Risk Analysis of Breast Cancer by Using Bilateral Mammographic Density Differences: A Case-Control Study

Zhang Zhang,[1] Xiaoyong Zhang,[2,3] Jiaqi Chen,[4] Yumi Takane,[5] Satoru Yanagaki,[6] Naoko Mori,[7] Kei Ichiji,[4] Katsuaki Kato,[8] Mika Yanagaki,[9] Akiko Ebata,[9,10] Minoru Miyashita,[9,10] Takanori Ishida[9,10] and Noriyasu Homma[1,4]

[1]Department of Intelligent Biomedical Systems Engineering Laboratory, Graduate School of Biomedical Engineering, Tohoku University, Sendai, Miyagi, Japan
[2]Smart-Aging Research Center, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Miyagi, Japan
[3]Department of General Engineering, National Institute of Technology, Sendai College, Sendai, Miyagi, Japan
[4]Department of Radiological Imaging and Informatics, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan
[5]Clinical Technology Department, Tohoku University Hospital, Sendai, Miyagi, Japan
[6]Department of Diagnostic Radiology, Tohoku University Hospital, Sendai, Miyagi, Japan
[7]Department of Radiology, Akita University Graduate School of Medicine, Akita, Akita, Japan
[8]Cancer Detection Center, Miyagi Cancer Society, Sendai, Miyagi, Japan
[9]Department of Surgery, Tohoku University Hospital, Sendai, Miyagi, Japan
[10]Department of Breast and Endocrine Surgical Oncology, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan

The identification of risk factors helps radiologists assess the risk of breast cancer. Quantitative factors such as age and mammographic density are established risk factors for breast cancer. Asymmetric breast findings are frequently encountered during diagnostic mammography. The asymmetric area may indicate a developing mass in the early stage, causing a difference in mammographic density between the left and right sides. Therefore, this paper aims to propose a quantitative parameter named bilateral mammographic density difference (BMDD) for the quantification of breast asymmetry and to verify BMDD as a risk factor for breast cancer. To quantitatively evaluate breast asymmetry, we developed a semi-automatic method to estimate mammographic densities and calculate BMDD as the absolute difference between the left and right mammographic densities. And then, a retrospective case−control study, covering the period from July 2006 to October 2014, was conducted to analyse breast cancer risk in association with BMDD. The study included 364 women diagnosed with breast cancer and 364 matched control patients. As a result, a significant difference in BMDD was found between cases and controls (P < 0.001) and the case−control study demonstrated that women with BMDD > 10% had a 2.4-fold higher risk of breast cancer (odds ratio, 2.4; 95% confidence interval, 1.3-4.5) than women with BMDD ≤ 10%. In addition, we also demonstrated the positive association between BMDD and breast cancer risk among the subgroups with different ages and the Breast Imaging Reporting and Data System (BI-RADS) mammographic density categories. This study demonstrated that BMDD could be a potential risk factor for breast cancer.

Introduction

Risk factors are used in the prediction of breast cancer risk and jointly contribute to breast cancer diagnosis, management, and treatment. Some of them are genetic and related to family history, whereas others are based on individual situations (Barlow et al. 2006; Lee et al. 2019). Quantitative risk factors such as mammographic density

and breast asymmetry have also been described to affect the interpretation of screening mammography (Scutt et al. 1997; Rosenberg et al. 1998; McCormack and dos Santos Silva 2006; Zheng et al. 2012; Fieselmann et al. 2019; Kashyap et al. 2022).

Increased mammographic density has been reported to be a risk factor for breast cancer in women. Mammographic density is defined as the relative amount of fibroglandular tissue in the entire breast (Nayeem et al. 2014). The presence of fibroglandular tissue in the breast on mammograms is known to indicate an increased risk of breast cancer (Whitehead et al. 1985; Wolfe et al. 1987; Amir et al. 2010). McCormack and dos Santos Silva (2006) reported that women with high mammographic density have a 2- to 6-fold greater risk of developing breast cancer than women with low mammographic density. In addition, Sartor et al. (2020) conducted a case−control study and found that women with breast cancer showed increasing mammographic density over time.

Humans show bilateral symmetry in paired morphological traits, including ear size, digit length, and breast volume (Scutt et al. 2006). Nevertheless, even in healthy women, absolute symmetry of the left and right breasts is rarely observed (Youk et al. 2009). Breast symmetry may be disturbed by several intrinsic and extrinsic factors, including the secretion of hormones such as estrogen (Manning et al. 1996, 1997). The breasts rapidly develop just before and during puberty, and the importance of estrogen in the development, growth, and carcinogenesis of the mammary gland is well established (McGuire et al. 1975). The role of local estrogen production is more apparent in breast cancer (Tekmal and Santen 1999). Therefore, the relationship between breast asymmetry and breast cancer warrants attention.

Radiologists examine the asymmetry patterns of left and right breast tissues on mammography for making clinical decisions (Blanks et al. 1999). The Breast Imaging Reporting and Data System (BI-RADS) defines four types of asymmetric breast findings: asymmetry, global asymmetry, focal asymmetry, and developing asymmetry (Youk et al. 2009). These asymmetric breast findings are important signs in making a breast cancer diagnosis. Asymmetric breast findings are frequently encountered during screening mammography and are relevant because they may indicate a lesion, especially if an associated mass is present (Samardar et al. 2002). Manning et al. (1997) conducted a multiple regression analysis and found significant associations between breast asymmetry and existing risk factors such as body mass, breast volume, breast density, and age. Radiologists routinely assess the asymmetry of fibroglandular tissue in bilateral mammograms and use the findings to identify women at a risk of having or developing abnormalities (Wang et al. 2010). Breast asymmetry is usually benign and common in women; however, it may occasionally be a secondary sign of malignancy (Kopans 2007). Several studies have also shown that asymmetric areas in

the breasts may indicate a developing mass or an underlying cancer in the early stage (Kopans et al. 1989; Samardar et al. 2002; Youk et al. 2009).

Breast cancer risk assessment models have been developed to assess the risk of breast cancer. Several models are available for estimating individual breast cancer risk based on risk factors (Wood et al. 2019). However, current breast cancer risk assessment models, such as the Gail model (Gail et al. 1989), do not include breast asymmetry despite its potential to indicate an additional risk of breast cancer. The risk assessment models can be improved through the addition of identified risk factors (Barlow et al. 2006) such as breast asymmetry. It is important that the risk factors could be conveniently incorporated into routine breast cancer screening and used to calculate the breast cancer risk in individual women (Tice et al. 2008).

In this study, we proposed a quantitative parameter named bilateral mammographic density difference (BMDD), the absolute difference between left and right mammographic densities, to assess breast asymmetry. We aimed to assess breast asymmetry using BMDD through a case−control study and to verify BMDD as a potential risk factor for breast cancer.

Materials and Methods

As a quantitative parameter of breast asymmetry, BMDD assessed the difference between left and right mammographic densities, so the estimation of mammographic densities was important. Therefore, firstly, we developed a semi-automatic method to estimate mammographic densities and calculate BMDD. The performance of the proposed estimator was subsequently evaluated. And then, we conducted a hypothetical test and a case−control study to analyze the association of BMDD with the risk of breast cancer.

