Distribution of mammographic density and its influential factors among Chinese women

Hongji Dai,†1 Ye Yan,†1 Peishan Wang,1 Peifang Liu,2 Yali Cao,3 Li Xiong,3 Yahong Luo,4 Tie Pan,5 Xiangjun Ma,6 Jie Wang,6 Zhenhua Yang,1 Xueou Liu,1 Chuan Chen,1 Yubei Huang,1 Yi Li,7 Yaogang Wang,8 Xishan Hao,1,9 Zhaoxiang Ye7* and Kexin Chen1*

1Department of Epidemiology and Biostatistics and 2Department of Breast Imaging, Key Laboratory of Cancer Prevention and Therapy, Tianjin, Key Laboratory of Breast Cancer Prevention and Therapy, Ministry of Education, National Clinical Research Center for Cancer, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China, 3Prevention and Cure Center of Breast Disease, Third Hospital of Nanchang, Nanchang, China, 4Department of Medical Image and 5Department of Cancer Prevention and Control, Liaoning Cancer Institute and Hospital, Shenyang, China, 6Center for Breast Disease, Haidian Maternal and Child Health Hospital, Beijing, China, 7Department of Radiology, Key Laboratory of Cancer Prevention and Therapy, Tianjin, Key Laboratory of Breast Cancer Prevention and Therapy, Ministry of Education, National Clinical Research Center for Cancer, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China, 8Department of Health Statistics, School of Public Health, Tianjin Medical University, Tianjin, China and 9Chinese Anti-Cancer Association, Tianjin, China

*Corresponding authors. Kexin Chen, Department of Epidemiology and Biostatistics, Key Laboratory of Cancer Prevention and Therapy, Tianjin, Key Laboratory of Breast Cancer Prevention and Therapy, Ministry of Education, National Clinical Research Center for Cancer, Tianjin Medical University Cancer Institute and Hospital, Huanhu Xi Road, Tiyuan Bei, Hexi District, Tianjin 300060, P.R. China. E-mail: chenkexin@tjmu.edu.cn; Zhaoxiang Ye, Department of Radiology, Key Laboratory of Cancer Prevention and Therapy, Tianjin, Key Laboratory of Breast Cancer Prevention and Therapy, Ministry of Education, National Clinical Research Center for Cancer, Tianjin Medical University Cancer Institute and Hospital, Huanhu Xi Road, Tiyuan Bei, Hexi District, Tianjin 300060, P.R. China. E-mail: yezhaoxiang@163.com.

†These authors contributed equally to this work.

Accepted 4 February 2014

Abstract

Background: Mammographic density (MD) has not been systematically investigated among Chinese women. Breast cancer screening programmes provided detailed information on MD in a large number of asymptomatic women.

Methods: In the Multi-modality Independent Screening Trial (MIST), we estimated the association between MD and its influential factors using logistic regression, adjusting for age, body mass index (BMI) and study area. Differences between Chinese and other ethnic groups with respect to MD were also explored with adjustment for age and BMI.

Results: A total of 28 388 women aged 45 to 65 years, who had been screened by mammography, were enrolled in the study. Of these, 49.2% were categorized as having dense breasts (BI-RADS density 3 and 4) and 50.8% as fatty breasts (BI-RADS density 1 and 2).
Postmenopausal status [odds ratio (OR) = 0.66; 95% confidence interval (CI): 0.62–0.70] and higher number of live births (OR = 0.56; 95% CI: 0.46–0.68) were inversely associated with MD, whereas prior benign breast disease (OR = 1.48; 95% CI: 1.40–1.56) and later age at first birth (OR = 1.17; 95% CI: 1.08–1.27) were positively associated with MD. In comparison with the data from the Breast Cancer Surveillance Consortium, we found that women in MIST were more likely to have fatty breasts than Americans (from the Breast Cancer Surveillance Consortium) in the older age group (≥50 years) but more likely to have dense breasts in the younger age group (<50 years).

**Conclusions:** This study suggests that several risk factors for breast cancer were associated with breast density in Chinese women. Information on the determinants of mammographic density may provide valuable insights into breast cancer aetiology.

