

## Is Mammographic Breast Density a Risk Factor for Breast Cancer in Japanese Women ?

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### 乳房密度は日本人女性でも乳がん罹患危険因子か

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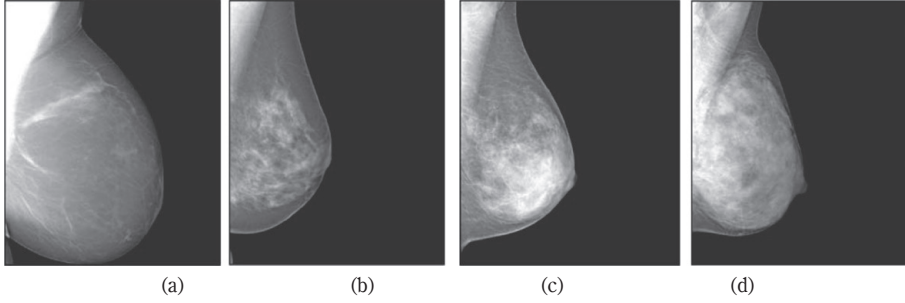
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To analyze the association between mammographic breast density and breast cancer risk, a graphic user interface (GUI) software was developed in this study. Given a mammogram image, the GUI software is capable of segmenting fibroglandular tissues from the breast region and of calculating the mammographic breast density automatically. Using this software, a preliminary case-control study based on a Japanese women mammography database is conducted to analyze the breast cancer risk associated with the mammographic breast density. The study demonstrated that the mammographic breast density is strongly associated with the breast cancer for Japanese women.

### 1. Introduction

The radiographic appearance of female breast varies among individuals because of differences in the relative amounts of fat, fibroglandular tissue, and the different X-ray attenuation characteristics<sup>1)</sup>. In a mammogram image, the fat appears dark due to its

radiolucent characteristic, and the fibroglandular tissue is radiodense and relatively bright. Pioneering studies by Wolfe<sup>2,3)</sup> have shown that the relative amount of fibroglandular tissues in the breast as assessed mammographically, also referred to as mammographic breast density, is an independent risk factor for breast cancer, in fact the most significant after



**Fig. 1.** Four categories of mammographic breast density in ACR-BIRADS. (a) Category I: the breasts are almost entirely fatty, and fibro glandular tissue is less than 25%. (b) Category II: there are scattered fibroglandular tissues, ranging from 25%–50% of the breast. (c) Category III: The breasts are heterogeneously dense, and fibroglandular tissue ranges 51%–75% of the breast tissue. (d) The breasts are extremely dense and contains greater than 75% fibroglandular tissue.

age<sup>1)</sup>.

To assess the mammographic breast density, the most commonly used method is to categorize the mammogram images into different categories based on radiologist visual judgment. As shown in Fig. 1, American College of Radiology (ACR) established a four-category mammographic breast density in the breast-imaging reporting and data system (BIRADS)<sup>4)</sup>. Over the past three decades, more than 40 studies<sup>5–10)</sup> have been devoted to analyze the relationship between the mammographic breast density and breast cancer risk. These studies have demonstrated that the mammographic breast density is strongly associated with the breast cancer. However, they are almost based on the database obtained from American and European women. To our knowledge, no publication has been reported that the mammographic breast density in Japanese women also strongly associated with the breast cancer. In this study, we aim to conduct a preliminary investigation on a mammogram database acquired from Japanese women to conform this hypothesis.

## 2. Method and Materials

### 2.1 Data Set

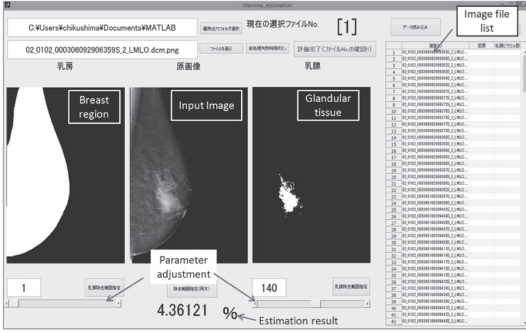
The data sets observed in this study were obtained from a digital mammogram database provided

by Tohoku University Hospital. Using the medical records of this database, we designed a case-control study to analyze the association between the mammographic breast density and risk of breast cancer. We selected 316 medio-lateral oblique (MLO) mammogram images in one-year observation, in which breast cancer or its typical signs (microcalcification cluster, mass, and architecture distortion) are verified by radiologists, as case subjects. As control subjects, 268 MLO mammograms, in which no breast cancer was developed in a similar period of observation, were selected in the study.

