

Influential factors and prediction model of mammographic density among Chinese women

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Abstract

To evaluate the characteristics and influential factors of breast density and establish a new model for predicting breast density in Chinese women, so as to provide a basis for breast cancer screening techniques and duration.

A total of 9412 women who were selected from screening and intervention techniques for Breast and Cervical Cancer Project between April 2018 and June 2019 were enrolled in this study. Selected women were randomly assigned to training and validation sets in a ratio of 1:1. Univariable and multivariable analyses were performed by Logistic regression model. Nomogram was generated according to the results of multivariate analysis. Calibration, area under curve (AUC) and akaike information criterion (AIC) were used for measuring accuracy of prediction model.

There were 377 (4.0%) women in breast imaging reporting and data system (BI-RADS) A category, 2164 (23.0%) in B category, 5749 (61.1%) in C category and 1122 (11.9%) in D category. Age duration, educational attainment, history of benign diseases, breastfeeding history, menopausal status, and body mass index (BMI) were imputed as independent influential factors for breast density in multivariable analysis. The AUC and AIC of training and validation set were 0.7158, 0.7139, and 4915.378, 4998.665, respectively.

This study indicated that age, educational attainment, history of benign breast disease, breastfeeding history, menopausal status and BMI were independent influential factors of breast density. Nomogram generated on the basis of these factors could relatively predict breast density, which in turn could be used for recommendations of breast cancer screening techniques.

Abbreviations: AIC = akaike information criterion, AUC = area under curve, BI-RADS = breast imaging reporting and data system, BMI = body mass index.

Keywords: breast density, Chinese women, nomogram, predictive model

1. Introduction

Breast cancer is one of the most common causes of cancer-related mortality among women worldwide, and it is the most frequently diagnosed type of malignant tumor in women.^[1] Global cancer statistics suggest that around 2.1 million new cases of breast cancer are diagnosed in women on yearly basis, which is almost a

quarter of all female cancers.^[2] Many factors have been found to be associated breast cancer, including modifiable environmental, reproductive and lifestyle factors, and unmodified genetic factors.^[3,4,5]

Breast cancer screening at an early stage was considered to reduce breast cancer mortality. The effect of breast density on

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The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional board of Liaoning Cancer Hospital. (NO: 20180106) and individual consent for this retrospective analysis was obtained.

The authors have no conflicts of interests to disclose.

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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screening sensitivity has been studied previously with film-screen mammography.^[6] Breast density is determined by the breast appearance on the X-ray, which reflects the percentage of epithelial and stromal breast tissue. Breast density is a known risk factor for breast cancer^[7,8] and women with dense breast tissue are 4 to 6 times more likely to develop breast cancer compared to those with non-dense breast tissue.^[9] Literature estimates of positive predictive value, negative predictive value, and specificity were generally lower in women with increased breast density.

Currently, the American College of Radiology's Breast Imaging Reporting and Data System (BI-RADS) is the most common classification method in clinic.^[10] It divides breast density into 4 categories (Category A, B, C, D). Previous studies have indicated that among American women aged 40 to 69 years, the proportion of dense breasts (BI-RADS category C and D) ranges from 57% to 31%.^[11] Chinese women were identified to have the highest percentage of dense breast compared to other races.^[12] Due to differences in breast density, mammography-based breast cancer screening may not be applicable to Chinese women. Screening of breast cancer among young Chinese women revealed that sensitivity to ultrasonography was higher than mammography, especially in those with high breast density and relatively small breast volume.^[13] Therefore, it is critical to arrange different screening methods for women with different breast density.

Similar to breast cancer, breast density is affected by multiple factors. Age, body mass index (BMI), reproduction and fertility have all been reported to be associated with breast density.^[11,12,14] Besides these, life styles choices such as physical activity are also considered as influential factors of breast density.^[15]

However, there are few relevant studies among Chinese women and the results are still inconsistent. Besides, there was no research to establish a prediction model for breast density. Thus, the aim of this study was to evaluate characteristics and influencing factors of breast density in Chinese women. Accordingly, a model for breast density prediction was established to contribute to the selection of breast cancer screening techniques in China.

2. Methods

2.1. Study populations

Study subjects were recruited from screening and intervention techniques for Breast and Cervical Cancer Project and prospectively enrolled between April 2018 and June 2019. The project aims to improve the early detection rate of breast and cervical cancer in China. Inclusion criteria were: women aged 45 to 70 years, with no history of breast cancer, no obvious mass detected during self-examination, no serious organ dysfunction or mental disorders, local residence for more than 3 years, and those who volunteered to participate and fill out questionnaires. The exclusion criteria were: women with diagnosed tumors, being treated for other serious conditions, pregnant and lactating women and those with unknown breast density. Eligible women underwent clinical breast examination (CBE), mammography, digital breast tomosynthesis, breast ultrasound and glucose test. Breast density was classified by BI-RADS and determined according to the examination results of digital breast tomosynthesis. Two radiologists independently reviewed the plain film to reduce relative bias. BI-RADS category A and B were defined as low breast density whereas category C and D were defined as high

breast density. Included women were randomly assigned to training and validation sets. The consort diagram is shown in (Supplementary Figure S1, <http://links.lww.com/MD/G237>).