Development and evaluation of a mammographic density estimator

In this study, mediolateral oblique (MLO)-view mammograms were used to perform the estimation. The estimator employs digital image processing techniques that help radiologists easily segment a mammogram into the breast region, pectoral muscle area, and fibroglandular tissue area. Fig. 1 shows a screenshot of the proposed estimator. The mammographic density can be estimated as the ratio of the fibroglandular tissue area to the breast area (Byng et al. 1998).

The procedures for mammographic density estimation were as follows: First, given an input mammogram, the area of the pectoralis major muscle was manually trimmed (Fig. 2a). Second, we used an automatic algorithm to segment the breast region from the trimmed image as shown in Fig. 2b. Then, as shown in Fig. 2c, the fibroglandular tissue area was segmented from the breast area using histogram-based thresholding (Otsu's method) (Otsu 1979). Finally, visual confirmation of the segmentation results was per-
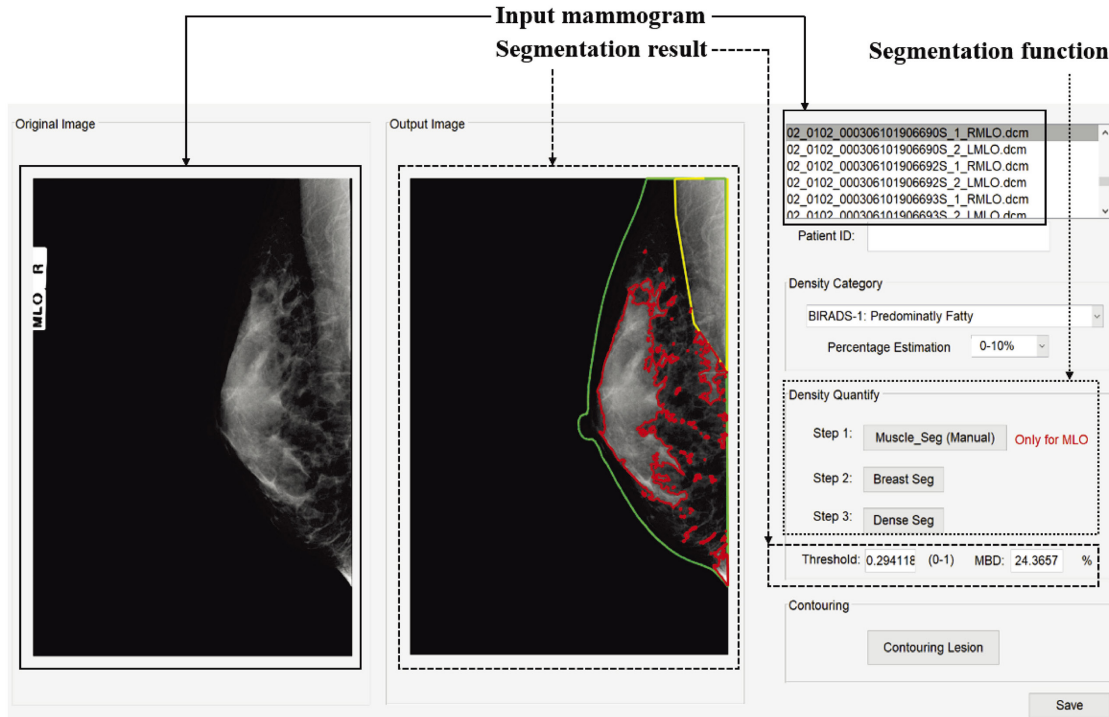
Fig. 1. Screenshot of the proposed estimator for mammographic density estimation.
MLO, mediolateral oblique view.

(a)   (b)   (c)
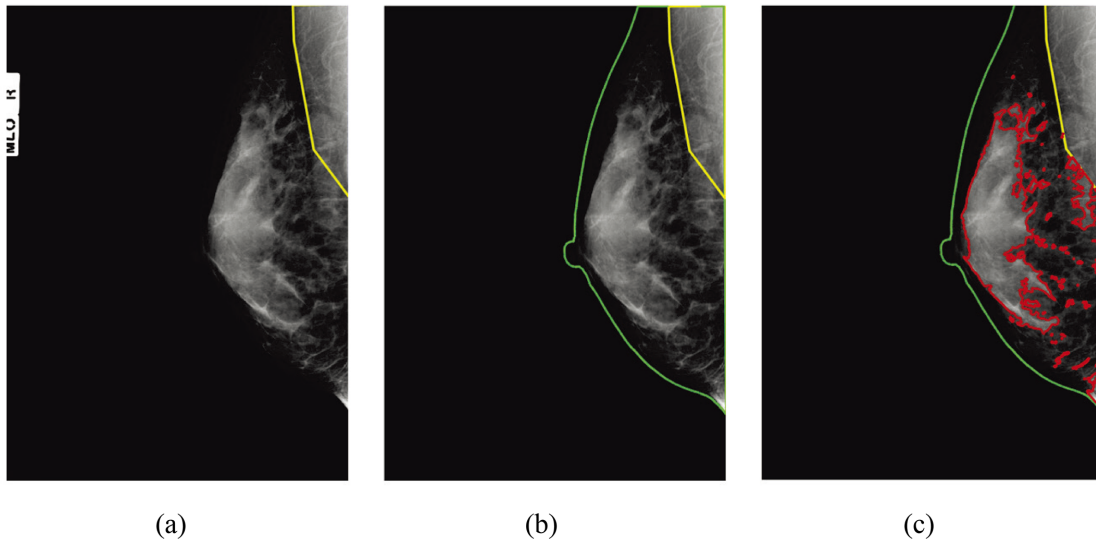
Fig. 2. Example of the proposed method for estimating mammographic density.
(a) The original mediolateral oblique view mammogram. The area of the pectoralis major muscle was manually identified. (b) The entire breast area after manually removing the muscles. (c) Fibroglandular tissues in the breast region (green) and segmented using the proposed method (red).

formed by a radiologist with 6 years of experience in reading mammograms. If the segmentation result was not reasonable, the radiologist performed manual adjustments based on visual observations. Major adjusted instances were women with a very low proportion of fibroglandular tissue in breasts. The mammographic density was calculated by dividing the number of pixels in the fibroglandular tissue area by the total pixel numbers of the breast area.

To evaluate the performance of the proposed estimator, we calculated the correlation coefficients between the mammographic density estimations and the BI-RADS density categories (Martin et al. 2006; Wang et al. 2020). The BI-RADS categories were assessed by three radiologists. The assessment was performed blinded by the first two

radiologists. Any disagreement was resolved through a discussion. The third radiologist was responsible for the final confirmation, which was performed without blinding. The Pearson's and Spearman's correlation coefficients between the mammographic density estimations and BI-RADS categories were calculated to perform the evaluation.