**Key words:** Mammography, breast density, hormone, reproduction, ethnicity

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**Key Messages**

- In the current literature, there were no data regarding breast density available for a representative sample of asymptomatic Chinese women.
- In this present study, we found that postmenopausal status and more parity were inversely associated with MD whereas prior breast benign disease and later age at first birth were positively associated with MD in Chinese women.
- We found the breasts of Chinese women were fattier than those of American women in the older age group, but the opposite was found in the younger age group.

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**Introduction**

Breast cancer is one of the most frequently diagnosed cancers among Chinese women. The incidence of female breast cancer was 47.64 per 100 000 in 2008, and the rate was 1.6 times higher in urban areas than in rural areas. Several genetic and environmental factors have been reported to be associated with an increased risk of breast cancer, including mutations in BRCA1 and BRCA2, family or personal history of breast cancer, advanced age, nulliparity, short lifetime duration of breastfeeding, early menarche and older age at menopause.

Breast density, a reflection of breast tissue composition, is reported to be associated with breast cancer risk, sometimes more strongly than most of the other risk factors for this disease. Higher breast density has repeatedly been shown to be associated with increased risk of breast cancer among White, African American and Asian American women, but there is currently no information available for Mainland Chinese women. Breast density was usually assessed by mammography and classified by Wolfe, Tabar and the Breast Imaging Reporting and Data System (BI-RADS) qualitatively. The BI-RADS classification system, developed by the American College of Radiology, ranks the amount of mammographically dense (white in image) relative to the total projected breast area into four consecutive categories. In recent years, the BI-RADS category has been widely used in clinical practice for diagnostic mammography and mammographic density (MD) measurement in China.

The percentage of dense breasts (BI-RADS density 3 and 4) in White women ranged from 35% to 61% at different ages, and Asian women were reported to have a higher proportion of dense breasts than other ethnicities. Since large-scale mammography screening has not previously been carried out in China, there were no data on breast density available for a representative sample of asymptomatic Chinese women. There was a need to evaluate differences in breast density between Chinese and other ethnicities.

Mammographic density varies among individuals. Age and body mass index (BMI) are strong influential factors for mammographic density. Several known breast cancer risk factors, including hormonal and reproductive factors, were reported to be associated with mammographic breast density. Analysis from genome-wide association studies (GWAS) suggested that mammographic density and breast cancer have a shared genetic basis. However, the magnitude of the influence of breast cancer risk factors on mammographic density in Chinese women is largely unknown.
The current study presents the distribution of mammographic density and examines the associations between known and suspected breast cancer risk factors and breast density among a large number of women attending the Multi-modality Independent Screening Trial (MIST) in China. To examine the possible ethnic differences in mammographic density, variations in densities between Chinese women and other ethnicities were also evaluated.

**Methods**

**Study population**

This study was approved by Tianjin Medical University Cancer Institute and Hospital (TMUCIH) Institutional Review Board. All participants provided written informed consent before breast cancer screening was performed. Study subjects were identified from a Multi-modality Independent Screening Trial (MIST), resident in one of the four geographical areas (Tianjin, Nanchang, Beijing and Shenyang) in China. The MIST study was initiated by the Chinese Anti-Cancer Association (CACA) and conducted between 1 July 2008 and 30 December 2010. In this trial, asymptomatic women aged 45–65 years, who had lived in their residential communities for ≥3 years, and had not previously been diagnosed with breast cancer, were invited to the screening according to a cluster sampling. The participation rate was 85.13%. Eligible women were examined by clinical breast examination (CBE), mammography (MAM) and breast ultrasound (BUS). A blinding method was used to keep each screening test independent by not informing the examiners of each preceding result prior to their performing successive tests. All patients who were determined by their primary physicians to have a lesion considered suspicious or highly suggestive of a malignancy with any modality, were scheduled for a biopsy. Participants in MIST were followed up annually to validate the true negative results.