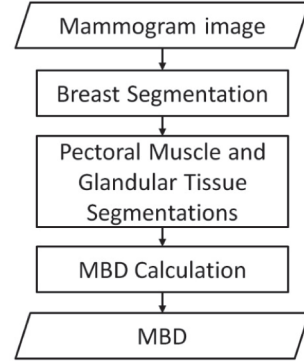
The original mammographic images are acquired at a resolution 0.025 mm/pixel using 12-bit gray-level depth. For computational efficiency, the original images are converted into 8-bit gray-level with resolution 0.1 mm/pixel.

### 2.2 Quantitative Breast Density Assessment

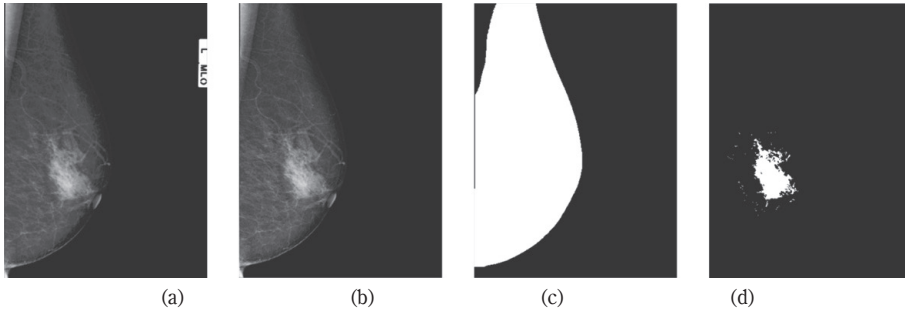
For quantitative breast density assessment, a Graphic Use Interface (GUI) program using MATLAB was developed. The GUI program employs digital image processing techniques that allow radiologists to easily segment an observed mammogram image into breast region, pectoral muscle, and dense tissue, and to calculate the mammographic density percentage. The GUI program also allows radiologists to adjust parameters manually for improving



**Fig. 2.** A screenshot of the GUI program for mammographic density estimation.



**Fig. 3.** A flowchart of GUI program for mammographic density estimation.



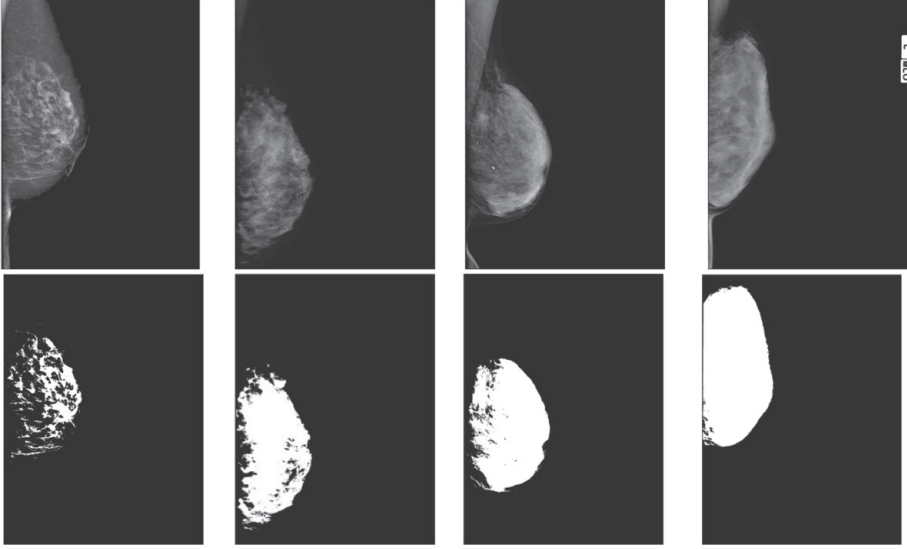
**Fig. 4.** An example of image segmentation for mammographic breast density estimation. (a) An original mammogram image. (b) Image labels are removed from the original image. (c) The breast region in which the pectoral muscle is removed by a manual delineation. (d) The fibroglandular tissue segmented by a semi-automatic thresholding processing.

the accuracy of the image segmentation. Fig. 2 shows a screenshot of the GUI for estimation of the mammographic density.

