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Distribution of mammographic density and its influential factors among Chinese women

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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 ($\geq$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

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.

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.[1] 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.[2,3]

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.[4] Higher breast density has repeatedly been shown to be associated with increased risk of breast cancer among White, African American and Asian American women,[5–8] but there is currently no information available for Mainland Chinese women. Breast density was usually assessed by mammography and classified by Wolfe,[9] Tabar[10] and the Breast Imaging Reporting and Data System (BI-RADS)[11] 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,[7] amd Asian women were reported to have a higher proportion of dense breasts than other ethnicities.[7,12,13] 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.[14–16] Several known breast cancer risk factors, including hormonal and reproductive factors, were reported to be associated with mammographic breast density.[17–20] Analysis from genome-wide association studies (GWAS) suggested that mammographic density and breast cancer have a shared genetic basis.[21,22] 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 $\geq$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. As a result, mammographic density with a BI-RADS density category was recorded for 28 388 (81.2%) of the screening subjects.

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/m^2).

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 $\geq$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)[23] 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,[11] 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 I^2 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 $\geq 25\,kg/m^2$). 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 TMUCIH 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 ($\kappa = 0.74$ on a four-grade scale) and even higher [$\kappa = 0.92$ on a two-grade scale (1–2 and 3–4)]. Average inter-observer agreement was moderate ($\kappa = 0.49$ on a four-grade scale) and substantial ($\kappa = 0.64$ 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 ($\pm$5.20) years, and 44.4% of the participants were premenopausal. Among the women included, 66.2% had more than 9 years of education; smokers (2.5%) and alcohol drinkers (4.0%) were rare. The mean BMI was 23.60 ($\pm$3.03) kg/m^2. Nearly 3% of the women reported a family history of breast cancer, and 34.3% reported having ever had one or more benign breast diseases. About 2% of the participants reported ever having used hormones. Significant differences ($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 ($N = 28\,302$) 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).

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

Characteristic	Area				
	Nanchang (*N* = 9008)	Tianjin (*N* = 7052)	Shenyang (*N* = 6433)	Beijing (*N* = 5895)	Total (*N* = 28388)
Age (years)					
Mean ± SD	51.4 ± 5.2	53.4 ± 5.3	52.1 ± 5.1	50.2 ± 4.7	51.8 ± 5.2
BMI (kg/m^2)					
Mean ± SD	22.7 ± 2.9	24.3 ± 3.2	23.6 ± 2.9	24.1 ± 2.9	23.6 ± 3.0
Marriage age (years)					
Mean ± SD	24.3 ± 3.1	26.6 ± 3.7	25.7 ± 3.5	25.3 ± 4.4	25.4 ± 3.7
Marital status					
Married	8618 (95.7)	6696 (95.0)	5997 (93.2)	5599 (95.0)	26910 (94.8)
Sgl/div/sep/wid[a]	377 (4.2)	319 (4.5)	436 (6.8)	242 (4.1)	1374 (4.8)
Unknown	13 (0.1)	37 (0.5)	0 (0.0)	54 (0.9)	104 (0.4)
Menopausal status					
Pre	4580 (50.8)	2054 (29.1)	2564 (39.9)	3403 (57.7)	12601 (44.4)
Post	4398 (48.8)	4822 (68.4)	3868 (60.1)	2385 (40.5)	15473 (54.5)
Unknown	30 (0.3)	176 (2.5)	1 (0.0)	107 (1.8)	314 (1.1)
Education duration					
≤9 years	3339 (37.1)	2721 (38.6)	2163 (33.6)	1230 (20.9)	9453 (33.3)
>9 years	5632 (62.5)	4300 (61.0)	4270 (66.4)	4605 (78.1)	18807 (66.2)
Unknown	37 (0.4)	31 (0.4)	0 (0.0)	60 (1.0)	128 (0.5)
Family income (per month, RMB)					
<1000	735 (8.2)	527 (7.5)	751 (11.7)	119 (2.0)	2132 (7.5)
1000-1999	2284 (25.4)	1641 (23.3)	1548 (24.1)	387 (6.6)	5860 (20.6)
2000-2999	2595 (28.8)	2173 (30.8)	1482 (23.0)	1194 (20.3)	7444 (26.2)
3000-4999	2304 (25.6)	1656 (23.5)	1584 (24.6)	2256 (38.3)	7800 (27.5)
≥5000	1065 (11.8)	799 (11.3)	1068 (16.6)	1680 (28.5)	4612 (16.2)
Unknown	25 (0.3)	256 (3.6)	0 (0.0)	259 (4.4)	540 (1.9)
Medical expenditure					
Self-paying	2577 (28.6)	484 (6.9)	473 (7.4)	435 (7.4)	3969 (14.0)
Medical insurance	4764 (52.9)	6015 (85.3)	5491 (85.4)	3719 (63.1)	19989 (70.4)
Rural cooperative medical care	88 (1.0)	13 (0.2)	23 (0.4)	305 (5.2)	429 (1.5)
Free medical service	1557 (17.3)	368 (5.2)	446 (6.9)	1279 (21.7)	3650 (12.9)
Unknown	22 (0.2)	172 (2.4)	0 (0.0)	157 (2.7)	351 (1.2)