2.2. Questionnaires

Questionnaires included questions related to age, height, weight (BMI was calculated as weight (kg) divided by square height (m)), marital status (unmarried; married; divorce; widowed), educational attainment (primary or less; secondary; tertiary), breast cancer family history (yes; no), history of benign breast diseases (yes; no), age at menarche (≤ 12 years; > 12 years), breastfeeding history (yes; no), number of births (0; 1; 2 or more), menopause status (premenopausal; postmenopausal), menopausal age (≤ 50 years; > 50 years), menopausal ways (induced menopause; natural menopause), smoking status (yes (smoking was defined as at least 1 cigarette per day for 3 months); no), drinking status (yes (drinking was defined as consuming at least 50 mL of wine per week); no), fruit intake (never, ≤ 1.25 kg/week, > 1.25 kg/week), vegetable intake (never; ≤ 2.5 kg/week; > 2.5 kg/week), meat intake (never; ≤ 0.35 kg/week; > 0.35 kg/week), coarse grains intake (never; ≤ 0.35 kg/week; > 0.35 kg/week), exercise (≤ 1 hour/week; > 1 hour/week) and living region (urban, rural). This study was conducted at Department of Breast Surgery and Radiology, Liaoning Cancer Hospital and was approved by the Liaoning Cancer Hospital & Institution institutional review board (ID: 20180106) and all participants signed the informed consent.

2.3. Statistical analysis

Categorical variables were compared using the χ^2 test. Continuous variables were expressed as mean \pm standard deviation and analyzed by Student *t* test. Random digits generated by SPSS version 23.0 were used to randomly assign included populations to training and validation sets in a ratio of 1:1. Univariate and multivariate analysis were performed by logistic regression model. Nomogram was generated based on independently influential factors of breast density. Calibration, AUC and Akaike information criteria (AIC) were used to assess predictive ability of the model. All data were analyzed by STATA version 15.0, SPSS version 23.0 and R version 3.5.3. *P* value $< .05$ was considered statistically significant.

3. Results

3.1. Baseline data

A total of 9412 women were identified from the Screening and Intervention Techniques for Breast and Cervical Cancer Project. The consort diagram is listed in eFigure 1. There were 377 (4.0%), 2164 (23.0%), 5749 (61.1%), and 1122 (11.9%) women in BI-RADS category A, B, C, and D, respectively. As age increased, the proportion of dense breast declined from 93.13% for women aged 40 to 44 years to 51.52% for women aged 65 to 69 years (Fig. 1A). The frequency of extremely dense breasts declined from 26.54% in women aged 40 to 44 years to 9.70% in women aged 65 to 69 years with an overall frequency of 12.03% among women aged 40 to 79 years.

The proportion of dense breast also declined with the increase of BMI: from 86.2% in women with BMI < 18.5 kg/m² to 58.2% in women with BMI ≥ 30.0 kg/m² (Fig. 1B). Next, the whole

