Original Article
pISSN 1738-2637 / eISSN 2288-2928
J Korean Soc Radiol 2018;79(1):18-26
https://doi.org/10.3348/jksr.2018.79.1.18

대한영상의학회지

Association of Volumetric Breast Density with Clinical and Histopathological Factors in 205 Breast Cancer Patients
205명의 유방암 환자에서 용적 유방 밀도와 임상적 및 조직병리학적 인자와의 관련성 연구

Nari Jung, MD, Won Hwa Kim, MD*
Department of Radiology, School of Medicine, Kyungpook National University, Kyungpook National University Chilgok Hospital, Daegu, Korea

Purpose: To evaluate the association of volumetric breast density with clinicopathological factors in breast cancer patients.
Materials and Methods: A total of 205 Korean patients with breast cancer who underwent mammography for initial staging between January 2015 and June 2016 were enrolled. Volumetric breast density was measured using a fully automated commercial method (Volpara®). in the contralateral breast. The association of volumetric breast density with clinical and histopathological factors was evaluated using *t*-test and analysis of variance as appropriate.
Results: Mean volumetric breast density in all patients was 13.5% (range, 4.1–34.9%). The mean volumetric breast density in patients with symptom-detected cancers was significantly higher than that in those with screening-detected cancers (14.9% vs. 11.8%, $p = 0.002$). Mean volumetric breast density tended to decrease with age (20–39 years: 19.0%, 40–59 years: 14.3%, 60–80 years: 7.7%). The mean volumetric breast density in postmenopausal women was significantly lower than that in premenopausal women (9.8% vs. 17.6%, $p < 0.001$). Other histopathological factors including histologic grade or hormone receptor status were not associated with volumetric breast density.
Conclusion: Our results suggest that volumetric breast density is associated with the method of detection, age, and menopausal status.

Index terms
Breast Cancer
Mammography
Breast Density

Received July 28, 2017
Revised October 18, 2017
Accepted March 7, 2018
***Corresponding author:** Won Hwa Kim, MD
Department of Radiology, School of Medicine, Kyungpook National University, Kyungpook National University Chilgok Hospital, 807 Hoguk-ro, Buk-gu, Daegu 41404, Korea.
Tel. 82-53-200-2527 Fax. 82-53-200-3349
E-mail: greenoaktree9@gmail.com

INTRODUCTION

Mammographic density has been known to be an independent risk factor for breast cancer. Some studies have shown that the risk of breast cancer in women with dense breasts is four- to six-fold higher than that in women with fatty breasts (1-3). Other studies have demonstrated that hormonal treatments (e.g., tamoxifen) can change the mammographic density and modify the breast cancer risk (4-6). Moreover, the sensitivity of mammography is lower in women with dense breasts compared to those with fatty breasts because fibroglandular tissue (FGT) in dense breasts may obscure cancer (7, 8). For these reasons, the mammographic density assessment based on the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) four-category system (almost entirely fat, scattered FGT, heterogeneously dense, or extremely dense) is routinely provided in mammographic reporting (9).

However, the use of BI-RADS categories has several limitations. First, interobserver and intraobserver variabilities are substantial because the BI-RADS categories are based on subjective assessment. Second, four broad categories limit the evaluation of small changes that might be clinically significant in the quantitative analysis of mammographic density. These limitations were overcome by the development of quantitative methods, including the visual estimation of percentage density and semi-automated assessment (3, 10-12). These methods are

still limited by measurement variabilities due to subjective evaluation or thresholding and two-dimensional (2D)-based assessment. Therefore, at present, volumetric breast density is assessed using a fully automated software. However, information about volumetric breast density is still limited that the associations of volumetric breast density with determinants for mammographic sensitivity or prognostic profile of clinicopathological factors has not been fully evaluated. The objective of this study was to evaluate the association of breast density with clinicopathological factors in breast cancer patients using a fully automated software for quantitative volumetric breast density. We also evaluated comparative associations of qualitative breast density assessed visually and assigned by the software with clinicopathological factors.

MATERIALS AND METHODS

Patients

This retrospective study was approved by the Institutional Review Board (IRB No. KNUCH 2017-07-020) of our institution, and requirement for written informed consent was waived. A total of 205 Korean women diagnosed with breast cancer underwent curative surgery in our institution between January 2015 and June 2016. Mammography was performed for all women in our institution prior to surgery for preoperative staging. Among the 220 initial patients, women with a history of resection of contralateral breast cancer (n = 10) and bilateral breast cancer (n = 5) were excluded. The remaining 205 patients were included in this study.

