasts undergoing screening. *JAMA* 2020;323:746-756
7. Bakker MF, de Lange SV, Pijnappel RM, Mann RM, Peeters PHM, Monninkhof EM, et al. Supplemental MRI screening for women with extremely dense breast tissue. *N Engl J Med* 2019;381:2091-2102
8. Cho N, Han W, Han BK, Bae MS, Ko ES, Nam SJ, et al. Breast cancer screening with mammography plus ultrasonography or magnetic resonance imaging in women 50 years or younger at diagnosis and treated with breast conservation therapy. *JAMA Oncol* 2017;3:1495-1502
9. Melnikow J, Fenton JJ, Whitlock EP, Miglioretti DL, Weyrich MS, Thompson JH, et al. Supplemental screening for breast cancer in women with dense breasts: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2016;164:268-278
10. Sprague BL, Gangnon RE, Burt V, Trentham-Dietz A, Hampton JM, Wellman RD, et al. Prevalence of mammographically dense breasts in the United States. *J Natl Cancer Inst* 2014;106:dju255
11. Hong S, Song SY, Park B, Suh M, Choi KS, Jung SE, et al. Effect of digital mammography for breast cancer screening: a comparative study of more than 8 million Korean women. *Radiology* 2020;294:247-255
12. Kerlikowske K, Sprague BL, Tosteson ANA, Wernli KJ, Rauscher GH, Johnson D, et al. Strategies to identify women at high risk of advanced breast cancer during routine screening for discussion of supplemental imaging. *JAMA Intern Med* 2019;179:1230-1239
13. Singletary SE. Rating the risk factors for breast cancer. *Ann Surg* 2003;237:474-482
14. Kuhl CK. Predict, then act: moving toward tailored prevention. *J Clin Oncol* 2019;37:943-945
15. Mendelson EB, Böhm-Vélez M, Berg WA, Whitman GJ, Feldman MI, Madjar H, et al. *ACR BI-RADS ultrasound*. In: Orsi CJ, Sickles EA, Mendelson EB, Morris EA, eds. *ACR BI-RADS Atlas, breast imaging reporting and data system, 5th ed*. Reston: American College of Radiology, 2013:128-130
16. Izumori A, Horii R, Akiyama F, Iwase T. Proposal of a novel method for observing the breast by high-resolution ultrasound imaging: understanding the normal breast structure and its application in an observational method for detecting deviations. *Breast Cancer* 2013;20:83-91
17. Stavros AT. *Breast ultrasound*. Philadelphia: Lippincott Williams & Wilkins, 2004:65-78
18. McKian KP, Reynolds CA, Visscher DW, Nassar A, Radisky DC, Vierkant RA, et al. Novel breast tissue feature strongly associated with risk of breast cancer. *J Clin Oncol* 2009;27:5893-5898
19. Ghosh K, Hartmann LC, Reynolds C, Visscher DW, Brandt KR, Vierkant RA, et al. Association between mammographic density and age-related lobular involution of the breast. *J Clin Oncol* 2010;28:2207-2212
20. Kim WH, Lee SH, Chang JM, Cho N, Moon WK. Background echotexture classification in breast ultrasound: inter-observer agreement study. *Acta Radiol* 2017;58:1427-1433
21. Pashayan N, Antoniou AC, Ivanus U, Esserman LJ, Easton DF, French D, et al. Personalized early detection and prevention of breast cancer: ENVISION consensus statement. *Nat Rev Clin Oncol* 2020;17:687-705
22. Kerlikowske K, Grady D, Barclay J, Frankel SD, Ominsky SH, Sickles EA, et al. Variability and accuracy in mammographic interpretation using the American College of Radiology breast imaging reporting and data system. *J Natl Cancer Inst* 1998;90:1801-1809
23. Berg WA, Blume JD, Cormack JB, Mendelson EB. Operator dependence of physician-performed whole-breast US: lesion detection and characterization. *Radiology* 2006;241:355-365
24. Melsaether A, McDermott M, Gupta D, Pysarenko K, Shaylor SD, Moy L. Inter- and intrareader agreement for categorization of background parenchymal enhancement at baseline and after training. *AJR Am J Roentgenol* 2014;203:209-215
25. Lee SH, Ryu HS, Jang MJ, Yi A, Ha SM, Kim SY, et al. Glandular tissue component and breast cancer risk in mammographically dense breasts at screening breast US. *Radiology* 2021;301:57-65
26. Kim WH, Moon WK, Kim SJ, Yi A, Yun BL, Cho N, et al. Ultrasonographic assessment of breast density. *Breast Cancer Res Treat* 2013;138:851-859
27. Arasu VA, Miglioretti DL, Sprague BL, Alsheik NH, Buist DSM, Henderson LM, et al. Population-based assessment of the association between magnetic resonance imaging background parenchymal enhancement and future primary breast cancer risk. *J Clin Oncol* 2019;37:954-963
28. Kim SH, Kim HH, Moon WK. Automated breast ultrasound screening for dense breasts. *Korean J Radiol* 2020;21:15-24
29. Chang RF, Hou YL, Lo CM, Huang CS, Chen JH, Kim WH, et

 https://doi.org/10.3348/kjr.2022.0099

al. Quantitative analysis of breast echotexture patterns in automated breast ultrasound images. *Med Phys* 2015;42:4566-4578

30. Yala A, Mikhael PG, Lehman C, Lin G, Strand F, Wan YL, et al. Optimizing risk-based breast cancer screening policies with reinforcement learning. *Nat Med* 2022;28:136-143

https://doi.org/10.3348/kjr.2022.0099