SD, standard deviation.
[a]Single, divorced, separated or widowed.

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

BI-RADs density category	Breast cancer *N* (%)	No breast cancer *N* (%)	OR (95% CI)[a]
Category 1	8 (9.3)	3518 (12.4)	1.00
Category 2	40 (46.5)	10868 (38.4)	2.06 (0.95, 4.48)
Category 3	34 (39.5)	11483 (40.6)	2.06 (0.90, 4.68)
Category 4	4 (4.7)	2433 (8.6)	1.45 (0.41, 5.15)
P trend			0.353

[a]Odds 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.

Table 3. Association of mammographic density and potential breast cancer risk factors

Variables	Density category, *N* (%)				OR (95% CI)[a]
	① <25%	② 25-50%	③ 51-75%	④ >75%	
Age at menarche, years					
≤12	323 (9.7)	1139 (34.1)	1536 (45.9)	346 (10.3)	1.00
>12	3193 (12.8)	9739 (39.0)	9939 (39.8)	2088 (8.4)	0.97 (0.89, 1.05)
Menopause					
Pre	733 (5.8)	3873 (30.7)	6333 (50.3)	1662 (13.2)	1.00
Post	2775 (17.9)	6952 (44.9)	5019 (32.4)	727 (4.7)	0.66 (0.62, 0.70)*
Number of live births					
0	31 (5.6)	199 (36.1)	256 (46.5)	65 (11.8)	1.00
1	2097 (9.3)	8437 (37.5)	9785 (43.5)	2181 (9.7)	0.82 (0.68, 0.98)**
≥2	1254 (26.7)	2068 (44.1)	1222 (26.1)	145 (3.1)	0.56 (0.46, 0.68)*
Age at first birth, years					
<30	3099 (12.6)	9391 (38.3)	9902 (40.4)	2111 (8.6)	1.00
≥30	351 (11.6)	1211 (40.0)	1230 (40.7)	232 (7.7)	1.17 (1.08, 1.27)*
Hormone use					
Never	3291 (12.6)	10059 (38.6)	10506 (40.3)	2235 (8.6)	1.00
Ever	235 (10.2)	849 (37.0)	1010 (44.0)	202 (8.8)	1.01 (0.92, 1.12)
Dysmenorrhoea					
Never	2532 (12.7)	7568 (38.1)	8035 (40.5)	1728 (8.7)	1.00
Ever	967 (11.7)	3248 (39.3)	3355 (40.6)	689 (8.3)	1.01 (0.96, 1.07)
Family history of breast cancer					
No	3447 (12.5)	10584 (38.4)	11189 (40.6)	2362 (8.6)	1.00
Yes	79 (9.8)	324 (40.2)	328 (40.7)	75 (9.3)	1.09 (0.93, 1.27)
Prior breast benign disease					
No	2693 (14.8)	7432 (40.7)	6919 (37.9)	1199 (6.6)	1.00
Yes	799 (8.2)	3306 (33.9)	4429 (45.4)	1212 (12.4)	1.48 (1.40, 1.56)*
Ever smoking					
No	3397 (12.5)	10502 (38.5)	11026 (40.4)	2335 (8.6)	1.00
Yes	94 (13.4)	244 (34.8)	296 (42.2)	67 (9.6)	1.11 (0.94, 1.31)
Ever alcohol drinking					
No	3369 (12.6)	10244 (38.4)	10780 (40.4)	2272 (8.5)	1.00
Yes	102 (9.0)	423 (37.5)	485 (43.0)	118 (10.5)	1.06 (0.93, 1.21)