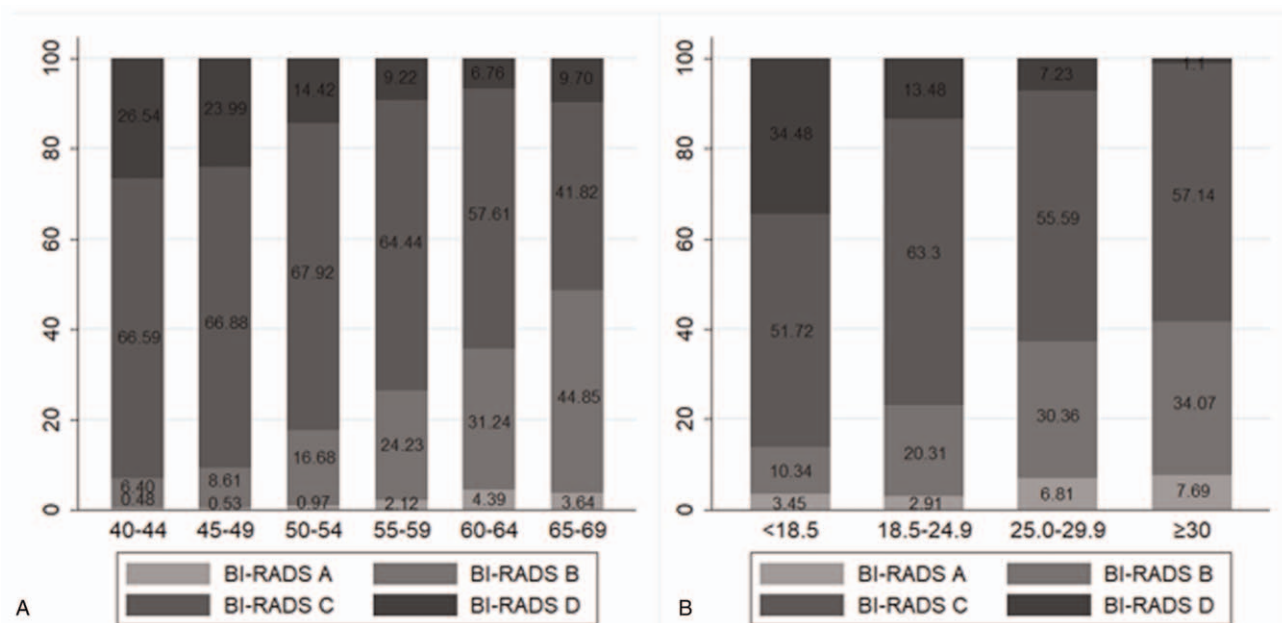


Figure 1. Distribution of breast density in different (A) age groups (B) BMI groups for all populations.

cohort was assigned to the training set and validation set at a ratio of 1:1. As listed in Table 1, there were no significant differences in the age ($P=.679$); age duration ($P=.329$); breast density ($P=.228$); marital status ($P=.795$); educational attainment ($P=.688$); breast cancer family history ($P=.465$); history of benign breast diseases ($P=.057$); age at menarche ($P=.503$); breastfeeding history ($P=.334$); number of births ($P=.773$); menopausal status ($P=.103$); menopausal age ($P=.790$); menopausal ways ($P=.518$); glucose ($P=.984$); BMI ($P=.387$); smoking status ($P=.609$); drinking status ($P=.497$); fruit intake ($P=.523$); vegetable intake ($P=.068$); meat intake ($P=.829$); exercise ($P=.095$) and living region ($P=.662$) between the groups. Women in validation group had a significantly higher rate of coarse grains intake (never: 11.0% vs 9.6%, $P=.030$).

3.2. Establishment and validation of the predictive model

Univariate analysis revealed that, age duration; educational attainment (tertiary), history of benign disease (yes); breastfeeding history (No); number of births (0); menopausal status (premenopausal); BMI ($<18.5 \text{ kg/m}^2$); glucose ($<6.1 \text{ mmol/L}$); smoking status (No); fruit intake; vegetable intake; coarse grains intake; living region (rural) were associated with dense breast tissue (Table 2). Consequently, these factors were included in the multivariate analysis. Multivariate analysis showed that age duration; tertiary educational attainment (tertiary vs primary or less: OR, 1.53; 95% CI, 1.12–2.08; $P \text{ value}=.008$), history of benign diseases (yes vs no: OR, 2.06; 95% CI, 1.47–2.90; $P \text{ value} <.001$); no breastfeeding history (yes vs no: OR, 0.78; 95% CI, 0.63–0.95; $P \text{ value}=.013$); premenopausal (postmenopausal vs premenopausal: OR, 0.42; 95% CI, 0.33–0.53; $P \text{ value} <.001$); and BMI ($<18.5 \text{ kg/m}^2$) were independent protective factors for dense breast (Table 2).

We further generated nomogram based on the results of multivariate analysis (Fig. 2). The scores of each factor are listed in (Supplementary Table S1, <http://links.lww.com/MD/G237>).

Next, we evaluated this prediction model in validation set. Calibrations of training and validation set both exhibited good fitness between predictive breast density and actual breast density (Fig. 3A and B). The AUC and AIC of training and validation set were 0.7158, 0.7139, and 4915.378, 4998.665, respectively, which suggested relative predictive accuracy (Table 3).

4. Discussion

In this study, we evaluated breast density distribution in Chinese woman and relevant influential factors. Age duration, educational attainment, history of breast benign diseases, menopausal status and BMI were identified as independent influential factors of breast density. Nomogram was further established based on these factors to predict the probability of dense breast. For example, for a woman aged 45 to 49 years, with tertiary education, and no history of benign breast diseases, nor history of breastfeeding, who is premenopausal and with a BMI of 18.5 to 24.9, the score for each factor was 87, 19, 0, 13, 48, and 39, respectively, totaling to a final score of 206, which could be interpreted as a high probability (nearly 0.90) of dense breasts. The AUC of logistic regression model based on influential factors was more than 0.7 in both training and validation set. Meanwhile the AIC of 2 sets were similar, which confirms the certain utility of the models established in this study. Compared with previous studies, this is the first study that used nomogram to predict breast density. This prediction model can more accurately evaluate breast density and offer further support for the detection of breast cancer.