Image Acquisition and Analysis

Mammography was performed using full-field digital mammography units (Lorad Selenia, Hologic, Bedford, MA, USA). Mammograms comprised two standard views (craniocaudal and mediolateral oblique) for each breast. Volumetric breast density was measured by a United States Food and Drug Administration-approved, fully automated software (VolparaDensity, Volpara Algorithm version 1.5.12, Volpara Health Technologies, Wellington, the New Zealand). The results of the analysis using this software were obtained from the unaffected breast. The algorithm of the VolparaDensity software was described in detail previously (13). This algorithm determines the attenuation of the X-ray between the image detector and the X-ray source by the pixel signals of the mammographic images. A pixel signal of pure fat tissue is used as a reference, and all other pixels are compared to this reference for calculation of the thickness of fat tissue and FGT. As the pixel dimension of the image is calculated, the volumes of fat and FGT are summed in the whole breast. Volumetric breast density is calculated as a percentage of the ratio of the volume of FGT to the volume of the entire breast. For qualitative density assessment, the quantitative volumetric breast density is mapped to an automated density scale (Volpara Density Grade) using the VolparaDensity software and this scale is an approximation of the BI-RADS density scale. The threshold for grade a, b, c, and d was 0.0–4.5%, 4.5–7.5%, 7.5–15.5%, and ≥ 15.5% (in percent dense volume), respectively. Visual density was also assessed by two radiologists (N.J. and W.H.K., with 2 years and 10 years of experience, respectively) in consensus based on ACR BI-RADS four category system 4th edition (1: almost entirely fatty, 2: scattered fibroglandular densities, 3: heterogeneously dense, 4: extremely dense) (9).

Data Collection and Analysis

The clinicopathological factors were obtained from the patient records. The clinical factors included age, method of detection (screening-detected vs. symptom-detected), presence of family history of breast cancer, menopausal status, presence of hormone replacement therapy (HRT) experience, parity (nulliparous vs. parous), and type of breast surgery (breast-conserving surgery vs. mastectomy). The histopathological factors included histologic type, histologic grade, lymphovascular invasion, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor (HER2) status, and axillary nodal status. The expression of ER, PR, and HER2 was assessed using immunohistochemical staining (Allred score). Allred scores > 2 were considered positive for ER or PR. An HER2 score of 0 or 1 was considered negative (HER2-negative) and a score of 3 was assumed to be positive (HER2-positive). An HER2 score of 2 was considered equivocal. In equivocal cases, silver-enhanced *in situ* hybridization was performed, and an HER2/chromosome enumeration probe 17 (CEP17) ratio ≥ 2.0 or an HER2/CEP17 ratio < 2.0 with an average HER2 copy number ≥ 6.0 was considered positive (HER2-positive). Hormone receptor (HR)-positive status was defined as the presence of tu-

mors expressing ER and/or PR.

The comparisons of breast/FGT volume, volumetric breast density, and mean BI-RADS (both visual and Volpara-assigned) grade according to clinical and histopathological factors were performed using *t*-test or analysis of variance test with Bonferroni post-hoc analysis as appropriate. The comparison of the BI-RADS grades (both visual and Volpara-assigned) between the groups with screening-detected cancers and the groups with symptom-detected cancers was performed using the chi-square test for trend analysis. Statistical analyses were conducted using the software SPSS Statistics version 24.0 (IBM, Armonk, NY, USA) and MedCalc Statistical version 17.1 (MedCalc Software, Ostend, Belgium). *p* values of less than 0.05 were considered to indicate a statistically significant difference.

RESULTS

The mean age of the 205 patients was 51.6 years (range, 29–80 years). The mean breast and FGT volume was 500.9 cm^3 (standard deviations, 258.6 cm^3; range, 100.0–1927.4 cm^3) and 60.5 cm^3 (standard deviations, 36.5 cm^3; range, 16.4–207.7 cm^3). The mean volumetric breast density was 13.5% (standard deviations, 7.0%; range, 4.1–34.9%), which equated to an automated density scale of c. Of the 205 patients, 115 (56.1%) patients had breast cancer diagnosed with symptoms, including palpable mass (n = 107) and pain or nipple discharge (n = 8), and 90 (43.9%) patients had breast cancer diagnosed with screening mammography or an additional ultrasound examination. Almost 50% of the patients (n = 98, 47.8%) were premenopausal. Other clinical and histopathological factors are described in Tables 1, 2.