Women with data on both digitized images and mammographic density measurements were included in this study. Among the 34 964 eligible women in the MIST trial, 6357 (18.2%) lacked mammographic density information and 219 (0.6%) were outside the age range of 45–65 years. A total of 36 719 records were selected from the database for this comparison.

**Questionnaire data and variable definitions**

A face-to-face interview questionnaire collected information regarding demographical data, hormonal and reproductive factors, breast disease history, family history of breast cancer, behaviour patterns and social/psychological characteristics. Age at screening, body weight (kg) and height (m) were acquired by personal report. Body mass index (BMI) was calculated as the weight divided by the height squared (kg/m²).

Items related to hormonal and reproductive factors included age at menarche, menopausal status, number of live births, age at first birth, hormone use and ever suffered from dysmenorrhoea. Women who reported no menstruation during the past 12 months were considered postmenopausal. Ages at first birth were grouped using a cutoff of 30 and nulliparous women were excluded from the analysis. Dysmenorrhoea refers to women who had ever suffered from pain during menstruation that had disturbed their daily activities. Hormone use included estrogens alone and estrogens in combination with a progestin for treatment of menopausal syndrome. Breast disease history only included benign breast disease such as hyperplasia and fibroadenoma. Family history of breast cancer was defined as breast cancer occurring in first-degree relatives (mother, sisters or daughters). Ever smoking was defined as at least one cigarette per day for ≥3 months. Ever having drunk alcohol was defined as at least 50 ml liquor per week.

Variation in the distribution of mammographic density by ethnicity was compared between Chinese women from the MIST study and American women from the Breast Cancer Surveillance Consortium (BCSC) in the same age and BMI groups. A dataset with 280 660 records was obtained from BCSC Research Resource (http://breastscreening.cancer.gov/). We included women (non-Hispanic White, African American and Asian/Pacific Islanders) aged 45 to 64 years with no missing data on breast density category and BMI. We also extracted another four variables (i.e. menopausal status, age at first birth, family history of breast cancer, and hormone use) for adjustment. As a result, a total of 36 719 records were selected from the database for this comparison.

**Mammography performance and assessment of breast density**

During mammography screening, craniocaudal (CC) and mediolateral oblique (MLO) views were used to calculate density measures. Bilateral mammograms were obtained using a full-field digital mammography system (Senographe 2000D, General Electric, and Selenia Digital Mammography, Hologic). Qualitative assessment was according to the BI-RADS coding system, with category 1 indicating breast tissue that was less than 25% glandular or almost entirely fat; category 2, breast tissue that was approximately 25–50% glandular or scattered...
fibroglandular; category 3, breast tissue that was 51–75% glandular or heterogeneously dense; and category 4, breast tissue that was more than 75% glandular or extremely dense. The density assessments were performed by radiologists who had been trained by Z.Y. before the study began at each screening site. The readers were blinded to all subject characteristics.

Statistical analysis
In order to increase the degree of certainty about the density measurement, MD was analysed as a dichotomous outcome, by comparing women with dense breasts (BI-RADS category 3 and 4) with those with fatty breasts (BI-RADS category 1 and 2). Kappa coefficient (κ) was calculated to generate the agreement index between readers.

The association between breast density and breast cancer risk, and the association between breast density and potential breast cancer risk factors, were measured by unconditional logistic regression, controlling for other factors including age at screening (continuous), BMI (continuous), and study area (categorical). Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for the association between mammographic patterns and the selected factors. In addition, we reported the associations between MD and risk factors in different study areas and performed a meta-analysis to combine the results from these regions. Random effect model was used when there was heterogeneity among the four regional groups and fixed effect model when there was no heterogeneity among these groups. The I² statistic was calculated to determine the degree of heterogeneity.

Variation in the distribution of mammographic density by ethnicity was compared among Chinese, White, Asian American and African American women, stratified by age and adjusted for BMI. Stratified analyses were done within each age group (45–49, 50–54, 55–59 and 60–64 years) and BMI group (<25 and ≥25 kg/m²). Unconditional logistic regression was performed for dense breasts (BI-RADS density 3 and 4) relative to fatty breasts (BI-RADS density 1 and 2) and adjusted OR with 95% CI was calculated.