Menopausal status and BMI have been shown to have impact on occurrence of breast cancer.^[16,17] Renehan et al conducted meta-analysis revealing that as BMI increased by 5 kg/m^2 , breast cancer risk declined approximately 8% (RR, 0.92; 95% CI, 0.88–0.97 ($P=.001$)) in premenopausal women.^[18] We also found 86.2% of dense breast in women with BMI $<18.5 \text{ kg/m}^2$; moreover, premenopausal women had higher proportion of dense breasts compared with postmenopausal women.

Table 1
Baseline data of study populations.

| Variables | Training set N = 4706 n (%) | Validation set N = 4706 n (%) | P value |
|-----------------------------------|-----------------------------------|-------------------------------------|---------|
| Age (yr) | | | .679 |
| Mean ± SD | 52 ± 6.41 | 52 ± 6.40 | |
| Age duration | | | .329 |
| 40–44 | 664 (14.1) | 697 (14.8) | |
| 45–49 | 1177 (25.0) | 1210 (25.7) | |
| 50–54 | 1161 (24.7) | 1107 (23.5) | |
| 55–59 | 1002 (21.3) | 1045 (22.2) | |
| 60–64 | 628 (13.3) | 582 (12.4) | |
| 64–69 | 74 (1.6) | 65 (1.4) | |
| BI-RADS | | | .228 |
| 1 | 207 (4.4) | 170 (3.6) | |
| 2 | 1087 (23.1) | 1077 (22.9) | |
| 3 | 2846 (60.5) | 2903 (61.7) | |
| 4 | 566 (12.0) | 556 (11.8) | |
| Marital status | | | .795 |
| Unmarried | 125 (2.7) | 140 (3.0) | |
| Married | 4412 (93.8) | 4399 (93.5) | |
| Divorce | 110 (2.3) | 112 (2.4) | |
| Widowed | 59 (1.3) | 55 (1.2) | |
| Educational attainment | | | .688 |
| Primary or less | 235 (5.0) | 243 (5.2) | |
| Secondary | 1459 (31.0) | 1422 (30.2) | |
| Tertiary | 3012 (64.0) | 3041 (64.6) | |
| Breast cancer family history | | | .465 |
| Yes | 178 (3.9) | 192 (4.4) | |
| No | 4376 (96.1) | 4368 (95.6) | |
| History of benign breast diseases | | | .057 |
| Yes | 296 (6.5) | 255 (5.6) | |
| No | 4227 (93.5) | 4306 (94.4) | |
| Age at menarche (yr) | | | .503 |
| ≤12 | 385 (8.2) | 403 (8.6) | |
| >12 | 4321 (91.8) | 4303 (91.4) | |
| Breastfeeding history | | | .334 |
| Yes | 3936 (83.6) | 3901 (82.9) | |
| No | 770 (16.4) | 805 (17.1) | |
| Number of birth | | | .773 |
| 0 | 1016 (21.6) | 1017 (21.6) | |
| 1 | 3251 (69.1) | 3230 (68.7) | |
| ≥2 | 439 (9.3) | 459 (9.8) | |
| Menopause status | | | .103 |
| Premenopausal | 2192 (46.6) | 2273 (48.3) | |
| Postmenopausal | 2514 (53.4) | 2433 (51.7) | |
| Menopause age | | | .790 |
| ≤50 | 1715 (68.2) | 1669 (68.6) | |
| >50 | 799 (31.8) | 765 (31.4) | |
| Menopause ways | | | .518 |
| Induced menopause | 90 (3.5) | 79 (3.2) | |
| Natural menopause | 2424 (96.5) | 2355 (96.8) | |
| Plasma glucose (mmol/L) | | | .984 |
| ≤6.1 | 3953 (88.1) | 3933 (88.0) | |
| >6.1 | 536 (11.9) | 534 (12.0) | |
| BMI (kg/m ²) | | | .387 |
| <18.5 | 59 (1.3) | 57 (1.2) | |
| 18.5–24.9 | 3343 (71.0) | 3393 (72.1) | |
| 25.0–29.9 | 1220 (25.9) | 1157 (24.6) | |
| ≥30.0 | 84 (1.8) | 98 (2.1) | |
| Smoke | | | .609 |
| Yes | 470 (10.0) | 485 (10.3) | |
| No | 4236 (90.0) | 4221 (89.7) | |
| Drink | | | .497 |

(continued)

Table 1
(continued).