To demonstrate the accuracy of the mammographic density estimator, we compared the performance of the proposed estimator with that of Laboratory for Individualized Breast Radiodensity Assessment (LIBRA) (Keller et al. 2012), a publicly available automated software. LIBRA can be used for analyzing digital mammography images from machines manufactured by two vendors: GE Healthcare (Chicago, IL, USA) and Hologic Inc. (Marlborough, MA, USA). Since our mammography images were obtained using machines from three vendors: GE Healthcare, Fujifilm (Tokyo, Japan), and Konica Minolta Inc. (Tokyo, Japan), 13% of mammograms in our database could not be assessed by LIBRA. The Pearson's and Spearman's correlation coefficients between the LIBRA estimations and BI-RADS categories were also calculated. Bland−Altman plots were used to clarify the agreement between the proposed method and LIBRA.

Study design and data acquisition

Women who underwent screening mammography at Tohoku University Hospital and Miyagi Cancer Society between July 2006 and October 2014 were included in this study. The inclusion criterion was available bilateral mammograms. The exclusion criterion was the presence of markers identifying the position of abnormalities on mammograms. These markers may result in high-intensity areas and affect the segmentation results. All mammograms used in this study were obtained at the time of screening. Informed consent was obtained from patients before the mammographic examination. Ethical approval for this study was obtained from the Ethics Committee Tohoku University Graduate School of Medicine (Ethical number: 2022-1-530).

The eligible cases comprised 364 women who underwent screening mammography at Tohoku University Hospital and Miyagi Cancer Society and subsequently received a diagnosis of breast cancer verified with a biopsy. All controls were selected on the basis of matching to ensure similar age and mammographic density distribution to cancer patients. For each case patient, a corresponding control was selected on the basis of matching according to age (± 5 years) and BI-RADS density categories (± 1). As control patients, 364 women who did not develop breast cancer during the observation period were selected from the same institutions. Control women were not diagnosed with cancer within 2 years. A few healthy women with benign findings were included in this study.

Statistical analysis

We conducted hypothesis testing to verify the signifi-cant differences between the two groups and subsequently conducted a case−control study for risk analysis. P values of < 0.001 were referred as statistically highly significant. Statistical analyses were performed using SPSS software (version 21.0; SPSS Inc., Chicago, IL, USA).

We used the Mann−Whitney U test to confirm the existence of a significant difference in BMDD between cases and controls (McKnight and Najab 2010). We designed a case−control study to investigate the association between quantitatively estimated breast asymmetry and the risk of breast cancer based on BMDD assessed using mammograms. Unconditional logistic regression models were applied to compute odds ratios (ORs) and 95% confidence intervals (CIs) for analyzing the association of BMDD with the risk of breast cancer. Potential confounders including age, BI-RADS density category, left mammographic density and right mammographic density were adjusted. In the case−control study, the exposure status of breast asymmetry was defined as BMDD > 10%. According to the experimental results, 10% had better confidence intervals for odds ratios than the other cut-off points. According to a previous study conducted by the Japan Cancer Surveillance Research Group (Hori et al. 2015), the incidence rate of breast cancer differs among three major age groups. For Japanese women aged ≤ 45 years, the incidence rate of breast cancer is increasing. For Japanese women aged 46-65 years, the incidence rate remains at the peak value. For Japanese women aged > 65 years, the incidence rate is beginning to slowly decrease. To examine the association of BMDD with the risk of breast cancer in different age groups, the participants were divided into three age subgroups (≤ 45, 46-65, and > 65 years). To investigate the relationship between BMDD and breast cancer risk in women with different mammographic densities, the participants were divided into a low mammographic density subgroup (BI-RADS 1 & 2) and a high mammographic density subgroup (BI-RADS 3 & 4). In addition, we conducted the same case−control study by calculating BMDD using LIBRA. Some mammograms were not supported by LIBRA because of the machine vendor. Therefore, 321 cases and 307 controls were included in this case−control study with an exposure status defined as BMDD (LIBRA) > 10%.

Results

Characteristics of the case−control study

A total of 728 patients were recruited for the case−control study between July 2006 and October 2014. Of them, 364 eligible patients diagnosed with breast cancer (age, 57 ± 12 years; mean ± standard deviation) formed the case group, whereas 364 healthy women without breast cancer (age, 55 ± 11 years) were selected as the control group. The characteristics of the women with breast cancer and the control population are shown in Table 1.

Table 1. Demographic characteristics of cases and controls.

Variables	Patients with breast cancer	Control patients
No. of women	364	364
BMDD (%)[a]	3.7 (1.8, 6.7)	2.6 (1.2, 4.6)
Age (years)	57 ± 12	55 ± 11
Age group (years)[b]		
≤ 40	32 (8.8)	28 (7.7)
41-50	96 (26.4)	107 (29.4)
51-60	95 (26.1)	118 (32.4)
61-70	79 (21.2)	78 (21.4)
> 70	62 (17.0)	33 (9.1)
BI-RADS (mammographic density)[b]		
1	50 (13.7)	42 (11.5)
2	221 (60.7)	246 (67.6)
3	69 (19.0)	58 (15.9)
4	24 (6.6)	18 (4.9)

[a]Data are medians of BMDD with 25th and 75th percentiles in parentheses.
[b]Data are numbers of women, with percentages in parentheses.
Age is shown as means ± standard deviations.
BMDD, bilateral mammographic density difference; BI-RADS, Breast Imaging Reporting and Data System.

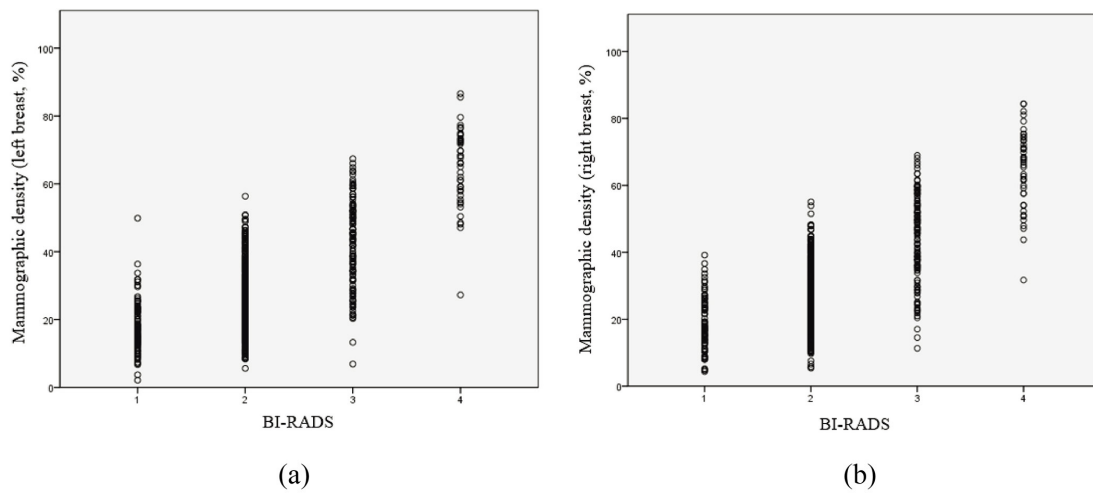(a)   (b)

Fig. 3. Plots used to clarify the relationship between the estimated mammographic densities and Breast Imaging Reporting and Data System (BI-RADS) categories.
The horizontal axis represents the BI-RADS categories, whereas the vertical axis represents the estimated mammographic densities by the proposed estimator. (a) and (b) show the mammographic densities on the left and right sides, respectively.