The mean volumetric breast density was significantly higher in patients with symptom-detected cancers than in those with screening-detected cancers (14.9% vs. 11.8%, p = 0.002). The patients aged 60–80 years had significantly lower FGT volume (41.8 cm^3) than those aged 20–39 years (68.4 cm^3) and 40–59 years (64.5 cm^3) (p = 0.014 and p = 0.001, respectively, in the post-hoc analysis). There was a stepwise reduction in volumetric breast density with increasing age-the percentage of patients aged 20–39 years, 40–59 years, and 60–80 years with volumetric breast density was 19.0%, 14.3%, and 7.7%, respectively (p <

Table 1. Association of Breast Volume, FGT Volume, and Volumetric Breast Density with Clinical Factors in 205 Breast Cancer Patients

	Breast Volume (cm^3)	*p*-Value	FGT Volume (cm^3)	*p*-Value	Breast Density (%)	*p*-Value
Age, years		0.124		0.001		< 0.001
20–39 (n = 23)	459.4 (395.9)		68.4 (38.7)		19.0 (8.2)	
40–59 (n = 142)	487.1 (236.4)		64.5 (38.3)		14.3 (6.5)	
60–80 (n = 40)	573.7 (228.6)		41.8 (19.7)		7.7 (3.4)	
Method of detection		0.271		0.078		0.002
Screening (n = 90)	523.4 (232.2)		55.5 (31.1)		11.8 (5.9)	
Symptom (n = 115)	483.3 (277.3)		64.3 (40.0)		14.9 (7.5)	
Family history of breast cancer		0.201		0.359		0.431
Absent (n = 191)	507.2 (258.7)		60.9 (37.3)		13.4 (7.1)	
Present (n = 14)	414.0 (251.4)		54.2 (24.8)		14.9 (6.2)	
Menopausal status		0.130		< 0.001		< 0.001
Premenopausal (n = 98)	472.1 (274.7)		75.2 (40.0)		17.6 (6.7)	
Postmenopausal (n = 107)	527.2 (241.3)		47.0 (26.8)		9.8 (4.9)	
HRT experience		0.561		0.699		0.542
Absent (n = 174)	496.6 (261.8)		60.0 (36.4)		13.7 (7.1)	
Present (n = 31)	524.7 (242.8)		62.9 (38.0)		12.9 (6.6)	
Parity		0.307		0.022		0.183
Nulliparous (n = 27)	560.8 (332.0)		75.0 (33.4)		15.2 (6.6)	
Parous (n = 178)	491.8 (245.5)		58.3 (36.6)		13.3 (7.1)	
Type of breast surgery		0.077		0.633		0.499
Breast-conserving (n = 163)	517.1 (270.1)		58.1 (35.6)		14.2 (7.0)	
Mastectomy (n = 42)	437.9 (198.9)		61.1 (2.9)		13.4 (7.0)	

Data are mean values, with standard deviations in parenthesis.
FGT = fibroglandular tissue, HRT = hormone replacement therapy

Table 2. Association of Breast Volume, FGT Volume, and Volumetric Breast Density with Histopathological Factors in 205 Breast Cancer Patients

	Breast Volume (cm^3)	*p*-Value	FGT Volume (cm^3)	*p*-Value	Breast density (%)	*p*-Value
Histologic type		0.754		0.259		0.736
Invasive ductal carcinoma (*n* = 165)	498.0 (244.0)		60.1 (35.9)		13.7 (7.3)	
DCIS (*n* = 17)	480.6 (396.9)		51.3 (29.1)		12.3 (5.6)	
Others (*n* = 23)	536.8 (245.4)		70.1 (44.8)		13.5 (5.7)	
Histologic grade*		0.016		0.093		0.465
Low (*n* = 23)	645.4 (403.8)		76.6 (47.5)		13.8 (7.5)	
Intermediate (*n* = 110)	472.6 (243.6)		60.4 (34.4)		14.3 (7.1)	
High (*n* = 55)	488.8 (215.2)		56.8 (37.7)		12.9 (7.1)	
Lymphovascular invasion*		0.344		0.604		0.154
Absent (*n* = 133)	513.6 (251.1)		62.2 (40.4)		13.2 (6.7)	
Present (*n* = 55)	476.5 (225.4)		59.1 (27.7)		14.8 (8.1)	
Hormone receptor status		0.442		0.492		0.976
Negative (*n* = 58)	480.6 (220.0)		57.8 (33.1)		13.5 (6.9)	
Positive (*n* = 147)	208.9 (272.7)		61.5 (37.9)		13.6 (7.1)	
HER2 status		0.126		0.699		0.185
Negative (*n* = 169)	511.3 (270.0)		60.0 (35.7)		13.2 (6.7)	
Positive (*n* = 36)	452.2 (192.3)		62.8 (40.7)		15.2 (8.1)	
Tumor size*		0.487		0.280		0.515
≤ 2 cm (*n* = 134)	494.8 (241.1)		59.5 (37.0)		13.4 (7.0)	
> 2 cm (*n* = 54)	522.3 (251.6)		65.9 (37.1)		14.2 (7.4)	
Axillary nodal status		0.632		0.109		0.235
Negative (*n* = 159)	496.2 (259.9)		58.3 (34.3)		13.2 (6.8)	
Positive (*n* = 46)	517.0 (256.5)		68.1 (42.8)		14.6 (7.8)	