| Variables | Training set N = 4706 n (%) | Validation set N = 4706 n (%) | P value |
|------------------------------|-----------------------------------|-------------------------------------|---------|
| Yes | 589 (12.5) | 611 (13.0) | |
| No | 4117 (87.5) | 4095 (87.0) | |
| Fruit intake (kg/wk) | | | .523 |
| Never | 155 (3.3) | 142 (3.0) | |
| ≤1.25 | 2782 (59.4) | 2829 (60.3) | |
| >1.25 | 1751 (37.4) | 1717 (36.6) | |
| Vegetable intake (kg/wk) | | | .068 |
| Never | 149 (3.2) | 112 (2.4) | |
| ≤2.5 | 2771 (59.2) | 2783 (59.5) | |
| >2.5 | 1761 (37.6) | 1780 (38.1) | |
| Meat intake (kg/wk) | | | .829 |
| Never | 164 (3.5) | 153 (3.3) | |
| ≤0.35 | 3696 (78.8) | 3698 (78.9) | |
| >0.35 | 832 (17.7) | 833 (17.8) | |
| Coarse grains intake (kg/wk) | | | .030 |
| Never | 514 (11.0) | 450 (9.6) | |
| ≤0.35 | 3707 (78.8) | 3807 (81.2) | |
| >0.35 | 465 (9.9) | 429 (9.2) | |
| Exercise (h/wk) | | | .095 |
| ≤1 | 4108 (87.3) | 4053 (86.1) | |
| >1 | 598 (12.7) | 653 (13.9) | |
| Region | | | .662 |
| Urban | 2658 (56.5) | 2679 (56.9) | |
| Rural | 2048 (43.5) | 2025 (43.1) | |

BI-RADS= the American College of Radiology's Breast Imaging Reporting and Data System, BMI = body mass index, SD = standard deviation.

Tertiary education was associated with dense breasts in the current study. We inferred that women receiving tertiary education were more likely to have late marriage and late childbirth. Dai et al proved that the age at marriage ≥ 30 years was related to dense breast in Chinese woman.^[12] Wong et al suggested that later age at first birth was also positively associated with dense breast among Asian populations.^[19] Due to failing to enquiry about the age at marriage and first childbirth, we could not identify which of these factors was the main influential factor of breast density. Further investigations are needed to evaluate the relationship between education attainment, age at marriage, age at first childbirth and breast density.

Lifestyle factors such as alcohol intake, smoking, diet, glucose and physical activity were not correlated with breast density. The relationship between smoking, drinking and breast density is still under debate. Previous studies have shown that smoking has anti-estrogen effects,^[20] while changes in serum estrogen levels can influence mammographic density,^[21] thus suggesting that smoking is correlated with lower breast density.^[22,23] However, other studies reported no such effect,^[12,22] which was consistent with our results. Drinking was also linked with breast cancer.^[24] It is possible that alcohol intake raises the levels of estrogen and progesterone in circulating blood, which increase breast density and further affect the occurrence of breast cancer.^[25] We did not find any effect of smoking and drinking on breast density, which might be due to the fact that we did not further stratify the amount of smoking and drinking, where relatively discrete quantities of smoke and alcohol intake might lead to negative outcomes.

Table 2
Univariate and multivariate analysis to identify interdependent influential factors of dense breast in training set.