Significant difference

Since dense side and less-dense side might be changed in the results of different estimators, we compared the estimation performance in left and right sides separately. A total of 1,456 mediolateral oblique (MLO)-view mammograms were used to estimate mammographic density with the proposed estimator. Fig. 3 shows scatter plots describing the relationship of the estimated values and the BI-RADS categories. The horizontal and vertical axes represent the BI-RADS categories and the estimated mammographic densities, respectively. A Pearson's correlation coefficient of 0.74 was obtained for the left side, indicating that the estimated left breast mammographic densities and BI-RADS categories were correlated. Similarly, the right side showed a Pearson's correlation coefficient of 0.74. Meanwhile, a Spearman's correlation coefficient of 0.64 was obtained for the left side, indicating that the estimated left breast mammographic densities and BI-RADS categories were correlated. Similarly, the right side showed a Spearman's correlation coefficient of 0.64. Thus, there was a close correlation between the proposed estimator and the BI-RADS categories. Mammography density estimation
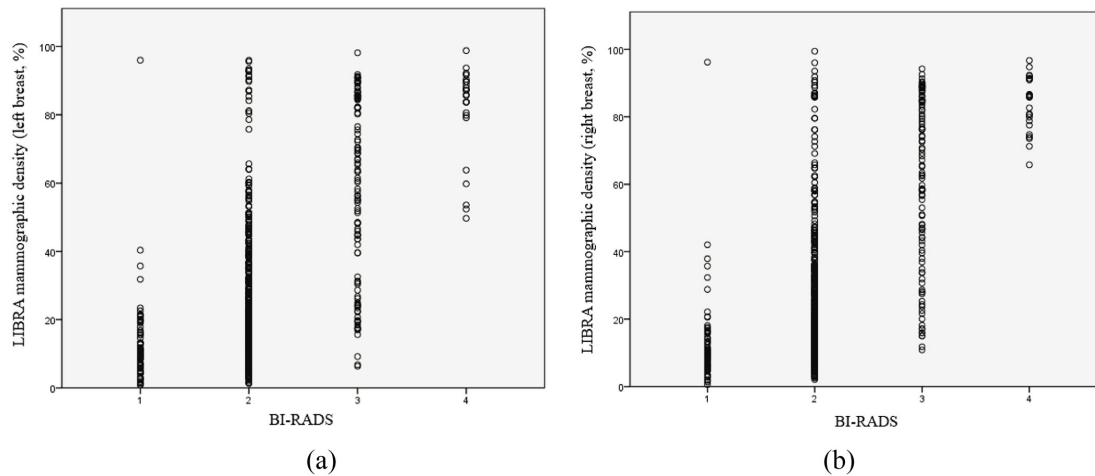
Fig. 4. Plots used to clarify the relationship between the Laboratory for Individualised Breast Radiodensity Assessment
(LIBRA) estimations and Breast Imaging Reporting and Data System (BI-RADS) categories.
The horizontal axis represents the BI-RADS categories, whereas the vertical axis represents the estimated mammographic
densities by LIBRA. (a) and (b) show the mammographic densities on the left and right sides, respectively.
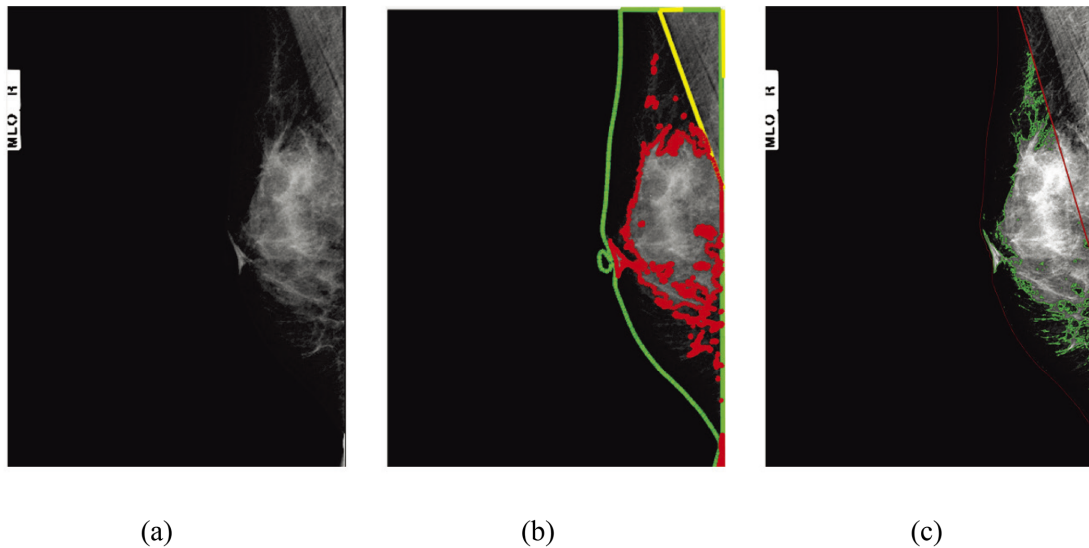

Fig. 5. An example comparing the proposed estimator and the Laboratory for Individualised Breast Radiodensity Assessment
(LIBRA) software (Keller et al. 2012).
(a) The original mediolateral oblique view mammogram. (b) The estimated result of the proposed estimator. The area
of the pectoralis major muscle in the image was manually identified. (c) The estimated result of LIBRA. The area of
the pectoralis major muscle in the image was automatically identified. Manual identification can ensure the accuracy of
the estimation by correctly removing the muscle area.

with LIBRA was further performed using 1,256 MLO-view mammograms. Fig. 4 shows the scatter plots of the LIBRA estimation distribution according to the BI-RADS categories. A Pearson's correlation coefficient of 0.62 was obtained for the left side, indicating that the estimated left breast mammographic densities and BI-RADS categories were correlated. The right side showed a Pearson's correlation coefficient of 0.64. Meanwhile, a Spearman's correlation coefficient of 0.58 was obtained for the left side, indicating that the estimated left breast mammographic densities and BI-RADS categories were correlated. The right side showed a Spearman's correlation coefficient of

0.60. According to the results, the proposed estimator obtained higher correlation with BI-RADS categories, so it performed more effectively than LIBRA in this study.