Data are mean values, with standard deviations in parenthesis.
*Patients with only invasive carcinoma (*n* = 188).
DCIS = ductal carcinoma *in situ*, FGT = fibroglandular tissue, HER2 = human epidermal growth factor receptor 2

0.05 in all post-hoc analyses). The family history or HRT experience was not associated with the breast volume, FGT volume, and volumetric breast density. The FGT volume and volumetric breast density were significantly lower in postmenopausal women compared with premenopausal women (FGT volume, 47.0 cm^3 vs. 75.2 cm^3, $p < 0.001$; volumetric breast density, 9.8% vs. 17.6%, $p < 0.001$), but no significant difference in breast volume was found between these two groups. The FGT volume was significantly lower in parous women compared with nulliparous women (58.3 cm^3 vs. 75.0 cm^3, $p = 0.022$), but no significant difference in breast volume and volumetric breast density was found between these two groups. The patients with mastectomy had a lower breast volume than those with breast-conserving surgery with borderline significance (437.9 cm^3 vs. 517.1 cm^3, $p = 0.077$).

For BI-RADS breast density, the patients aged 60–80 years had significantly lower density than those aged 20–39 years and 40–59 years in both visual grades and Volpara-assigned grades (both *p*s < 0.05) (Table 3). Mean breast density grade in patients with symptom-detected cancers was higher than those with screening-detected cancers for both visual and Volpara-assigned grades ($p = 0.013$ and $p = 0.034$). Mean breast density grade was significantly lower in postmenopausal women compared with premenopausal women for both visual and Volpara-assigned grades (both *p*s < 0.001). Other histopathological factors were not significantly associated with BI-RADS breast density (Table 4).

There was a trend toward higher density grade in patients with symptom-detected cancers compared with those with screening-detected cancers (Table 5, Figs. 1, 2) ($p = 0.034$ for Volpara-assigned grade and $p = 0.013$ for visual grade). Subgroup analyses according to clinical factors revealed that a higher mean breast density was found in patients with symptom-detected cancers compared with those with screening-detected cancers for subgroup with age 40–59 years ($p = 0.014$), absent family history of breast cancer ($p = 0.003$), absent HRT experience ($p < 0.001$), and parous women ($p < 0.001$). For postmenopausal women,

Table 3. Association of Breast Density Assessed Visually and Assigned by Volpara with Clinical Factors in 205 Patients

	Visual BI-RADS	*p*-Value	Volpara-Assigned BI-RADS	*p*-Value
Age, years		< 0.001		< 0.001
20–39 (*n* = 23)	3.3 (0.6)		3.5 ± 0.7	
40–59 (*n* = 142)	3.1 ± 0.5		3.2 ± 0.8	
60–80 (*n* = 40)	2.6* (0.7)		2.5 ± 0.6*	
Method of detection		0.013		0.034
Screening (*n* = 90)	2.9 ± 0.5		3.0 ± 0.8	
Symptom (*n* = 115)	3.1 ± 0.6		3.2 ± 0.8	
Family history of breast cancer		0.315		0.240
Absent (*n* = 191)	3.0 ± 0.6		3.1 ± 0.8	
Present (*n* = 14)	3.1 ± 0.5		3.4 ± 0.6	
Menopausal status		< 0.001		< 0.001
Premenopausal (*n* = 98)	3.2 ± 0.5		3.6 ± 0.6	
Postmenopausal (*n* = 107)	2.7 ± 0.6		2.7 ± 0.7	
Hormone replacement therapy experience		0.414		0.280
Absent (*n* = 174)	3.0 ± 0.6		3.1 ± 0.8	
Present (*n* = 31)	2.9 ± 0.8		3.0 ± 0.9	
Parity		0.066		0.203
Nulliparous (*n* = 27)	3.2 ± 0.5		3.3 ± 0.7	
Parous (*n* = 178)	3.0 ± 0.6		3.1 ± 0.8	
Type of breast surgery		0.457		0.178
Breast-conserving (*n* = 163)	3.0 ± 0.6		3.1 ± 0.8	
Mastectomy (*n* = 42)	3.0 ± 0.5		3.3 ± 0.7	

Data are mean values, with standard deviations in parenthesis.
*$p < 0.05$ for groups with 20–39 years and 40–59 years.
BI-RADS = Breast Imaging Reporting and Data System

there was a borderline significance between mean volumetric breast densities of patients with screening- and symptom-detected cancers ($p = 0.094$) (Supplementary Table 1 in the online-only Data Supplement). Subgroup analyses between patients with screening- and symptom-detected cancers according to the histopathological factors are demonstrated in Supplementary Table 2 in the online-only Data Supplement.