[a]Odds ratio adjusted by age, BMI and study area for dense breasts (BI-RADS 3 + 4) relative to fatty breasts (BI-RADS 1 + 2).
*$P < 0.001$.
**$P = 0.033$.

Variation in the distribution of mammographic density by ethnicity

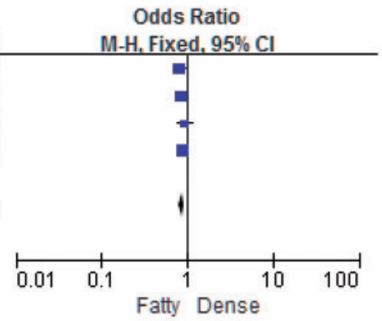
Data of women aged 45–64 years in the BCSC were used for this comparison. Baseline characteristics of Chinese women and American women are shown in Supplementary Table 2, available as Supplementary data at *IJE* online. Mammographic density distribution of Chinese women within the ages of 45 to 64 years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

Study or Subgroup	Dense Events	Dense Total	Fatty Events	Fatty Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Beijing	3328	4100	1487	1765	26.7%	0.81 [0.69–0.94]
Nanchang	3436	3829	4708	5163	28.1%	0.84 [0.73–0.97]
Shenyang	2209	2383	3773	4048	13.9%	0.93 [0.76–1.13]
Tianjin	3054	3597	2964	3418	31.3%	0.86 [0.75–0.99]
Total (95% CI)		**13909**		**14394**	**100.0%**	**0.85 [0.79–0.92]**
Total events	12027		12932			

Heterogeneity: Chi² = 1.24, df = 3 (P = 0.74); I² = 0%

Test for overall effect: Z = 4.19 (P < 0.0001)

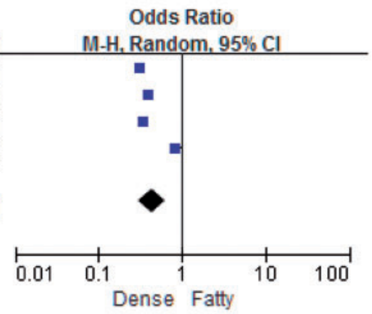


(**a**) Forest plot for the association between age at menarche (age>12 compared with age≤12) and mammographic density

Study or Subgroup	Dense Events	Dense Total	Fatty Events	Fatty Total	Weight	Odds Ratio M-H, Random, 95% CI
Beijing	1321	4038	1064	1750	25.0%	0.31 [0.28–0.35]
Nanchang	1365	3821	3033	5157	25.2%	0.39 [0.36–0.42]
Shenyang	1049	2384	2819	4048	25.1%	0.34 [0.31–0.38]
Tianjin	2011	2498	2811	3378	24.8%	0.83 [0.73–0.95]
Total (95% CI)		**12741**		**14333**	**100.0%**	**0.43 [0.30–0.62]**
Total events	5746		9727			

Heterogeneity: Tau² = 0.14; Chi² = 140.54, df = 3 (P < 0.00001); I² = 98%

Test for overall effect: Z = 4.45 (P < 0.00001)