An example comparing LIBRA and the proposed estimator is shown in Fig. 5. Fig. 5a shows the original MLO-view mammogram. Fig. 5b shows the estimations by the proposed estimator. The area of the pectoralis major muscle (Fig. 5b) was manually identified. Fig. 5c shows the estimations by LIBRA. The area of the pectoralis major muscle (Fig. 5c) was automatically identified and there was a segmentation error. We could find such segmentation errors in dense mammograms, in which the edges of muscle
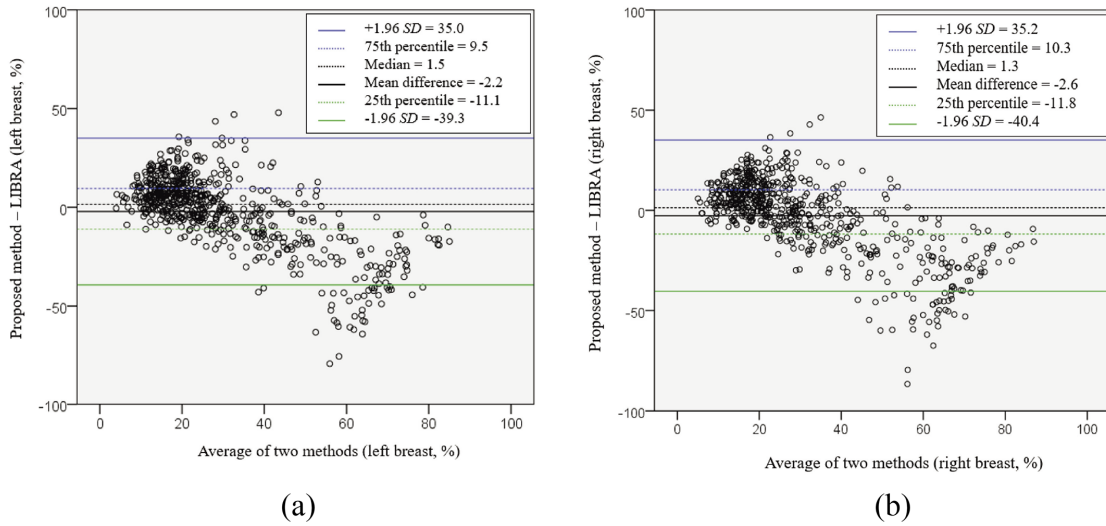
(a)   (b)

Fig. 6. Bland−Altman plots used to clarify the agreement between the proposed method and the Laboratory for Individualised
Breast Radiodensity Assessment (LIBRA).
The horizontal axis represents the average of the two methods, whereas the vertical axis represents the difference
between the two methods. (a) and (b) show the Bland−Altman plots for the left and right sides, respectively. The lines
represent the mean difference, median difference, interquartile range, and limits of agreement.

(a)   (b)
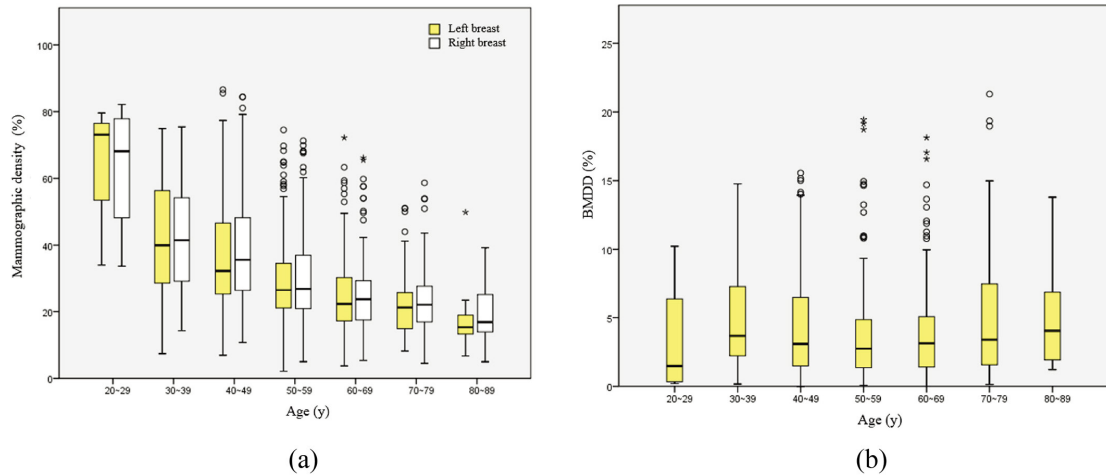
Fig. 7. Box plots used to clarify the difference between the estimated mammographic densities and bilateral mammographic
density (BMDD) according to age.
The horizontal axis represents the age categories, whereas the vertical axis represents the variables. (a) and (b) show the
mammographic densities and BMDD, respectively. BMDD was relatively stable in different age groups, whereas mam-
mographic density decreased with age. The line and whiskers indicate the median and interquartile range.

were not clear and thus the muscle could be hard to seg-
ment. Manual identification may be more costly but has
better estimation accuracy than the automatic method. The
Bland−Altman plots in Fig. 6 were used to clarify the
agreement in mammographic density estimations between
the proposed method and LIBRA. The difference between
the two methods was calculated as the estimated values
with the proposed method minus the estimated values with
LIBRA. The dotted lines represent the mean differences
and limits of agreement. For both sides of the breasts, the
Bland−Altman plots indicated the differences between the
two methods. The LIBRA estimation results were higher
than the standard levels in BI-RADS 2 & 3, caused by the

segmentation error (Fig. 4). Thus, the proposed method
showed better performance in estimating mammographic
density than LIBRA.

To clarify the difference between the estimated mam-
mographic densities and BMDD according to age, two box
plots were generated (Fig. 7). The horizontal axis represents
the age categories, whereas the vertical axis represents the
variables. BMDD was relatively stable in different age
groups, whereas mammographic density decreased with age.

Association of BMDD with breast cancer
The Mann−Whitney U test was performed to confirm
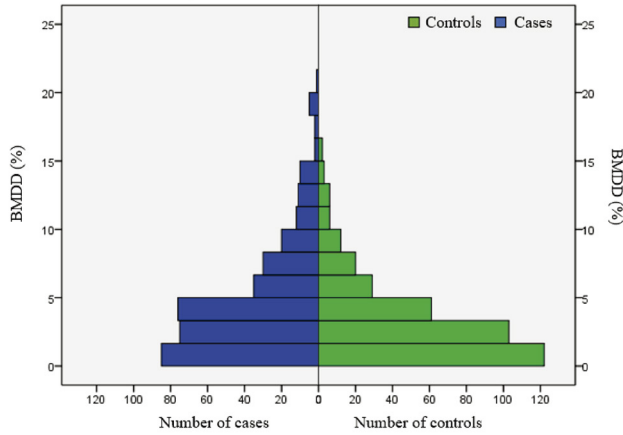the existence of a significant difference in BMDD between

Fig. 8. Distribution of breast asymmetry based on bilateral mammographic density difference (BMDD) in cases (blue) and controls (green).
BMDD was statistically different between cases and controls (P < 0.001, Mann−Whitney *U* test). The vertical axis represents BMDD, whereas the horizontal axis represents the number of participants. The data distribution of BMDD in the healthy group was more compact and had a shorter distribution tail than that in the cancer group.

cases and controls. Fig. 8 shows the comparison of BMDD values between the case and control groups. A significant difference in BMDD was found between cases and controls (P < 0.001). This result indicates that cancer patients and healthy women have significantly different BMDD.