DISCUSSION

The results of the analysis using a fully automated software indicated that volumetric breast density was significantly associated with the mode of detection of breast cancer. This result is partly in line with the previous study by Destounis et al. (14) in which they found a higher volumetric breast density in patients with interval cancers (13.2% vs. 9.0%) than in patients with screening-detected cancers. In subgroups with different clinical factors, higher mean breast densities were consistently found in symptom-detected cancers with or without statistical significance except for the subgroup aged 20–39 years and the subgroup with ductal carcinoma *in situ*. These results may suggest that women with denser breasts have a higher risk of having symptom-detected cancer and this risk association may be seen across the variable clinico-histopathological factors. The strength of the present study is that we were able to show the association of volumetric breast density measured by commercial automated software with risk having symptom-detected cancers in Asian countries in which the patients and breast cancer characteristics were different compared to other countries (15). However, future studies are needed to evaluate the association of volumetric breast density with the interval cancers and differences in mammographic sensitivity according to the threshold of volumetric breast density in Asian countries because symptom-detected cancers are not equivalent to interval cancers.

In this study, we also found that the mean estimates of Volpara-assigned BI-RADS and visual BI-RADS density were higher in patients with symptom-detected cancers than in those with

screening-detected cancers. The association with breast density and clinical and histological factors was generally consistent between Volpara-assigned BI-RADS and visual BI-RADS density. Furthermore, the association strength of breast density with mode of detection appeared to be stronger in visual BI-RADS density than Volpara-assigned BI-RADS. These findings may suggest that visual BI-RADS density assessment is non-inferior to Volpara-assigned BI-RADS to predict the risk of having interval cancers.

In this study, our findings confirmed a previous observation about the determinants of breast density using a fully automated software in Korean women. We found that age and menopausal status were strong determinants of volumetric breast density. The mean volumetric breast density in postmenopausal women was almost 50% of that in premenopausal women (9.8% vs. 17.6%). Boyd et al. (16) found that the difference in the percentage density between mammograms before and after menopause using a 2D-based semi-automated tool was 3.3% reduction. The higher difference in volumetric breast density (7.8%

Table 5. Volumetric Density Grade by the Method of Detection of Breast Cancer

	Screening-Detected (*n* = 90)	Symptom-Detected (*n* = 115)
Volpara-assigned (%)		
a	0	2 (1.7)
b	30 (33.3)	20 (17.4)
c	32 (35.6)	44 (38.3)
d	28 (31.1)	49 (42.6)
Visual (%)		
a	1 (1.1)	2 (3.5)
b	17 (18.9)	7 (6.1)
c	65 (72.2)	80 (69.6)
d	7 (7.8)	24 (20.9)

For Volpara-assigned density, the quantitative volumetric breast density is mapped to an automated density scale (Volpara Density Grade) using the VolparaDensity software (Volpara Health Technologies, Wellington, the New Zealand). The threshold for grade a, b, c, and d was 0.0–4.5%, 4.5–7.5%, 7.5–15.5%, and ≥ 15.5% (in percent dense volume), respectively. Visual density was assessed based on American College of Radiology Breast Imaging Reporting and Data System four category system 4th edition (1: almost entirely fatty, 2: scattered fibroglandular densities, 3: heterogeneously dense, and 4: extremely dense) (9).