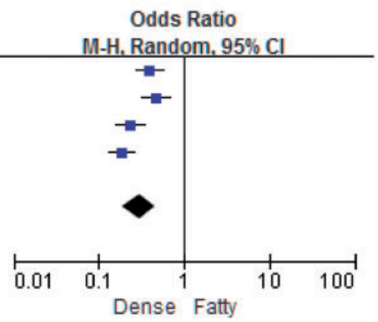


(**b**) Forest plot for the association between menopausal status (post-menopause compared with pre-menopause) and mammographic density

Study or Subgroup	Dense Events	Dense Total	Fatty Events	Fatty Total	Weight	Odds Ratio M-H, Random, 95% CI
Beijing	279	394	274	319	25.0%	0.40 [0.27–0.58]
Nanchang	758	807	1710	1761	24.6%	0.46 [0.31–0.69]
Shenyang	114	171	642	716	24.6%	0.23 [0.15–0.34]
Tianjin	216	316	696	756	25.8%	0.19 [0.13–0.27]
Total (95% CI)		**1688**		**3552**	**100.0%**	**0.30 [0.19–0.46]**
Total events	1367		3322			

Heterogeneity: Tau² = 0.15; Chi² = 15.09, df = 3 (P = 0.002); I² = 80%

Test for overall effect: Z = 5.53 (P < 0.00001)

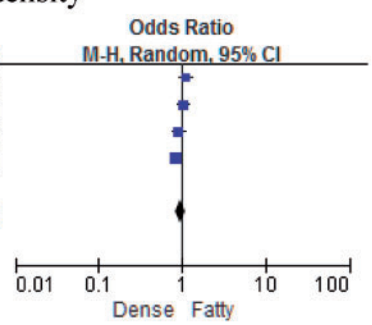


(**c**) Forest plot for the association between number of live birth (number of live births≥2 compared with number of live births=0) and mammographic density

Study or Subgroup	Dense Events	Dense Total	Fatty Events	Fatty Total	Weight	Odds Ratio M-H, Random, 95% CI
Beijing	392	3979	155	1710	21.6%	1.10 [0.90–1.33]
Nanchang	260	3743	340	5066	24.6%	1.04 [0.88–1.23]
Shenyang	210	2342	391	3986	23.7%	0.91 [0.76–1.08]
Tianjin	600	3411	676	3290	30.1%	0.83 [0.73–0.93]
Total (95% CI)		**13475**		**14052**	**100.0%**	**0.95 [0.83–1.09]**
Total events	1462		1562			

Heterogeneity: Tau² = 0.01; Chi² = 8.12, df = 3 (P = 0.04); I² = 63%

Test for overall effect: Z = 0.76 (P = 0.44)



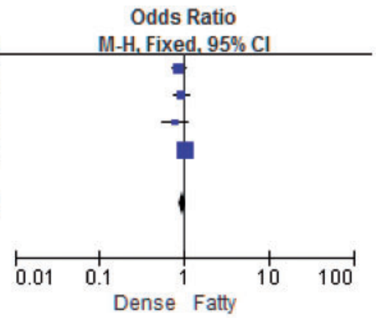
(**d**) Forest plot for the association between age at first birth (age≥30 compared with age<30) and mammographic density

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)

Study or Subgroup	Dense Events	Dense Total	Fatty Events	Fatty Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Beijing	389	4119	190	1776	24.6%	0.87 [0.72–1.05]
Nanchang	140	3838	203	5170	17.0%	0.93 [0.74–1.15]
Shenyang	47	2384	101	4049	7.5%	0.79 [0.55–1.12]
Tianjin	637	3613	590	3439	50.9%	1.03 [0.91–1.17]
Total (95% CI)		**13954**		**14434**	**100.0%**	**0.96 [0.87–1.05]**
Total events	1213		1084			