A case−control study was conducted to clarify whether BMDD is a specific risk factor for breast cancer. Table 2 summarizes the results of this case−control study. Using BMDD ≤ 10% as the reference, a 2.4-fold (95% CI, 1.3-4.5) increased risk of breast cancer was found in women with BMDD > 10%. The positive association between BMDD and breast cancer risk differed among the subgroups with different age and BI-RADS mammographic density categories. Women aged ≤ 45 years with BMDD > 10% may have no additional risk of breast cancer (OR, 1.0; 95% CI, 0.3-3.6). Women aged > 45 and < 65 years had an increased risk of breast cancer (OR, 3.0; 95% CI, 1.2-7.6), whereas women aged > 65 years had an OR of 4.2 (95% CI, 0.9-21.0). Women with BMDD > 10% and BI-RADS 1 & 2 mammographic density had an increased risk of breast cancer (OR, 2.7; 95% CI, 1.4-5.3). This result indicated that BMDD could show cancer risk even for cases with low mammographic densities. Women with BMDD > 10% and BI-RADS 3 & 4 mammographic density also had an increased risk of breast cancer (OR, 2.2; 95% CI, 0.6-8.4). The results demonstrated positive associations between

Table 2. Odds ratios for the risk of breast cancer associated with bilateral mammographic density difference (BMDD) by age and mammographic density.

Risk factor	Controls	Cases	Odds ratio[†]	CI
Overall				
BMDD ≤ 10%	347	321	1.0*	NA
BMDD > 10%	17	43	2.4	1.3-4.5
Age (years)				
≤ 45				
BMDD ≤ 10%	81	64	1.0*	NA
BMDD > 10%	8	7	1.0	0.3-3.6
46–65				
BMDD ≤ 10%	206	175	1.0*	NA
BMDD > 10%	7	23	3	1.2-7.6
> 65				
BMDD ≤ 10%	60	82	1.0*	NA
BMDD > 10%	2	13	4.2	0.9-21.0
BI-RADS				
1 & 2				
BMDD ≤ 10%	275	236	1.0*	NA
BMDD > 10%	13	35	2.7	1.4-5.3
3 & 4				
BMDD ≤ 10%	72	85	1.0*	NA
BMDD > 10%	4	8	2.2	0.6-8.4

*Reference.
[†]Adjusted for age, BI-RADS density category, left mammographic density and right mammographic density.
BI-RADS, Breast Imaging Reporting and Data System; CI, 95% confidence interval; NA, not applicable.

Table 3. Odds ratios for the risk of breast cancer associated with bilateral mammographic density difference (BMDD) (Laboratory for Individualised Breast Radiodensity Assessment, LIBRA) by age and mammographic density.

Risk factor	Controls	Cases	Odds ratio[†]	CI
Overall				
BMDD ≤ 10%	220	125	1.0*	NA
BMDD > 10%	87	196	1.4	0.9-1.9
Age (years)				
≤ 45				
BMDD ≤ 10%	55	16	1.0*	NA
BMDD > 10%	26	40	2.1	0.9-4.7
46-65				
BMDD ≤ 10%	120	68	1.0*	NA
BMDD > 10%	53	110	1.3	0.8-2.1
> 65				
BMDD ≤ 10%	45	41	1.0*	NA
BMDD > 10%	8	46	0.9	0.4-2.3
BI-RADS				
1 & 2				
BMDD ≤ 10%	191	105	1.0*	NA
BMDD > 10%	61	142	1.5	1.0-2.2
3 & 4				
BMDD ≤ 10%	29	20	1.0*	NA
BMDD > 10%	26	54	1.1	0.5-2.4

*Reference.

[†]Adjusted for age, BI-RADS density category, left mammographic density and right mammographic density.

BI-RADS, Breast Imaging Reporting and Data System; CI, 95% confidence interval; NA, not applicable.

BMDD and breast cancer risk.

The case−control study based on BMDD calculated using LIBRA showed a similar tendency in the breast cancer risk assessment. Table 3 summarizes the results of this case−control study. Using BMDD (LIBRA) ≤ 10% as the reference, a 1.4-fold (95% CI, 0.9-1.9) increased risk of breast cancer was found in women with BMDD > 10%. Women aged ≤ 45 years with BMDD (LIBRA) > 10% had an increased risk of breast cancer (OR, 2.1; 95% CI, 0.9-4.7). Women aged > 45 and < 65 years had a minor risk of breast cancer (OR, 1.3; 95% CI, 0.8-2.1), whereas women aged ≥ 65 years had an OR of 0.9 (95% CI, 0.4-2.3). Women with BMDD (LIBRA) > 10% and BI-RADS 1 & 2 mammographic density had an increased risk of breast cancer (OR, 1.5; 95% CI, 1.0-2.2). Women with BMDD (LIBRA) > 10% and BI-RADS 3 & 4 mammographic density had a minor risk of breast cancer (OR, 1.1; 95% CI, 0.5-2.4). The results demonstrated positive associations between BMDD (LIBRA) and breast cancer risk.

Discussion

In this study, we performed quantitative estimation of breast asymmetry using BMDD. We found that BMDD was positively associated with breast cancer risk. BMDD > 10% may be a risk factor for breast cancer. With BMDD ≤ 10% as the reference, a 2.7-fold increased risk of breast cancer was found in women with BMDD > 10%. Importantly, the subgroup analyses according to different age and BI-RADS mammographic density categories indicated different positive associations between BMDD and breast cancer risk. In addition, BMDD may provide a robust estimation of breast asymmetry. Although LIBRA was not as good as the proposed method in processing the mammograms from our database, the case−control study based on BMDD (LIBRA) indicated a similar tendency in breast cancer risk assessment.

This study contributes to the growing evidence that quantitative estimation of breast asymmetry is an efficient method of breast cancer risk assessment (Scutt et al. 1997; Wang et al. 2010; Zheng et al. 2012). Our results indicated a positive association between BMDD and breast cancer risk in a matched case−control study. The data distribution of BMDD was consistent with the breast volume asymmetry distribution in a previous study (Scutt et al. 1997). The distribution of BMDD in healthy women was more compact and had a shorter distribution tail than the BMDD distribution in cancer patients. Many mammographic density studies have suggested that women with low mammographic density have a lower risk of breast cancer than women with high mammographic density (Martin et al. 2006; Amir et al. 2010;

Jeffers et al. 2017). Our study indicated that even in women with low mammographic density, BMDD may indicate an additional risk of breast cancer. Thus, BMDD may be a marker of breast cancer susceptibility, regardless of age or BI-RADS mammographic density category.

Current breast cancer risk models, such as the Gail model (Gail et al. 1989), do not include quantitative breast asymmetry. The incorporation of BMDD into risk assessment models might help better identify women at an increased risk of developing breast cancer. Considering the incidence of breast cancer in women, BMDD evaluation may benefit women aged > 45 years during an individual risk assessment for breast cancer (Hori et al. 2015). Furthermore, our results showed that BMDD was relatively stable in different age groups. High-density mammograms in younger women may decrease the effectiveness of mammographic density in estimating breast cancer risk, whereas BMDD is unaffected in this situation. Our study results indicated that the application of BMDD will help radiologists in creating an effective mammographic screening plan for patients (Schousboe et al. 2011).