Table 4. Association of Breast Density Assessed Visually and Assigned by Volpara with Histopathological Factors in 205 Patients

	Visual BI-RADS	*p*-Value	Volpara-Assigned BI-RADS	*p*-Value
Histologic type		0.968		0.836
Invasive ductal carcinoma (*n* = 165)	3.0 ± 0.6		3.1 ± 0.8	
DCIS (*n* = 17)	3.0 ± 0.4		3.0 ± 0.7	
Others (*n* = 23)	3.0 ± 0.6		3.1 ± 0.8	
Histologic grade*		0.992		0.440
Low (*n* = 23)	3.0 ± 0.3		3.1 ± 0.8	
Intermediate (*n* = 110)	3.0 ± 0.6		3.2 ± 0.8	
High (*n* = 55)	3.0 ± 0.7		3.0 ± 0.9	
Lymphovascular invasion*		0.291		0.301
Absent (*n* = 133)	3.0 ± 0.6		3.1 ± 0.8	
Present (*n* = 55)	2.9 ± 0.7		3.2 ± 0.8	
Hormone receptor status		0.769		0.923
Negative (*n* = 58)	3.0 ± 0.5		3.1 ± 0.8	
Positive (*n* = 147)	3.0 ± 0.7		3.1 ± 0.8	
HER2 status		0.645		0.368
Negative (*n* = 169)	3.0 ± 0.6		3.1 ± 0.8	
Positive (*n* = 36)	3.0 ± 0.7		3.2 ± 0.8	
Tumor size		0.287		0.784
≤ 2 cm (*n* = 134)	3.0 ± 0.6		3.1 ± 0.8	
> 2 cm (*n* = 54)	2.9 ± 0.7		3.1 ± 0.9	
Axillary nodal status		0.462		0.426
Negative (*n* = 159)	3.0 ± 0.6		3.1 ± 0.8	
Positive (*n* = 46)	3.0 ± 0.6		3.2 ± 0.8	

*Patients with only invasive carcinoma (*n* = 188).
BI-RADS = Breast Imaging Reporting and Data System, DCIS = ductal carcinoma *in situ*, HER2 = human epidermal growth factor receptor 2

reduction) found in our study was probably due to the synergistic effect of menopause and aging. Future studies are needed to evaluate the effect of menopause on the change of volumetric breast density.

It is of note that the breast volumes of patients with mastectomy were lower than those of patients with breast-conserving surgery, with borderline significance (437.9 cm^3 vs. 517.1 cm^3, p = 0.077). This result suggests that breast volume measured on a fully automated software may help clinicians to decide on the type of breast surgery. Several techniques can measure breast volume using magnetic resonance imaging or other specialized tools, including 3D laser scanners and thermoplastic casting (17-19). The automated measurement of breast volume using mammography is fast and cost-effective. However, further studies are needed to evaluate whether the automated measurement of breast volume using mammography can be used in the

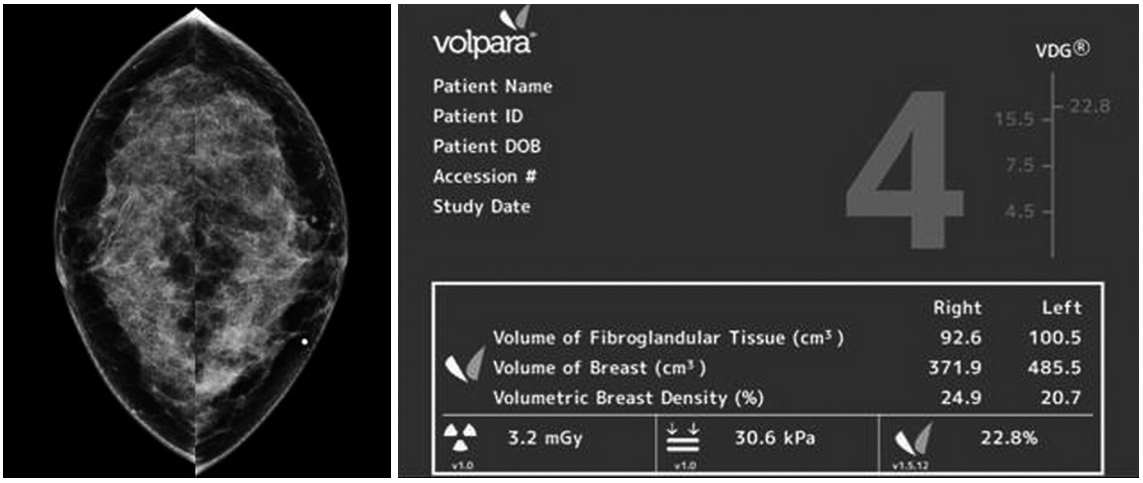

Fig. 1. Right **(A)** and left **(B)** craniocaudal mammograms in 49-year-old woman diagnosed with breast cancer for palpable mass in her left inner breast. A fully automated software (Volpara; Volpara Health Technologies, Wellington, the New Zealand) for volumetric breast density assessment shows that the percentage mammographic density of her right breast is 24.9% (Volpara-assigned BI-RADS grade d). Two radiologists assessed BI-RADS grade d for visual assessment in consensus.
BI-RADS = Breast Imaging Reporting and Data System