Here, we briefly introduce the computing procedure of the mammographic density estimation system. As shown in Fig. 3, the developed system consists of three major procedures. Given an observed mammogram image, the first procedure is to utilize an automatic algorithm to convert a gray-level mammogram image into a binary image and to remove the image labels from the binary image. Fig. 4 (a) shows an observed mammogram images in which the image labels are located at the top-right of image. Fig. 4 (b) shows the processed image in which the breast region is segmented from the origi-

nal image, and the image labels are removed from the original image.

The second procedure is to segment the pectoral muscle and the dense tissues from the breast region. In this procedure, a semi-automatic processing is used to delineate and remove the pectoral muscle manually from the breast region. Subsequently, the dense fibroglandular tissue can be separated from the remainder breast region by using a user-defined thresholding processing. Fig. 4 (c) shows a binary image in which the pectoral muscle is removed manually by using the GUI program. As shown in Fig. 4 (d), the dense fibroglandular tissue is segmented from the breast region and converted into binary image.



**Fig. 5.** Four mammographic images in the observed data and the corresponding dense fibroglandular segmented by the GUI program.

Finally, the mammographic breast density is calculated as a ratio of the dense tissues area to the breast area, given by

$$d = \frac{\Omega_T}{\Omega_B} \times 100\% \quad (1)$$

where  $\Omega_T$  is the area of dense tissues corresponding to Fig. 4 (d), and  $\Omega_B$  is the breast area obtained from image in Fig. 4 (c).

### 3. Results

Using the above described GUI program, quantitative assessments of mammographic breast density were conducted on the case-control subjects. Fig. 5 shows four mammographic images in the observed data and the corresponding dense fibro glandular segmented by the GUI program. The mammographic breast densities (from left to right) were eventually calculated as 17%, 48%, 66%, and 85%, respectively. According to the density category of BI-RADS, the observed mammogram images, including the case and control subjects, were then

classified into four categories. Base on the four-categorized results, a relative incidence rate of breast cancer for each category was calculated by

$$R_i = \frac{\frac{N_{\text{case}}^i}{N_{\text{case}}}}{\frac{N_{\text{case}}^i}{N_{\text{case}}} + \frac{N_{\text{control}}^i}{N_{\text{control}}}} \times 100\% \quad (2)$$

where  $i \in \{1, 2, 3, 4\}$  is the category index,  $N_{\text{case}}$  and  $N_{\text{control}}$  are the total numbers of case and control objects, respectively, and  $N_{\text{case}}^i$  and  $N_{\text{control}}^i$  are the numbers of case and control objects in the  $i$ -th category. Table 1 summarizes the density categories in the observed subjects. From the results, we note that the relative incidence rate of category IV (highest density) is more than twice of that of the category I (lowest density).

In addition, according the quantitative density assessment, we classified the observed mammogram image into 10 density categories, and calculated the relative incidence rate of breast cancer for each category. Table 2 summarizes the 10-density catego-

**Table 1.** Four-category mammographic breast density classification and relative incidence rate of breast cancer

| Category |                         | Control Objects |      | Case Objects |      | $R_i$ (%) |
|----------|-------------------------|-----------------|------|--------------|------|-----------|
| No.      | Density                 | RMLO            | LMLO | RMLO         | LMLO |           |
| I        | ( $0 \leq d < 25\%$ )   | 129             | 142  | 79           | 79   | 41.3      |
| II       | ( $25 \leq d < 50\%$ )  | 20              | 16   | 43           | 42   | 71.2      |
| III      | ( $50 \leq d < 75\%$ )  | 6               | 3    | 11           | 10   | 67.8      |
| IV       | ( $75 \leq d < 100\%$ ) | 0               | 0    | 2            | 2    | 100       |
| Total    |                         | 316             |      | 268          |      |           |

