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Original Article

Factors Influencing Breast Density in Japanese Women Aged 40–49 in Breast Cancer Screening Mammography

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A relatively large number of women in their 40s with high-density breasts, in which it can be difficult to detect lesions, are encountered in mammography cancer screenings in Japan. Here, we retrospectively investigated factors related to breast density. Two hundred women (40–49 years old) were examined at the screening center in our hospital. Multivariate analysis showed that factors such as small abdominal circumference, high HDL cholesterol, and no history of childbirth were related to high breast density in women in their 40s undergoing mammography. Other non-mammographic screening methods should be considered in women with abdominal circumferences $<$ 76 cm, HDL-C $\geq$ 53 mg/dl, and no history of childbirth, as there is a strong possibility of these women having high-density breasts that can make lesion detection difficult.

Key words: high-density breasts, abdominal circumference, high-density lipoprotein cholesterol, childbirth, mammography

It is difficult to detect tumors in high-density breasts using mammography [1–3]. The percentage of women in their 40s with high breast density is high [4], and this age group has the highest breast cancer incidence in Japan [5]; this indicates a possible association between breast density and the risk for breast cancer. Prior to performing mammography for breast cancer screening in women in this age group, it would be helpful to be able to predict the breast density, so that other modalities, such as mammary ultrasonography, could be selected as required. In this retrospective study we investigated the factors related to breast density in Japanese women aged 40–49 as it affects breast cancer screening.

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Subjects and Methods

Data from 200 women aged 40–49 who underwent mammography at the screening center in our hospital from April 1 to August 31, 2009, were retrospectively collected. We used logistic regression models to calculate the risk factors for high-density breasts. We calculated the minimum sample size based on the work of Peduzzi *et al.* [6], in which the minimum number of cases to include is calculated as follows: N = 10 k/p (p: the smallest of the proportions of negative or positive cases in the population; k: the number of independent variables). In our study, we analyzed 10 independent variables, and the smallest proportion of negative or positive cases in the population was 0.5. The minimum number of cases to include was thus calculated as $100/0.5 = 200$.

The characteristics of the subjects are given in

Table 1. According to the definition of the Central Committee on Quality Control of Mammographic Screening (Table 2) [7], patients with "high-density" or "non-uniform high-density" breasts were assigned to the high-density group, and those with "fatty" or "dispersed" breasts were assigned to the low-density group (Fig. 1 and 2, respectively). Cases were assigned to either group in the order of the screening date until each group had 100 members. Breast density was determined by 2 doctors certified for image interpretation by the Central Committee on Quality Control of Mammographic Screening. This clinical study was approved by the Medical Ethics Committee at our hospital.

The photographic apparatus used was a Mermaid (Toshiba Medical Systems, Tokyo, Japan); the direct digitizer was a REGIUS V stage Model 190 (Konica Minolta Medical and Graphic, Tokyo, Japan); the

Table 1 Baseline characteristics

	High-density group	Low-density group	*p* value
Age (y), median (IQR)	44 (42–47)	45.5 (42–47)	0.4446
Height (cm), median (IQR)	158 (154–161)	158 (154–162)	0.5324
Weight (kg), median (IQR)	52.5 (48.0–57.6)	55.0 (51.7–60.7)	0.0011
BMI, median (IQR)	20.7 (19.3–22.9)	22.4 (20.4–24.5)	0.0005
AC (cm), median (IQR)	74.0 (70.0–78.0)	77.5 (73.0–85.0)	0.0002
TCHO (mg/dl), median (IQR)	199.5 (182.3–224.3)	197.5 (178.3–218.0)	0.6155
TG (mg/dl), median (IQR)	59.5 (48.0–80.5)	68.5 (56.3–101.5)	0.0082
HDL (mg/dl), median (IQR)	67.5 (59.0–78.8)	63.5 (52.0–77.0)	0.1023
LDL (mg/dl), median (IQR)	112.0 (97.7–132.0)	109.9 (93.6–130.5)	0.6087
Childbirth			
Yes, no. (%)	79 (79.0)	92 (92.0)	
No, no. (%)	21 (21.0)	8 (8.0)	0.0149

IQR, interquartile range; BMI, body mass index; AC, abdominal circumference; TCHO, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; no., number of patients.

Table 2 Definitions of the Central Committee on Quality Control of Mammographic Screening (Igaku-Shoin: Mammography Guideline, 2nd edition) [7]

Fatty	The breasts have been almost completely replaced by fat.
Dispersed breast	Dispersed mammary parenchyma inside the breasts have been replaced by fat.
Non-uniform high density	Coexisting fat inside the mammary parenchyma, displaying a non-uniform density.
High density	Almost no coexisting fat inside the mammary parenchyma (so-called dense breast).