| Variables | Univariate analysis | | Multivariate analysis | |
|-----------------------------------|---------------------|---------|-----------------------|---------|
| | OR (95% CI) | P value | OR (95% CI) | P value |
| Age duration | | | | |
| 40–44 | 1 | | 1 | |
| 45–49 | 0.68 (0.51–0.91) | .009 | 0.79 (0.59–1.06) | .120 |
| 50–54 | 0.38 (0.29–0.50) | <.001 | 0.71 (0.51–0.98) | .038 |
| 55–59 | 0.21 (0.16–0.28) | <.001 | 0.51 (0.36–0.73) | <.001 |
| 60–64 | 0.13 (0.10–0.18) | <.001 | 0.33 (0.23–0.48) | <.001 |
| 64–69 | 0.07 (0.04–1.12) | <.001 | 0.18 (0.10–0.32) | <.001 |
| Marital status | | | | |
| Unmarried | 1 | | | |
| Married | 0.91 (0.61–1.37) | .647 | | |
| Divorce | 1.02 (0.57–1.84) | .947 | | |
| Widowed | 0.58 (0.30–1.12) | .106 | | |
| Educational attainment | | | | |
| Primary or less | 1 | | 1 | |
| Secondary | 1.24 (0.94–1.66) | .135 | 1.34 (0.98–1.85) | .070 |
| Tertiary | 1.87 (1.42–2.46) | <.001 | 1.53 (1.12–2.08) | .008 |
| Breast cancer family history | | | | |
| No | 1 | | | |
| Yes | 1.32 (0.92–1.89) | .129 | | |
| History of benign breast diseases | | | | |
| No | 1 | | 1 | |
| Yes | 2.09 (1.52–2.87) | <.001 | 2.06 (1.47–2.90) | <.001 |
| Age at menarche (yr) | | | | |
| ≤12 | 1 | | | |
| >12 | 0.82 (0.64–1.04) | .101 | | |
| Breastfeeding history | | | | |
| No | 1 | | 1 | |
| Yes | 0.78 (0.65–0.93) | .007 | 0.78 (0.63–0.95) | .013 |
| Number of birth | | | | |
| 0 | 1 | | 1 | |
| 1 | 1.60 (1.37–1.86) | <.001 | 0.98 (0.82–1.16) | .785 |
| ≥2 | 1.13 (0.89–1.44) | .302 | 0.89 (0.68–1.15) | .365 |
| Menopause status | | | | |
| Premenopausal | 1 | | 1 | |
| Postmenopausal | 0.26 (0.23–0.30) | <.001 | 0.42 (0.33–0.53) | <.001 |
| Menopause age | | | | |
| ≤50 | 1 | | | |
| >50 | 1.15 (0.97–1.37) | .119 | | |
| Menopause ways | | | | |
| Induced menopause | 1 | | | |
| Natural menopause | 1.23 (0.80–1.88) | .345 | | |
| Plasma glucose (mmol/L) | | | | |
| ≤6.1 | 1 | | 1 | |
| >6.1 | 0.63 (0.52–0.76) | <.001 | 0.89 (0.73–1.10) | .290 |
| BMI (kg/m ²) | | | | |
| <18.5 | 1 | | 1 | |
| 18.5–24.9 | 0.65 (0.33–1.29) | .221 | 0.73 (0.36–1.50) | .390 |
| 25.0–29.9 | 0.35 (0.17–0.69) | .003 | 0.41 (0.20–0.83) | .014 |
| ≥30.0 | 0.32 (0.14–0.71) | .005 | 0.36 (0.15–0.86) | .020 |
| Smoke | | | | |
| No | 1 | | 1 | |
| Yes | 0.71 (0.58–0.87) | .001 | 0.87 (0.69–1.11) | .270 |
| Drink | | | | |
| No | 1 | | | |
| Yes | 0.96 (0.79–1.16) | .681 | | |
| Fruit intake (kg/wk) | | | | |
| Never | 1 | | | |
| ≤1.25 | 1.43 (1.02–2.01) | .038 | 0.90 (0.57–1.43) | .664 |
| >1.25 | 1.73 (1.22–2.44) | .002 | 1.02 (0.61–1.72) | .930 |
| Vegetable intake (kg/wk) | | | | |
| Never | 1 | | 1 | |

(continued)

Table 2
(continued).

| Variables | Univariate analysis | | Multivariate analysis | |
|------------------------------|---------------------|---------|-----------------------|---------|
| | OR (95% CI) | P value | OR (95% CI) | P value |
| ≤2.5 | 1.35 (0.95–1.92) | .091 | 1.27 (0.81–2.02) | .300 |
| >2.5 | 1.48 (1.04–2.12) | .029 | 1.43 (0.87–2.35) | .158 |
| Meat intake (kg/wk) | | | | |
| Never | 1 | | | |
| ≤0.35 | 1.17 (0.83–1.64) | .369 | | |
| >0.35 | 1.30 (0.90–1.87) | .161 | | |
| Coarse grains intake (kg/wk) | | | | |
| Never | 1 | | 1 | |
| ≤0.35 | 1.31 (1.07–1.60) | .008 | 1.22 (0.93–1.58) | .150 |
| >0.35 | 1.26 (0.95–1.65) | .104 | 0.95 (0.68–1.33) | .780 |
| Exercise (h/wk) | | | | |
| ≤1 | 1 | | | |
| >1 | 0.91 (0.75–1.10) | .307 | | |
| Region | | | | |
| Urban | 1 | | 1 | |
| Rural | 1.15 (1.01–1.31) | .033 | 0.88 (0.74–1.04) | .142 |

BI-RADS = the American College of Radiology's Breast Imaging Reporting and Data System, BMI = body mass index, OR = odds ratio.