All statistical tests were two-sided. Analyses were performed using the SPSS 16.0 package. Meta-analysis was conducted with software Review Manager (version 5.1).

Quality control
For quality control, all assessments of breast density were double-checked at primary screening sites. A subsample of films (N=6167) was sent to TMUCHI and re-read by two radiologists (Y.L. and Z.Y.) throughout the entire study. A concordance analysis was undertaken to assess intra-observer and inter-observer agreement between the first and the second readings. Average intra-observer agreement was substantial (κ = 0.74 on a four-grade scale) and even higher (κ = 0.92 on a two-grade scale (1–2 and 3–4)). Average inter-observer agreement was moderate (κ = 0.49 on a four-grade scale) and substantial (κ = 0.64 on a two-grade scale).

Results
Baseline characteristics of the study participants
In each study area, the distributions of age and BMI were comparable between participants who were included in this analysis and those who were not (data not shown). Demographic characteristics of the study participants in the four geographical areas are shown in Table 1. For the whole study population, the mean age at screening was 51.81 (±5.20) years, and 44.4% of the participants were premenopausal. Among the women included, 66.2% had more than 9 years of education; smokers (2.5%) and alcohol drinkers (4.0%) were rare. The mean BMI was 23.60 (±3.03) kg/m². Nearly 3% of the women reported a family history of breast cancer, and 34.3% reported having ever had one or more benign breast diseases. About 2% of the participants reported ever having used hormones. Significant differences (P < 0.001) were found among the four areas for each variable mentioned above due to the large number of participants included in the analysis.

Mammographic density distribution and breast cancer risk
Overall, women in this study had a large percentage of ‘scattered fibroglandular’ (38.4%) and ‘heterogeneously dense’ breasts (40.6%), compared with a minority of ‘almost entirely fat’ (12.4%) and ‘extremely dense’ breasts (8.6%). The proportion of mammographically dense breasts decreased with age (P_trend < 0.001) and BMI (P_trend < 0.001) (Supplementary Table 1, available as Supplementary data at IJE online).

Distribution of mammographic density was compared between the screening-detected cancer cases (N=86) and the healthy women (N=28302) in the screening. Compared with women in category 1, women in category 2 (OR=2.06; 95% CI: 0.95–4.48), category 3 (OR=2.06; 95% CI: 0.90–4.68) and category 4 (OR=1.45; 95% CI: 0.41–5.15) had increased, but not statistically significant, risk of breast cancer (Table 2). When compared within specific age and BMI groups, this result did not change substantially (data not shown).
Factors associated with mammographic density

Reproductive and hormonal factors and potential risk factors for breast cancer were compared between women with dense breasts and those with fatty breasts. Generally, postmenopausal status (OR = 0.66; 95% CI: 0.62–0.70) and more live births (OR = 0.56; 95% CI: 0.46–0.68) for number ≥2 and OR = 0.82; 95% CI: 0.68–0.98 for number = 1, compared with number = 0) were negatively associated with MD. Prior benign breast disease (OR = 1.48; 95% CI: 1.40–1.56) and later age at first birth (OR = 1.17; 95% CI: 1.08–1.27 for age >30 compared with age <30 years) were positively associated with MD (Table 3).

Forest plots from meta-analysis for the association between mammographic density and its influential factors by study areas showed that later age at menarche (OR = 0.85; 95% CI: 0.79–0.92), postmenopausal status (OR = 0.43; 95% CI: 0.30–0.62) and more live births (OR = 0.30; 95% CI: 0.19–0.46) were negatively associated with MD, whereas prior benign breast disease (OR = 1.57; 95% CI: 1.38–1.78) was positively associated with MD (Figure 1). There is significant heterogeneity for menopausal status, number of live births, age at first birth and prior breast benign disease among the four study areas.