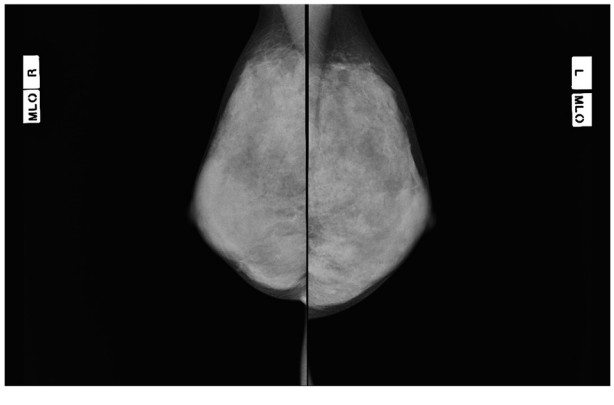

Fig. 1 Mammogram from the high-density group.

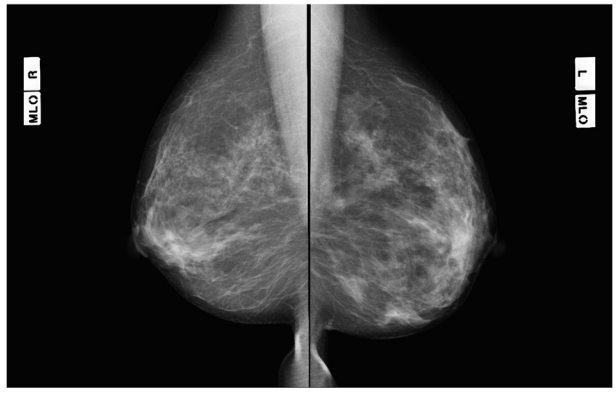

Fig. 2 Mammogram from the low-density group.

console was a REGIUS Console CS-3 (Konica Minolta Medical and Graphic, Tokyo, Japan); and the image interpretation system was Mammary, a dedicated mammography image diagnostic workstation (Climb Medical Systems, Osaka, Japan).

To investigate factors related to breast density, we analyzed the following items in the high-density and low-density groups: age, height, weight, body mass index (BMI), abdominal circumference (AC), total blood cholesterol (TCHO), triglycerides (TG), blood high-density lipoprotein cholesterol (HDL-C), blood low-density lipoprotein cholesterol (LDL-C), and history of childbirth. The data of these items are generally collected at screenings, and they are also items that appeared to be related to breast density as indicated by past research [8–10]. There were 5 menopausal women in the high-density group and 7 in the low-density group, though 11 persons were unclear about their menopausal status in the high-density group and 19 persons were unclear about their menopausal status in the low-density group. The Mann-Whitney U test was used to compare continuous variables for patient backgrounds, Fisher's exact test was used to compare categorical variables, and logistic regression analysis was used to calculate odds ratios for and analyses of the relationships between each factor and high breast density. The stepwise regression method was used for variable selection for multivariate analysis. Statistical significance was set at $p < 0.05$, and the statistical software used was JMP version 8.0.2 (SAS Institute, Cary, NC, USA).

Results

Receiver operating characteristic (ROC) analysis was performed to calculate the optimal cut-off line of each variable. ROC analyses returned the following cutoff values for predicting high breast density: height 161.5 cm, weight 53.1 kg, BMI 21.9, AC 76 cm, TCHO 175 mg/dl, TG 59 mg/dl, HDL-C 53 mg/dl, and LDL-C 96.8 mg/dl. Single variable analyses using logistic regression with these cutoff values showed that women with low weight, BMI, AC, and TG; high HDL-C; and no history of childbirth exhibited a significant tendency to have high-density breasts. The odds ratios for high-density breasts were: weight < 53.1 kg, 2.61 (95% CI 1.47–4.70, $p = 0.0011$); BMI < 21.9, 2.91 (95% CI 1.65–5.22, $p = 0.0003$); AC < 76 cm, 3.03 (95% CI 1.71–5.43, $p = 0.0002$); TG < 59 mg/dl, 2.09 (95% CI 1.17–3.77, $p = 0.0137$), HDL-C ≥ 53 mg/dl, 3.55 (95% CI 1.61–8.46, $p = 0.0024$), and no history of childbirth, 3.06 (95% CI 1.33–7.7, $p = 0.0116$). Multivariate logistic analysis using the stepwise regression adjusted for age showed AC < 76 cm (odds ratio 2.7, 95% CI 1.49–4.96, $p = 0.0012$); HDL-C ≥ 53 mg/dl (odds ratio 2.3, 95% CI 1.251–4.33, $p = 0.0077$); and no history of childbirth (odds ratio 2.87, 95% CI 1.19–7.52, $p = 0.0237$) to be significantly related to high breast density (Table 3).