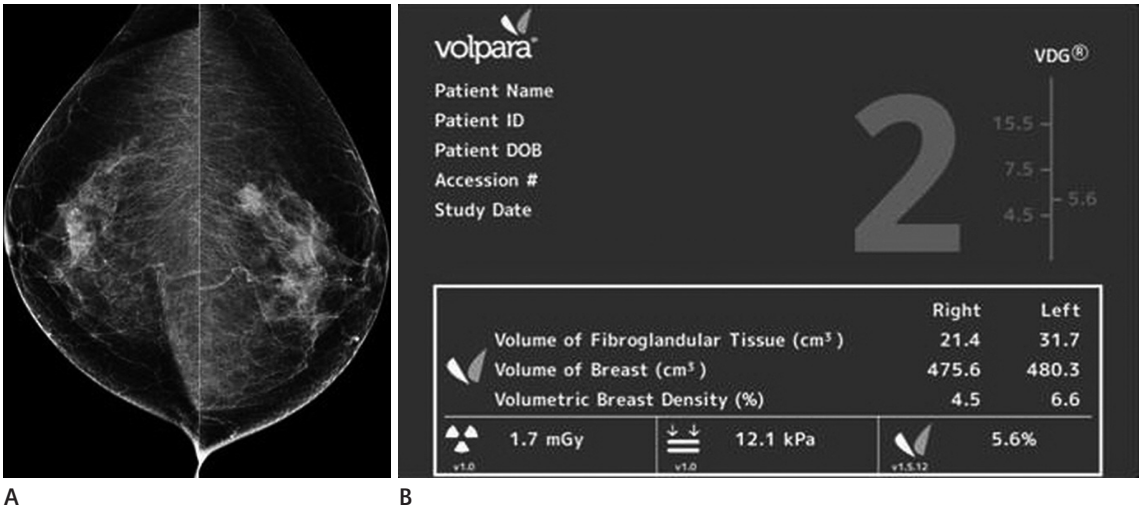

Fig. 2. Right **(A)** and left **(B)** craniocaudal mammograms in 60-year-old woman diagnosed with breast cancer patient detected in health screening in the left mid outer breast. A fully automated software (Volpara; Volpara Health Technologies, Wellington, the New Zealand) for volumetric breast density assessment shows that the percentage mammographic density of her right breast is 4.5% (Volpara-assigned BI-RADS grade b). Two radiologists assessed BI-RADS grade c for visual assessment in consensus.
BI-RADS = Breast Imaging Reporting and Data System

preoperative planning of the type of breast surgery or the planning of breast reconstruction (20).

Our study has several limitations. First, this study had a selection bias because all the subjects were breast cancer patients. Second, body mass index (BMI) is known to be inversely associated with breast density. However, BMI information could not be obtained owing to the retrospective nature of our study. Third, due to the limited sample size or lack of data for prognosis, the prognostic significance of breast density remains elusive in our study.

In conclusion, our study suggests that volumetric breast density is associated with the method of detection. The fully automated software VolparaDensity allowed the evaluation of the association of breast/FGT volume and volumetric breast density with various clinicopathological factors. Our results indicated an inverse association of volumetric breast density with age and menopause. However, the association with breast density and clinical and histological factors was generally consistent between Volpara-assigned BI-RADS and visual BI-RADS density that may suggest visual BI-RADS density assessment is non-inferior to Volpara-assigned BI-RADS to demonstrate its association with clinical and histological factors.

Supplementary Materials

The online-only Data Supplement is available with this article at http://dx.doi.org/10.3348/jksr.2018.79.1.18.