The main strength of this study was the availability of raw mammographic images and corresponding clinical reports, which allowed us to evaluate the performance of quantitative mammographic densities on all study images. To support this study, a clinical BI-RADS density category assessment was performed and confirmed by at least three radiologists. The proposed mammographic density estimator was more effective than LIBRA (Keller et al. 2012) and obtained sufficiently reasonable correlations between the mammographic density estimations and BI-RADS categories. The distribution of mammographic density estimations was consistent with that in a previous study (Nicholson et al. 2006): the range of mammographic densities was relatively narrow for the fatty and extremely dense categories but rather broad for the scattered fibroglandular dense and heterogeneously dense BI-RADS categories (Fig. 3). The proposed estimator could make BMDD easy to understand and clinically apply.

A second important strength of this study was the use of the MLO view based on full-field digital mammography (FFDM). FFDM has been reported to demonstrate improved image quality and superior detection performance compared with film-screen mammography (Fischmann et al. 2005). The MLO view is recommended as the first-choice view for screening as it allows observing the entire breast and has been predominantly used by radiologists to determine the mammographic density categories in the BI-RADS (Kwok et al. 2004; Mohamed et al. 2018). For example, a lesion in the axillary tail of the breast may sometimes not be imaged in the standard craniocaudal view but can be seen in the MLO view (Brenner 2001). Thus, high-quality MLO-view images based on FFDM include the entire breast and are suitable for evaluating breast asymmetry (De Paredes 2007).

Our study had several limitations. First, the available sample limited the statistical significance for older patients and patients in the high BI-RADS categories. Second, the patients' clinical information in our database was limited. Some risk factors were not considered in this study, such as body weight, menopausal status, BRCA1/BRCA2 gene mutations, and use of hormone therapy. Third, it would have been better to use mammograms taken before the development of cancer and to show differences in asymmetry that preceded a breast cancer diagnosis. Analyzing mammograms taken before cancer detection might clarify the effectiveness of BMDD in the early prediction of breast cancer risk. We look forward to supplementing the database and expanding the risk assessment using BMDD in future research. Fourth, in a case with high BMDD, which breast will have cancer is still unknown. Although there is a high possibility that cancer would occur in the breast with larger mammographic density, we have not demonstrated it in this study.

Fifth, since the mammographic densities were calculated as a ratio, the difference between the sizes of breast was not considered. Finally, the proposed method is semi-automatic and may be difficult to implement in a large screening population. Nevertheless, the proposed semi-automatic method was more reasonable and accurate than the automatic method (LIBRA), although the case−control study based on BMDD (LIBRA) showed a similar tendency. Our segmentation results will be useful for the development of an automatic estimation method based on deep learning to overcome this limitation in the future.

In conclusion, our results indicated that BMDD is positively associated with breast cancer risk and larger BMDD could be a potential risk factor for breast cancer in healthy women.

Acknowledgments

Conflict of Interest

The authors declare no conflict of interest.

References

Amir, E., Freedman, O.C., Seruga, B. & Evans, D.G. (2010) Assessing women at high risk of breast cancer: a review of risk assessment models. *J. Natl. Cancer Inst.*, **102**, 680-691.

Barlow, W.E., White, E., Ballard-Barbash, R., Vacek, P.M., Titus-Ernstoff, L., Carney, P.A., Tice, J.A., Buist, D.S.M., Geller, B.M., Rosenberg, R., Yankaskas, B.C. & Kerlikowske, K. (2006) Prospective breast cancer risk prediction model for women undergoing screening mammography. *J. Natl. Cancer Inst.*, **98**, 1204-1214.

Blanks, R.G., Wallis, M.G. & Given-Wilson, R.M. (1999) Observer variability in cancer detection during routine repeat (incident) mammographic screening in a study of two versus

one view mammography. *J. Med. Screen.*, **6**, 152-158.

Brenner, R.J. (2001) Asymmetric densities of the breast: strategies for imaging evaluation. *Semin. Roentgenol.*, **36**, 201-216.

Byng, J.W., Yaffe, M.J., Jong, R.A., Shumak, R.S., Lockwood, G.A., Tritchler, D.L. & Boyd, N.F. (1998) Analysis of mammographic density and breast cancer risk from digitized mammograms. *Radiographics*, **18**, 1587-1598.

De Paredes, E.S. (2007) *Atlas of Mammography*, 3rd ed., Lippincott Williams & Wilkins, Philadelphia, PA.

Fieselmann, A., Fornvik, D., Fornvik, H., Lang, K., Sartor, H., Zackrisson, S., Kappler, S., Ritschl, L. & Mertelmeier, T. (2019) Volumetric breast density measurement for personalized screening: accuracy, reproducibility, consistency, and agreement with visual assessment. *J. Med. Imaging (Bellingham)*, **6**, 031406.

Fischmann, A., Siegmann, K.C., Wersebe, A., Claussen, C.D. & Muller-Schimpfle, M. (2005) Comparison of full-field digital mammography and film-screen mammography: image quality and lesion detection. *Br. J. Radiol.*, **78**, 312-315.

Gail, M.H., Brinton, L.A., Byar, D.P., Corle, D.K., Green, S.B., Schairer, C. & Mulvihill, J.J. (1989) Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J. Natl. Cancer Inst.*, **81**, 1879-1886.

Hori, M., Matsuda, T., Shibata, A., Katanoda, K., Sobue, T. & Nishimoto, H.; Japan Cancer Surveillance Research Group (2015) Cancer incidence and incidence rates in Japan in 2009: a study of 32 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. *Jpn. J. Clin. Oncol.*, **45**, 884-891.

Jeffers, A.M., Sieh, W., Lipson, J.A., Rothstein, J.H., McGuire, V., Whittemore, A.S. & Rubin, D.L. (2017) Breast cancer risk and mammographic density assessed with semiautomated and fully automated methods and BI-RADS. *Radiology*, **282**, 348-355.

Kashyap, D., Pal, D., Sharma, R., Garg, V.K., Goel, N., Koundal, D., Zaguia, A., Koundal, S. & Belay, A. (2022) Global increase in breast cancer incidence: risk factors and preventive measures. *Biomed Res. Int.*, **2022**, 9605439.

Keller, B.M., Nathan, D.L., Wang, Y., Zheng, Y., Gee, J.C., Conant, E.F. & Kontos, D. (2012) Estimation of breast percent density in raw and processed full field digital mammography images via adaptive fuzzy c-means clustering and support vector machine segmentation. *Med. Phys.*, **39**, 4903-4917.

Kopans, D.B. (2007) Suspicious Lesions and Lesions with a High Probability of Malignancy. In *Breast Imaging*, 3rd ed., Lippincott Williams & Wilkins, Philadelphia, PA, pp. 513-553.

Kopans, D.B., Swann, C.A., White, G., McCarthy, K.A., Hall, D.A., Belmonte, S.J. & Gallagher, W. (1989) Asymmetric breast tissue. *Radiology*, **171**, 639-643.