Discussion

Most of the studies examining the relationship between breast density and obesity have been performed in Western countries [11–13], while only a few reports have focused on Asian populations. Sung *et al.* examined 730 Korean women ≥ 30 years old and found that present BMI, BMI at the age of 35 years, total fat percent, waist circumference, and waist-hip ratio were related to breast density [8]. Tseng *et al.* investigated 415 Chinese women living in the United States (average age, 43.9 years) and found breast density was related to BMI and adult weight gain. In their study, BMI < 23 was related to the incidence of high-density breast [9]. A relationship between breast density and first full-term pregnancy has also been reported [10]. Our study only involved women in their 40s, but the relationships of breast density with AC and childbirth were similar to those observed in past reports. A study from Canada reported a relationship between breast density and HDL-C [14], but a Korean study reported no significant difference with a multivariate analysis that included BMI [15]. Our investigations showed a relationship between breast density and HDL-C in multivariate analysis that included BMI.

The usefulness of mammography screening in women aged 50 and older has been widely recognized [16]. However, because a large number of women aged ≤ 49 have relatively high-density breasts [4], the rate of cancer detection using mammography is low in this age group [4, 11].

Previous reports have suggested the usefulness of ultrasonography for screening of breast cancer in women aged 40–49 [1, 17, 18]. Sueda *et al.* investigated the detection rates of breast cancer by mam-

Table 3 Results of univariate logistic regression analysis

	Univariate analysis			Multivariate analysis		
	OR	95CI	*p* value	OR	95CI	*p* value
Age						
≥45	1			1		
<45	1.38	0.79–2.41	0.258	1.34	0.73–2.44	0.342
Height						
≥161.5	1					
<161.5	1.21	0.66–2.25	0.533			
Weight						
≥53.1	1					
<53.1	2.61	1.47–4.70	0.0011			
BMI						
≥21.9	1					
<21.9	2.91	1.65–5.22	0.0003			
AC						
≥76	1			1		
<76	3.03	1.71–5.43	0.0002	2.7	1.49–4.96	0.0012
TCHO						
≥175	1					
<175	0.51	0.23–1.09	0.09			
TG						
≥59	1					
<59	2.09	1.17–3.77	0.0137			
HDL						
<53	1			1		
≥53	3.55	1.61–8.46	0.0024	2.8	1.22–6.90	0.018
LDL						
≥96.8	1					
<96.8	0.67	0.36–1.25	0.21			
Childbirth						
Yes	1			1		
No	3.06	1.33–7.70	0.0116	2.87	1.19–7.52	0.024

OR, odds ratio; CI, confidence interval; BMI, body mass index; AC, abdominal circumference; TCHO, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

mography and ultrasonography for 47 consecutive cases of breast cancers in women aged 40–49. Mammography achieved a detection rate of 78.7%, while ultrasonography had a higher detection rate of 89.4% [19]. Ultrasonography can thus be considered a more useful method than mammography for women in the age group of 40–49. However, considering the longer time required for ultrasonography and the need for skilled practitioners, screening all women in this age group with ultrasonography would not be possible. As a result, the most appropriate breast cancer screening method for women aged 40–49 in Japan is still not clear [20, 21]. The Randomized Trial (J-START) was begun in Japan to evaluate the effectiveness of ultrasound breast cancer screening of women aged 40–49, but the results of the trial are not yet available [21]. Other countries, such as the United States, conduct mammographies once a year in women aged ≥40 years. This approach poses few problems in the United States, where breast cancer

incidence peaks in the 50s. However, considering Japan's early occurrence of breast cancer and the differences in breast size and density between the populations, it is possible that the most appropriate screening method is different in Japan from that used in the West.

Our results showed that abdominal circumference, HDL-C, and history of childbirth are indices that can be used to determine breast cancer screening methods for women in their 40s. Among the cases in this study, 14% of the high-density group had AC < 76 cm, HDL-C ≥ 53 mg/dl, and no history of childbirth, while only 1% of the low-density group fell into this category.

Limitations of this investigation include a small sample size and not considering other factors thought to be related to breast density, such as breastfeeding history, number of deliveries, bodyweight fluctuations, exercise, hormone therapy, and diet. These factors were not investigated because they are unconventional in normal screenings or we were not able to obtain actual data on them. Studies involving more cases and surveying more items are necessary.

In conclusion, abdominal circumference, HDL-C, and history of childbirth are indices that can be used to determine breast cancer screening methods for women in their 40s. High breast density is a strong possibility in women with abdominal circumference < 76 cm, HDL-C ≥ 53 mg/dl, and no history of childbirth.

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