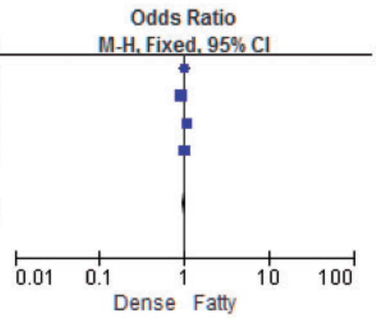
Heterogeneity: Chi² = 3.83, df = 3 (*P* = 0.28); I² = 22%
Test for overall effect: Z = 0.97 (*P* = 0.33)



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

Study or Subgroup	Dense Events	Dense Total	Fatty Events	Fatty Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Beijing	1146	4046	493	1746	18.0%	1.00 [0.89–1.14]
Nanchang	947	3826	1343	5153	31.3%	0.93 [0.85–1.03]
Shenyang	793	2384	1283	4048	23.1%	1.07 [0.96–1.20]
Tianjin	1158	3551	1096	3368	27.6%	1.00 [0.91–1.11]
Total (95% CI)		**13807**		**14315**	**100.0%**	**1.00 [0.95–1.05]**
Total events	4044		4215			

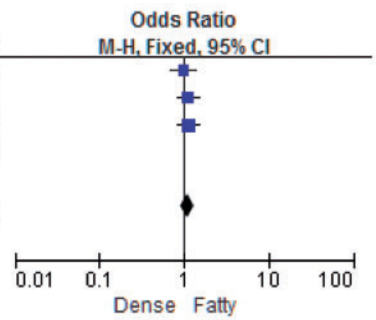
Heterogeneity: Chi² = 3.68, df = 3 (*P* = 0.30); I² = 18%
Test for overall effect: Z = 0.08 (*P* = 0.94)



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

Study or Subgroup	Dense Events	Dense Total	Fatty Events	Fatty Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Beijing	114	4119	50	1776	28.8%	0.98 [0.70–1.38]
Nanchang	76	3838	91	5170	32.2%	1.13 [0.83–1.53]
Shenyang	85	2384	129	4049	39.0%	1.12 [0.85–1.48]
Tianjin	128	3613	133	0		Not estimable
Total (95% CI)		**13954**		**10995**	**100.0%**	**1.08 [0.91–1.29]**
Total events	403		403			

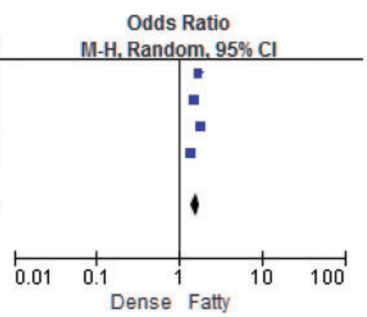
Heterogeneity: Chi² = 0.45, df = 2 (*P* = 0.80); I² = 0%
Test for overall effect: Z = 0.90 (*P* = 0.37)



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

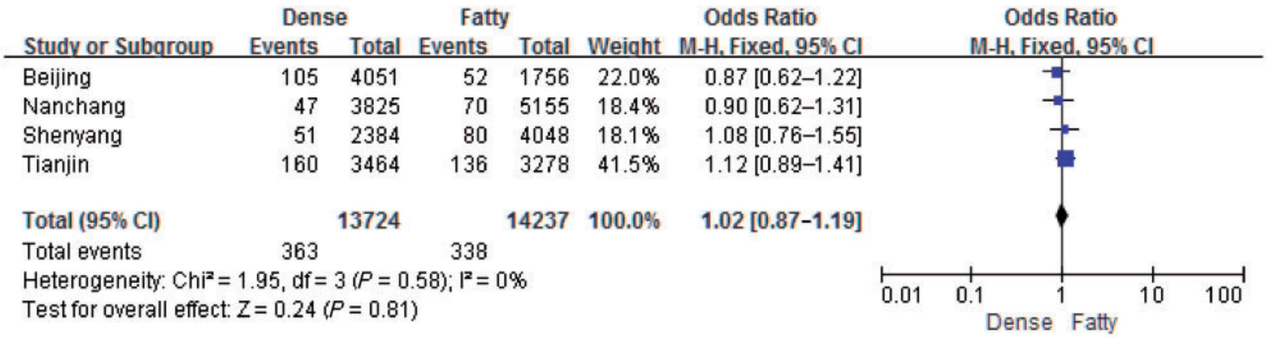
Study or Subgroup	Dense Events	Dense Total	Fatty Events	Fatty Total	Weight	Odds Ratio M-H, Random, 95% CI
Beijing	2312	4074	765	1748	24.4%	1.69 [1.51–1.89]
Nanchang	1112	3819	1120	5146	25.7%	1.48 [1.34–1.63]
Shenyang	1188	2382	1437	4045	25.2%	1.81 [1.63–2.00]
Tianjin	1029	3484	783	3291	24.8%	1.34 [1.20–1.50]
Total (95% CI)		**13759**		**14230**	**100.0%**	**1.57 [1.38–1.78]**
Total events	5641		4105			