REFERENCES

1. 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
2. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2006;15:1159-1169
3. Harvey JA, Bovbjerg VE. Quantitative assessment of mammographic breast density: relationship with breast cancer risk. *Radiology* 2004;230:29-41
4. Harvey JA, Holm MK, Ranganath R, Guse PA, Trott EA, Helzner E. The effects of bazedoxifene on mammographic breast density in postmenopausal women with osteoporosis. *Menopause* 2009;16:1193-1196
5. Cuzick J, Warwick J, Pinney E, Duffy SW, Cawthorn S, Howell A, et al. Tamoxifen-induced reduction in mammographic density and breast cancer risk reduction: a nested case-control study. *J Natl Cancer Inst* 2011;103:744-752
6. Harvey JA, Bovbjerg VE, Smolkin ME, Williams MB, Petroni GR. Evaluating hormone therapy-associated increases in breast density comparison between reported and simultaneous assignment of BI-RADS categories, visual assessment, and quantitative analysis. *Acad Radiol* 2005;12:853-862
7. Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. *Radiology* 2002;225:165-175
8. Pinsky RW, Helvie MA. Mammographic breast density: effect on imaging and breast cancer risk. *J Natl Compr Canc Netw* 2010;8:1157-1164; quiz 1165
9. American College of Radiology. *Breast Imaging Reporting and Data System (BI-RADS)*. 4th ed. Reston, VA: American College of Radiology, 2003
10. Byng JW, Yaffe MJ, Jong RA, Shumak RS, Lockwood GA, Tritchler DL, et al. Analysis of mammographic density and breast cancer risk from digitized mammograms. *Radiographics* 1998;18:1587-1598
11. Zhou C, Chan HP, Petrick N, Helvie MA, Goodsitt MM, Sahiner B, et al. Computerized image analysis: estimation of breast density on mammograms. *Med Phys* 2001;28:1056-1069
12. Chang YH, Wang XH, Hardesty LA, Chang TS, Poller WR, Good WF, et al. Computerized assessment of tissue composition on digitized mammograms. *Acad Radiol* 2002;9:899-905
13. Ng KH, Lau S. Vision 20/20: mammographic breast density and its clinical applications. *Med Phys* 2015;42:7059-7077
14. Destounis S, Johnston L, Highnam R, Arieno A, Morgan R, Chan A. Using volumetric breast density to quantify the potential masking risk of mammographic density. *AJR Am J Roentgenol* 2017;208:222-227
15. Leong SP, Shen ZZ, Liu TJ, Agarwal G, Tajima T, Paik NS, et al. Is breast cancer the same disease in Asian and Western countries? *World J Surg* 2010;34:2308-2324
16. Boyd N, Martin L, Stone J, Little L, Minkin S, Yaffe M. A lon-

gitudinal study of the effects of menopause on mammographic features. *Cancer Epidemiol Biomarkers Prev* 2002;11:1048-1053
17. Choppin SB, Wheat JS, Gee M, Goyal A. The accuracy of breast volume measurement methods: a systematic review. *Breast* 2016;28:121-129
18. Kovacs L, Eder M, Hollweck R, Zimmermann A, Settles M, Schneider A, et al. Comparison between breast volume measurement using 3D surface imaging and classical techniques. *Breast* 2007;16:137-145
19. Veitch D, Burford K, Dench P, Dean N, Griffin P. Measurement of breast volume using body scan technology (computer-aided anthropometry). *Work* 2012;41 Suppl 1:4038-4045
20. Teo I, Whelehan P, Macaskill JE, Vinnicombe S, Munnoch DA, Evans A. Volpara™ as a measurement tool for breast volume. *J Plast Reconstr Aesthet Surg* 2016;69:581-582

205명의 유방암 환자에서 용적 유방 밀도와 임상적 및 조직병리학적 인자와의 관련성 연구

정나리 · 김원화*

목적: 유방암 환자에서 용적 유방 밀도와 임상 및 병리학적 인자와의 연관성을 알아보고자 한다.
대상과 방법: 2015년 1월부터 2016년 6월까지 유방암 초기 진단을 위해 유방 촬영술을 시행한 총 205명의 한국인 유방암 환자를 대상으로 하였다. 용적 유방 밀도는 완전 자동화된 상업적 방법(Volpara®)을 사용하여 반대측 유방에서 측정하였다. 용적 유방 밀도와 임상 및 병리학적 인자와의 연관성을 t-검정 및 분산분석(analysis of variance)을 적절하게 사용하여 평가 하였다.
결과: 모든 환자에서 평균 용적 유방 밀도는 13.5% (범위, 4.1-34.9%)였다. 평균 용적 유방 밀도는 선별 검사로 확인된 암 환자보다 증상이 있어 시행한 암 환자에서 유의하게 높았다(14.9% vs. 11.8%, $p = 0.002$). 평균 용적 유방 밀도는 나이에 따라 감소하는 경향을 보였고 20-39세, 40-59세, 60-80세 환자의 밀도는 각각 19.0%, 14.3% 및 7.7%였다. 평균 용적 유방 밀도는 폐경 전 여성보다 폐경 후 여성에서 유의하게 낮았다(9.8% vs. 17.6%, $p < 0.001$). 조직학적 등급과 호르몬 수용체 상태를 포함한 기타 임상 및 병리학적 요인들은 용적 유방 밀도와 관련이 없었다.
결론: 본 연구는 용적 유방 밀도가 암이 진단된 방법, 연령 및 폐경 상태와 관련되어 있음을 시사한다.

칠곡경북대학교병원 영상의학과