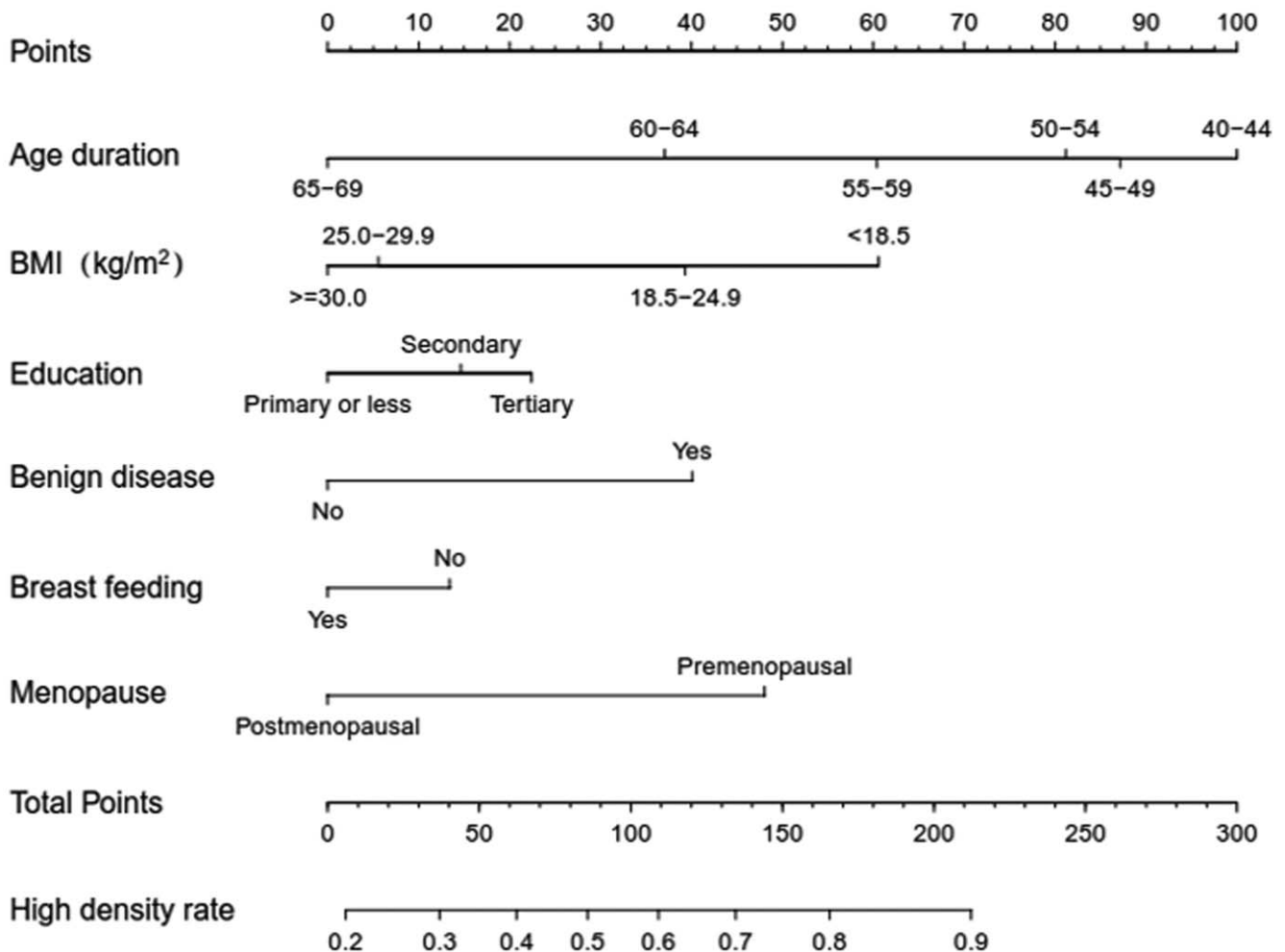


Figure 2. Nomogram of predicting dense breast in training set.

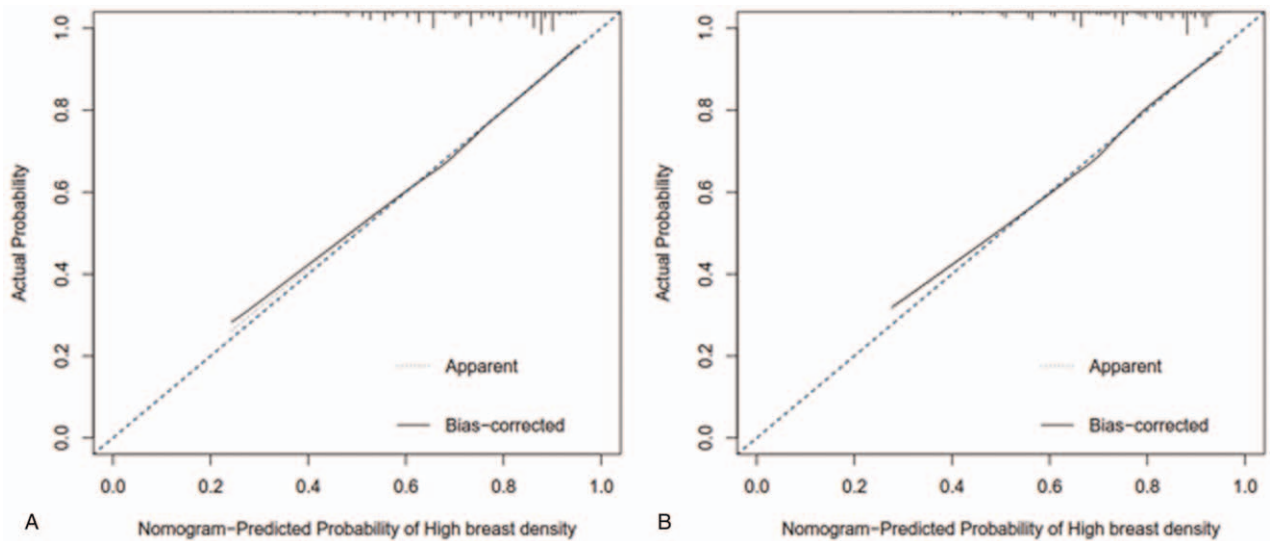


Figure 3. The calibration curves for predicting and actual breast density (A) training set, (B) internal validation set.