Table 1. Baseline characteristics of the study participants in four areas in China

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nanchang (N = 9008)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Marital status</td>
<td>Married</td>
</tr>
<tr>
<td></td>
<td>Married</td>
</tr>
<tr>
<td>Education duration</td>
<td>9 years</td>
</tr>
<tr>
<td></td>
<td>&gt;9 years</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>Pre</td>
</tr>
<tr>
<td></td>
<td>Post</td>
</tr>
<tr>
<td>Unknown</td>
<td>30 (0.3)</td>
</tr>
<tr>
<td>Family income (per month, RMB)</td>
<td>&lt;1000</td>
</tr>
<tr>
<td></td>
<td>1000–1999</td>
</tr>
<tr>
<td></td>
<td>2000–2999</td>
</tr>
<tr>
<td></td>
<td>3000–4999</td>
</tr>
<tr>
<td></td>
<td>≥5000</td>
</tr>
<tr>
<td>Unknown</td>
<td>37 (0.4)</td>
</tr>
<tr>
<td>Medical expenditure</td>
<td>Self-paying</td>
</tr>
<tr>
<td></td>
<td>Medical insurance</td>
</tr>
<tr>
<td></td>
<td>Rural cooperative medical care</td>
</tr>
<tr>
<td></td>
<td>Free medical service</td>
</tr>
<tr>
<td>Unknown</td>
<td>22 (0.2)</td>
</tr>
</tbody>
</table>

**Table 2. Distribution of mammographic density of screen-detected cancer cases and the healthy women**

<table>
<thead>
<tr>
<th>BI-RADS density category</th>
<th>Breast cancer N (%)</th>
<th>No breast cancer N (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>8 (9.3)</td>
<td>3518 (12.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Category 2</td>
<td>40 (46.5)</td>
<td>10868 (38.4)</td>
<td>2.06 (0.95, 4.48)</td>
</tr>
<tr>
<td>Category 3</td>
<td>34 (39.5)</td>
<td>11483 (40.6)</td>
<td>2.06 (0.90, 4.68)</td>
</tr>
<tr>
<td>Category 4</td>
<td>4 (4.7)</td>
<td>2433 (8.6)</td>
<td>1.45 (0.41, 5.15)</td>
</tr>
</tbody>
</table>

**P trend** 0.353

*Odds ratio ratio adjusted by age, BMI and study area for breast cancer relative to no breast cancer.

**Factors associated with mammographic density**

Reproductive and hormonal factors and potential risk factors for breast cancer were compared between women with dense breasts and those with fatty breasts. Generally, postmenopausal status (OR = 0.66; 95% CI: 0.62–0.70) and more live births (OR = 0.56; 95% CI: 0.46–0.68) for number ≥2 and OR = 0.82; 95% CI: 0.68–0.98 for number = 1, compared with number = 0) were negatively associated with MD. Prior benign breast disease (OR = 1.48; 95% CI: 1.40–1.56) and later age at first birth (OR = 1.17; 95% CI: 1.08–1.27 for age ≥30 compared with age <30 years) were positively associated with MD (Table 3).

Forest plots from meta-analysis for the association between mammographic density and its influential factors by study areas showed that later age at menarche (OR = 0.85; 95% CI: 0.79–0.92), postmenopausal status (OR = 0.43; 95% CI: 0.30–0.62) and more live births (OR = 0.30; 95% CI: 0.19–0.46) were negatively associated with MD, whereas prior benign breast disease (OR = 1.57; 95% CI: 1.38–1.78) was positively associated with MD (Figure 1). There is significant heterogeneity for menopausal status, number of live births, age at first birth and prior breast benign disease among the four study areas.
Variation in the distribution of mammographic density by ethnicity

Data of women aged 45–64 years in the BCSC were used for this comparison. Baseline characteristics of Chinese women and American women are shown in Supplementary Table 2, available as Supplementary data at IJE online.