Heterogeneity: Tau² = 0.01; Chi² = 18.19, df = 3 (*P* = 0.0004); I² = 84%
Test for overall effect: Z = 6.82 (*P* < 0.00001)

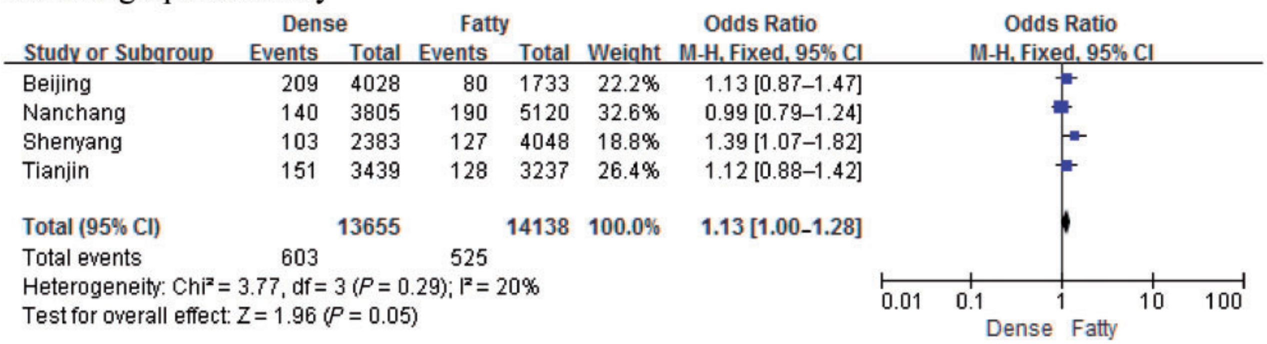


(**h**) Forest plot for the association between prior breast benign disease (yes compared with no) and mammographic density

Figure 1. Continued.



(i) Forest plot for the association between smoking (ever compared with never) and mammographic density



(j) Forest plot for the association between alcohol drinking (ever compared with never) and mammographic density

Figure 1. Continued.

Table 4. Mammographic density distribution between Chinese and American women

Race	Age < 50, *N* (%)			Age ≥ 50, *N* (%)		
	Fatty	Dense	OR (95% CI)[a]	Fatty	Dense	OR (95% CI)[a]
Chinese	595 (5.2)	10754 (94.8)	1.00	2816 (16.9)	13863 (83.1)	1.00
White	936 (13.1)	6225 (86.9)	0.60 (0.53, 0.69)*	3561 (16.5)	18084 (83.5)	1.52 (1.43, 1.62)*
Asian American	41 (4.1)	961 (95.9)	1.85 (1.30, 2.62)*	209 (6.4)	3038 (93.6)	3.67 (3.15, 4.27)*
African American	98 (10.2)	862 (89.8)	1.18 (0.86, 1.61)	389 (14.4)	2315 (85.6)	2.25 (1.94, 2.61)*

[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 ≥25 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,[4] we did not find this association among women participating in the MIST. This may be due to the small numbers of cancer 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-estrogenic 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 associations[33–35] and null association[36] 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 category[26,39] 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 fattier 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.[45] 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

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