**Table 2.** Ten-category mammographic breast density classification and relative incidence rate of breast cancer

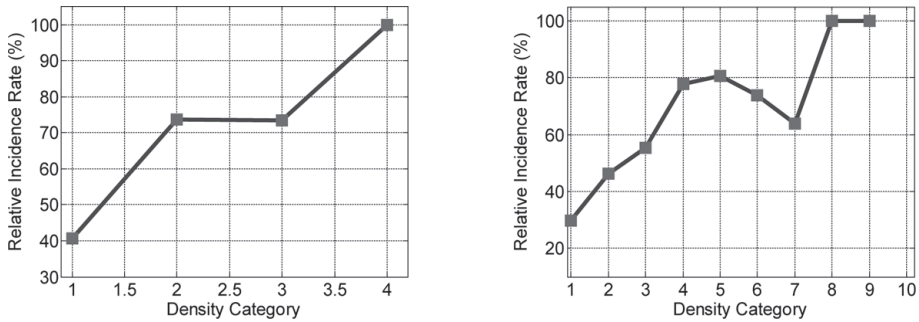
| Category |                         | Control Objects |      | Case Objects |      | $R_i$ (%) |
|----------|-------------------------|-----------------|------|--------------|------|-----------|
| No.      | Density                 | RMLO            | LMLO | RMLO         | LMLO |           |
| I        | ( $0 \leq d < 10\%$ )   | 59              | 58   | 19           | 23   | 29.7      |
| II       | ( $10 \leq d < 20\%$ )  | 68              | 49   | 48           | 37   | 46.1      |
| III      | ( $20 \leq d < 30\%$ )  | 23              | 32   | 24           | 34   | 55.4      |
| IV       | ( $30 \leq d < 40\%$ )  | 5               | 6    | 15           | 18   | 78.0      |
| V        | ( $40 \leq d < 50\%$ )  | 3               | 4    | 15           | 10   | 80.8      |
| VI       | ( $50 \leq d < 60\%$ )  | 3               | 2    | 6            | 7    | 73.9      |
| VII      | ( $60 \leq d < 70\%$ )  | 0               | 4    | 4            | 2    | 70.2      |
| VIII     | ( $70 \leq d < 80\%$ )  | 0               | 0    | 2            | 3    | 100       |
| IX       | ( $80 \leq d < 90\%$ )  | 0               | 0    | 1            | 1    | 100       |
| X        | ( $90 \leq d < 100\%$ ) | 0               | 0    | 0            | 0    | —         |
| Total    |                         | 316             |      | 268          |      |           |

ries in the observed subjects. Since the maximum mammographic breast density in the observed images was about 85%, the number of cases in the category X was zero. In this table, the relative incidence rates of category VIII and IX (highest density) was more than three times of that of the category I (lowest density). Figs. 6 (a) and 5 (b) plot the relative incidence rates of breast cancer as the function of two different categories summarized in Tables 1 and 2. The results demonstrated that the mammo-

graphic density can be a strong risk factor for breast cancer.

#### 4. Discussion

In this study, we developed a GUI program that allows radiologists to measure the mammographic breast density quantitatively and retrospectively. Compared with qualitative density categorization based on visual observation, the developed program can help radiologists to make a precision estimation



**Fig. 6.** Relative incidence of breast cancer as a function of breast density category. (a) Four density categories. (b) Ten density categories.

of the mammographic breast density and to measure the cancer risk in terms of the mammographic breast density. Although a completely automatic density estimator is desirable, observer intervention is still indispensable since the appearance of mammogram image would be variable due to several factors, such as irradiation condition, thickness of the breast, etc. Therefore, in our future work, we plan to improve the accuracy and precision of the estimation system by combining the digital image processing with pattern recognition technology.

In this study, we also conducted a preliminary study to analyze the relationship between the mammographic breast density and breast cancer risk. A case-control study based on Japanese women demonstrated that the mammographic breast density is strongly associated with risk of breast cancer. This result is in agreement with previous studies that are all based on American or European women. However, since the number of cohort used in this study is insufficient, the selections of case and control objects probably introduce a selection bias. Due to this limitation, our study may not be sufficient to prove if the ethnic group is associated with the mammographic breast density, but it can suggest if the result agrees with those for American or European women. In this study, we used a relative incidence rates for different mammographic breast densities to analyze the relationship between the

mammographic breast density and breast cancer. However, since the incidence rate is not based on a population study, the incidence rate obtained from the observation probably introduces estimation bias. A cohort collection is thus the most critical task to our further study.

## 5. Conclusions

An analysis of breast cancer risk factor based on quantitatively mammographic breast density estimation is presented in this paper. By utilizing digital image processing techniques, we developed a GUI software which is capable of calculating the mammographic breast density. On the base of a cohort obtained from Japanese women, a preliminary case-control study is conducted to analyze the relationship between mammographic breast density and breast cancer. The results suggested that mammographic breast density is strongly associated with breast cancer.

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