Mammographic density distribution of Chinese women within the ages of 45 to 64 years was compared with that of women in USA, and significant differences were found in Whites (P < 0.001), Asian Americans (P < 0.001) and African Americans (P < 0.001). Overall, dense breasts (BI-RADS density 3 and 4) accounted for 49.49% in Chinese, 48.77% in Whites, 61.66% in Asian Americans and 46.15% in African Americans. When stratified by age, Chinese women have denser breasts than American women only in those aged <50 years. In other age groups, the results were the opposite (Table 4). When further compared with different races, breasts of Chinese women were denser than those of Whites in age <50 group but fattier than those of other women in age ≥50 group. Chinese women have fattier breasts compared with Asian Americans and African Americans except in young women in high BMI groups (Supplementary Tables 3–5, available as Supplementary data at IJE online).

Since large differences in MD between Chinese women and Asian American women were found, we compared Chinese women participating in MIST in the four study areas separately. All women living in Nanchang, Tianjin and Shenyang and older women in Beijing had fattier breasts compared with Asian Americans (Supplementary...
(a) Forest plot for the association between age at menarche (age>12 compared with age≤12) and mammographic density

(b) Forest plot for the association between menopausal status (post-menopause compared with pre-menopause) and mammographic density

(c) Forest plot for the association between number of live birth (number of live births≥2 compared with number of live births=0) and mammographic density

(d) Forest plot for the association between age at first birth (age≥30 compared with age<30) and mammographic density

Figure 1. Forest plot of overall analysis for the association between mammographic density and its influential factors by study areas. (M-H: Mantel-Haenszel)

(Continued)
(e) Forest plot for the association between hormone use (ever use compared with never use) and mammographic density

(f) Forest plot for the association between dysmenorrhea (ever compared with never) and mammographic density

(g) Forest plot for the association between family history of breast cancer (yes compared with no) and mammographic density

(h) Forest plot for the association between prior breast benign disease (yes compared with no) and mammographic density

Figure 1. Continued.
Denser breasts (BI-RADS density 3 and 4) were only found in women in Beijing with ages between 45 and 49 years and BMIs $/C2125$ kg/m$^2$ (Supplementary Table 9, available as Supplementary data at IJE online).

Discussion

In the present study, we examined the distribution of the mammographic density in Chinese populations and assessed its associations with several potential breast cancer risk factors. In the analysis, we found differences in mammographic density distribution between women in China and women in the USA. This is the first time we have been able to systematically determine the potential role of mammographic density, a recognized risk factor among Western women, in breast cancer risk among women living in Mainland China.

Although it has been reported that mammographic density is a strong risk factor for breast cancer, we did not find this association among women participating in the MIST. This may be due to the small numbers of cancer

### Table 4. Mammographic density distribution between Chinese and American women

<table>
<thead>
<tr>
<th>Race</th>
<th>Age &lt; 50, N (%)</th>
<th>Age ≥ 50, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fatty</td>
<td>Dense</td>
</tr>
<tr>
<td>Chinese</td>
<td>595 (5.2)</td>
<td>10754 (94.8)</td>
</tr>
<tr>
<td>White</td>
<td>936 (13.1)</td>
<td>6225 (86.9)</td>
</tr>
<tr>
<td>Asian American</td>
<td>41 (4.1)</td>
<td>961 (95.9)</td>
</tr>
<tr>
<td>African American</td>
<td>98 (10.2)</td>
<td>862 (89.8)</td>
</tr>
</tbody>
</table>

$^a$Odds ratio adjusted by BMI for dense breasts (BI-RADS 2 to 4) vs (BI-RADS 1).

$^*$ $P < 0.001$.

Tables 6–8, available as Supplementary data at IJE online. Denser breasts (BI-RADS density 3 and 4) were only found in women in Beijing with ages between 45 and 49 years and BMIs $\geq 25$ kg/m$^2$ (Supplementary Table 9, available as Supplementary data at IJE online).
cases detected through screening, and needs further study with larger sample sizes to validate. The association of mammographic density with most hormone-related factors was consistent with that in previous reports,24–26 supporting the hypothesis that mammographic density represents accumulated exposure to risk factors that may stimulate growth of breast cells and cause breast cancer. Hormone use has been thought to increase breast density, though no associations were found in this study when adjusting for age, BMI and study area. This may be due to the scarcity of hormone users among the participating women. Older age, BMI, parity and menopause are reported to be associated with reductions in the epithelial and stoma tissues in the breasts, with an increase in fat. These histological changes are reflected in the mammographic images, suggesting that the mammographic density can be used for monitoring breast cancer risk.