Kwok, S.M., Chandrasekhar, R., Attikiouzel, Y. & Rickard, M.T. (2004) Automatic pectoral muscle segmentation on mediolateral oblique view mammograms. *IEEE Trans. Med. Imaging*, **23**, 1129-1140.

Lee, A., Mavaddat, N., Wilcox, A.N., Cunningham, A.P., Carver, T., Hartley, S., Babb de Villiers, C., Izquierdo, A., Simard, J., Schmidt, M.K., Walter, F.M., Chatterjee, N., Garcia-Closas, M., Tischkowitz, M., Pharoah, P., et al. (2019) BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors. *Genet. Med.*, **21**, 1708-1718.

Manning, J.T., Scutt, D., Whitehouse, G.H. & Leinster, S.J. (1997) Breast asymmetry and phenotypic quality in women. *Evol. Hum. Behav.*, **18**, 223-236.

Manning, J.T., Scutt, D., Whitehouse, G.H., Leinster, S.J. & Walton, J.M. (1996) Asymmetry and the menstrual cycle in women. *Ethol. Sociobiol.*, **17**, 129-143.

Martin, K.E., Helvie, M.A., Zhou, C., Roubidoux, M.A., Bailey, J.E., Paramagul, C., Blane, C.E., Klein, K.A., Sonnad, S.S. & Chan, H.P. (2006) Mammographic density measured with quantitative computer-aided method: comparison with radiologists' estimates and BI-RADS categories. *Radiology*, **240**, 656-665.

McCormack, V.A. & dos Santos Silva, I. (2006) Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol. Biomarkers Prev.*, **15**, 1159-1169.

McGuire, W.L., Carbone, P.P. & Vollmer, E.P. (1975) *Estrogen Receptors in Human Breast Cancer*, Raven Press, New York, NY.

McKnight, P.E. & Najab, J. (2010) Mann-Whitney U Test. In *The Corsini Encyclopedia of Psychology*, edited by Weiner I.B. & Craighead W.E., John Wiley & Sons, Inc., Hoboken, NJ, pp. 960-961.

Mohamed, A.A., Luo, Y., Peng, H., Jankowitz, R.C. & Wu, S. (2018) Understanding clinical mammographic breast density assessment: a deep learning perspective. *J. Digit. Imaging*, **31**, 387-392.

Nayeem, F., Ju, H., Brunder, D.G., Nagamani, M., Anderson, K.E., Khamapirad, T. & Lu, L.J. (2014) Similarity of fibroglandular breast tissue content measured from magnetic resonance and mammographic images and by a mathematical algorithm. *Int. J. Breast Cancer*, **2014**, 961679.

Nicholson, B.T., LoRusso, A.P., Smolkin, M., Bovbjerg, V.E., Petroni, G.R. & Harvey, J.A. (2006) Accuracy of assigned BI-RADS breast density category definitions. *Acad. Radiol.*, **13**, 1143-1149.

Otsu, N. (1979) A threshold selection method from gray-level histograms. *IEEE Trans. Syst. Man Cybern.*, **9**, 62-66.

Rosenberg, R.D., Hunt, W.C., Williamson, M.R., Gilliland, F.D., Wiest, P.W., Kelsey, C.A., Key, C.R. & Linver, M.N. (1998) Effects of age, breast density, ethnicity, and estrogen replacement therapy on screening mammographic sensitivity and cancer stage at diagnosis: review of 183,134 screening mammograms in Albuquerque, New Mexico. *Radiology*, **209**, 511-518.

Samardar, P., de Paredes, E.S., Grimes, M.M. & Wilson, J.D. (2002) Focal asymmetric densities seen at mammography: US and pathologic correlation. *Radiographics*, **22**, 19-33.

Sartor, H., Kontos, D., Ullen, S., Fornvik, H. & Fornvik, D. (2020) Changes in breast density over serial mammograms: a case-control study. *Eur. J. Radiol.*, **127**, 108980.

Schousboe, J.T., Kerlikowske, K., Loh, A. & Cummings, S.R. (2011) Personalizing mammography by breast density and other risk factors for breast cancer: analysis of health benefits and cost-effectiveness. *Ann. Intern. Med.*, **155**, 10-20.

Scutt, D., Lancaster, G.A. & Manning, J.T. (2006) Breast asymmetry and predisposition to breast cancer. *Breast Cancer Res.*, **8**, R14.

Scutt, D., Manning, J.T., Whitehouse, G.H., Leinster, S.J. & Massey, C.P. (1997) The relationship between breast asymmetry, breast size and the occurrence of breast cancer. *Br. J. Radiol.*, **70**, 1017-1021.

Tekmal, R.R. & Santen, R.J. (1999) Local Estrogen Production: Is Aromatase An Oncogene? In *Endocrinology of Breast Cancer*, edited by Manni, A., Humana Press, Totowa, NJ, pp. 79-92.

Tice, J.A., Cummings, S.R., Smith-Bindman, R., Ichikawa, L., Barlow, W.E. & Kerlikowske, K. (2008) Using clinical factors and mammographic breast density to estimate breast cancer risk: development and validation of a new predictive model. *Ann. Intern. Med.*, **148**, 337-347.

Wang, C., Brentnall, A.R., Mainprize, J., Yaffe, M., Cuzick, J. & Harvey, J.A. (2020) External validation of a mammographic texture marker for breast cancer risk in a case-control study. *J. Med. Imaging (Bellingham)*, **7**, 014003.

Wang, X., Lederman, D., Tan, J., Wang, X.H. & Zheng, B. (2010) Computerized detection of breast tissue asymmetry depicted on bilateral mammograms: a preliminary study of breast risk

stratification. *Acad. Radiol.*, **17**, 1234-1241.

Whitehead, J., Carlile, T., Kopecky, K.J., Thompson, D.J., Gilbert, F.I. Jr., Present, A.J., Threatt, B.A., Krook, P. & Hadaway, E. (1985) Wolfe mammographic parenchymal patterns. A study of the masking hypothesis of Egan and Mosteller. *Cancer*, **56**, 1280-1286.

Wolfe, J.N., Saftlas, A.F. & Salane, M. (1987) Mammographic parenchymal patterns and quantitative evaluation of mammographic densities: a case-control study. *AJR Am. J. Roentgenol.*, **148**, 1087-1092.

Wood, M.E., Farina, N.H., Ahern, T.P., Cuke, M.E., Stein, J.L., Stein, G.S. & Lian, J.B. (2019) Towards a more precise and individualized assessment of breast cancer risk. *Aging* (*Albany N. Y.*), **11**, 1305-1316.

Youk, J.H., Kim, E.K., Ko, K.H. & Kim, M.J. (2009) Asymmetric mammographic findings based on the fourth edition of BI-RADS: types, evaluation, and management. *Radiographics*, **29**, e33.

Zheng, B., Sumkin, J.H., Zuley, M.L., Wang, X., Klym, A.H. & Gur, D. (2012) Bilateral mammographic density asymmetry and breast cancer risk: a preliminary assessment. *Eur. J. Radiol.*, **81**, 3222-3228.

———————————————