With regards to diet, vegetables intake was found to be positively associated with breast density in Vietnamese women.^[26] Increased consumption of vegetables and olive oil had inverse relationship with high breast density among Italian women.^[27] Fat, meat, vegetables, fruit and milk made no difference in breast density of Japanese woman.^[28] The fruits, vegetables and cereals intake were negatively correlated with breast density in American premenopausal women.^[27] The observed inconsistent effect of diet on breast density might be related to ethnicity, food type and cooking methods. Several studies have indicated that high levels of recent physical activity are associated with increased area-based percent density only among postmenopausal women.^[15,29] Physical activity reduced body fat and further decreased peripheral conversion of androgens to estrogens through the enzyme aromatase, thus decreasing free circulating estrogen.^[3] Yet, decreased body fat can result in an increase of breast density. Exercise to reduce breast cancer risk should not be explained by breast density independently.

A total of 72.90% dense breasts (BI-RADS category C and D) were observed in our study among woman aged 40 to 69. A Statistical Coordinating Center for the Breast Cancer Surveillance Consortium (BCSC) study included 764507 women aged ≤ 40 and 43.3% of United States women aged 40 to 74 years who had dense breasts.^[11] Meanwhile, a Netherlands breast screening program indicated that dense breast was found in 36.9% women aged 50 to 64 years.^[30] In addition, several

studies have suggested that mammographic sensitivity significantly decreased in women with dense breasts.^[6,30] Due to the high percentage of dense breast tissue, Western results of mammography screening may not be applicable to women with dense breast tissue. Wang et al^[15] have found that among young Chinese women, ultrasound is more sensitive than mammography for the diagnosis of breast cancer, especially in women with high breast density and relatively small breasts. Ohuchi and colleagues randomly assigned 72,998 women aged 40 to 49 years to undergo mammography and ultrasonography or mammography alone, identifying dense breast in 60% of examined women. Mammography and ultrasonography group had a higher specificity and earlier breast detection.^[31] Owing to the decreased screening performance in women with dense breast, breast tumors might be missed during screening. Therefore, the model established in this study can be used to guide screening techniques: for example, women with high probability of dense breast should be advised to first undergo ultrasound examination.

The NCCN guidelines (2018.V3) recommend that women over 25 years should have clinical examination every 1 to 3 years, while women over 40 years should undergo annual mammography examination or digital breast tomosynthesis if necessary. Previous studies have pointed out that dense breast is a risk factor for interval breast cancer.^[6,30] Mandelson et al selected interval cancer and screen-detected cancer from the Group Health Cooperative of Puget Sound. After adjusting for other factors, women with heterogeneously dense breasts had a three-fold greater risk of interval cancer (OR, 3.02; 95% CI, 1.84–4.95), and women with extremely dense breasts had a six-fold greater risk (OR, 6.14; 95% CI, 1.95–19.4) when compared to women with predominantly fatty breasts.^[6] Furthermore, Wanders and his team included 234 interval cancers and 667 screen-detected cancers, revealing that the rates of interval cancer were 0.7, 1.9, 2.9, and 4.4% for BI-RADS categories A-D, respectively.^[30] Consequently, the screening interval for women with dense breasts could be appropriately shortened. This predictive model could also guide the screening duration.

Table 3

Discriminatory ability of predictive model in training and validation set.

| | Training set N=4706 | Validation set N=4706 |
|---------------------|------------------------|--------------------------|
| Prediction accuracy | | |
| AUC | 0.7158 | 0.7139 |
| AIC | 4915.378 | 4998.665 |

AUC = area under curve, AIC = akaike information criterion.

There are several limitations in the current study. First, compared with other age duration, there were fewer women aged 66 to 70 years, which might have impact on the results. Second, we did not evaluate the prediction model in the external cohort. Third, hormonal use or hormonal replacement therapy was reported to be associated with breast density. However, since this issue was not included in the questionnaire, we were not able to evaluate this factor.

In conclusion, this study indicated that age duration, educational attainment, history of benign breast diseases, breastfeeding history, menopausal status and BMI were independent influential factors of breast density. Nomogram generated on the basis of these factors could relatively predict dense breasts, which then could be used to make recommendations for breast cancer screening techniques. Further large-scale studies are needed to validate reported findings.

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