Smoking and alcohol drinking habits are inconsistently associated with mammographic density. Tobacco smoke could exert an anti-oestrogenic effect on breast tissue and could have a negative relation to mammographic density,27–30 although no association was reported in other studies.31,32 Alcohol consumption may have an influence on breast neoplasm formation. It remains unclear whether alcohol consumption increases the mammographic density, with both positive associations33–35 and null association36 reported previously. Our study did not find an association between alcohol consumption and smoking habits and mammographic density.

We did not find an increased mammographic density in familial subjects of the overall participants, as has been reported in some other studies. For example, it was reported that women with higher breast density were more likely to have a first-degree relative who had breast cancer than women with lower breast density,37,38 suggesting an association that may be the result of shared genetic and/or environmental factors among family members, which may affect breast density and breast cancer risk. Our negative result may be due to the low percentage of family history of breast cancer among Chinese women, possibly due to population difference.

Therefore, we compared population difference related to mammographic density between Chinese and Whites, African Americans and Asian/Pacific islanders of inhabitants in the USA. Comparison with previously published data may be biased, due to different MD category26,39 or unmatched age and BMI.7,40–43 Because a large number of our study participants were less than 50 years old, and in order to avoid losing information, we used data of US women from the BCSC website to acquire a comparative narrow age range. By comparison, we found that the density categories of Chinese women were fatter than those of American women in the older age group, which is not consistent with what has been reported in the literature, in which the proportion of women with extremely dense breasts was the greatest among Asian women in all age ranges.7 In recent decades, greatly influenced by the government ‘one-child’ policy, reproduction behaviour in China has changed significantly.44 As a result, the decreased number of childbirths, which are known to be associated with high mammographic density,45 have predominantly impacted on younger Chinese women. This may explain the age discrepancy on mammographic density we have observed. The discrepancy of mammographic density between Mainland Chinese women and Chinese women living abroad is probably due to the different origins of population, which still need future investigations.

Limitations of this study could result from visual estimation of mammographic density. Though characterization of breast density by mammography has several limitations,4 none of the other established means of measuring mammographic density is entirely satisfactory, because all are time consuming or subjective.46 Visual scales of mammographic density using BI-RADS were reported to be highly reproducible and concordant when appropriate training is provided.46 Our data were collected from well-established hospitals in four cities in China, utilizing the skills of senior radiologists, although not representing all parts of China. There may exist a large difference in diagnosis between radiologists in China and the USA, which also needs further validation.

Supplementary Data
Supplementary data are available at IJE online

Funding
This work was supported partially by the National Natural Science Foundation of China [Grant 81172762], programme for Changjiang Scholars and Innovative Research Team in University in China [Grant IRT1076], National Key Scientific and Technological Project [Grants 2011ZX09307–701–14 and 2014BAI09B09], Tianjin Science and Technology Committee Foundation [Grants 09ZCDZSF04700, 09ZCDZSF04800, 11ZCGYSY02200, 12ZCDZSY15500 and 12ZCDZSY16000] and the Special fund on National Public Health [200902002–2].

Data collection for BCSC’s work was supported by a NCIC-funded Breast Cancer Surveillance Consortium [U01CA63740, U01CA63742, U01CA80676, U01CA80682, U01CA63736, U01CA70013, U01CA69976, U01CA63731 and U01CA70040].

Acknowledgements
We thank the local doctors and the women who participated in our study from Tianjin, Liaoning, Beijing and Jiangxi provinces, as well as the Ministry of Health P.R China and the Chinese Anti-Cancer
Association for their generous support. We also thank Professors Wei Zhang and Qingyi Wei from University of Texas MD Anderson Cancer Center for editing this manuscript.

Conflict of interest: None declared.

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