HHS Public Access

Author manuscript

Breast Cancer Res Treat. Author manuscript; available in PMC 2020 June 19.

Published in final edited form as:

Breast Cancer Res Treat. 2019 September ; 177(2): 527–536. doi:10.1007/s10549-019-05325-6.

Associations between mammographic density and tumor characteristics in Chinese women with breast cancer

Erni Li[#1], **Jennifer L. Guida**[#2,3], **Yuan Tian**[1], **Hyuna Sung**[2,4], **Hela Koka**[2], **Mengjie Li**[2,5], **Ariane Chan**[6], **Han Zhang**[2], **Eric Tang**[2], **Changyuan Guo**[1], **Joseph Deng**[2], **Nan Hu**[2], **Ning Lu**[1], **Gretchen L. Gierach**[2], **Jing Li**[1], **Xiaohong R. Yang**[2]

[1]National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China [2]Division of Cancer Epidemiology & Genetics, National Cancer Institute, NIH, DHHS, 9609 Medical Center Drive, Bethesda, MD 20892-9761, USA [3]Division of Cancer Control and Population Sciences, National Cancer Institute, NIH, DHHS, 9609 Medical Center Drive, Bethesda, MD 20892-9761, USA [4]Cancer Surveillance and Health Services Program, American Cancer Society, Atlanta, GA 30303, USA [5]Vanderbilt University, Nashville, TN, USA [6]Volpara Health Technologies Ltd, Wellington, New Zealand

[#] These authors contributed equally to this work.

Abstract

Purpose—Mammographic density (MD) is a strong risk factor for breast cancer, yet its relationship with tumor characteristics is not well established, particularly in Asian populations.

Methods—MD was assessed from a total of 2001 Chinese breast cancer patients using Breast Imaging Reporting and Data System (BI-RADS) categories. Molecular subtypes were defined using immunohistochemical status on ER, PR, HER2, and Ki-67, as well as tumor grade. Multinomial logistic regression was used to test associations between MD and molecular subtype (luminal A = reference) adjusting for age, body mass index (BMI), menopausal status, parity, and nodal status.

Results—The mean age at diagnosis was 51.7 years (SD = 10.7) and the average BMI was 24.7 kg/m^2 (SD = 3.8). The distribution of BI-RADS categories was 7.4% A = almost entirely fat, 24.2% B = scattered fibroglandular dense, 49.4% C = heterogeneously dense, and 19.0% D = extremely dense. Compared to women with BI-RADS = A/B, women with BI-RADS = D were more likely to have HER2-enriched tumors (OR = 1.81, 95% CI 1.08–3.06, $p = 0.03$), regardless of menopausal status. The association was only observed in women with normal (< 25 kg/m^2) BMI (OR = 2.43, 95% CI 1.24–4.76, $p < 0.01$), but not among overweight/obese women (OR: 0.98, 95% CI 0.38–2.52, $p = 0.96$).

Jing Li, dr.lijing@163.com: Xiaohong R. Yang, royang@mail.nih.gov.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10549-019-05325-6) contains supplementary material, which is available to authorized users.

Conclusions—Among Chinese women with normal BMI, higher breast density was associated with HER2-enriched tumors. The results may partially explain the higher proportion of HER2+ tumors previously reported in Asian women.

Keywords

Mammographic density; Tumor subtype; Breast cancer; BI-RADS

Introduction

Variations in the composition of breast tissue, such as fat, stromal, and epithelial tissues, and their presentation on radiologic images have been shown to contribute differentially to the risk of breast cancer [1]. Mammographic density (MD) is an established, strong risk factor for breast cancer [2], and previous research suggests that MD may be associated with more aggressive tumor characteristics, including higher grade and larger tumor size [3, 4], and possibly, molecular tumor subtypes [5–8]. However, results from these studies have been inconsistent. Some studies suggest associations of similar magnitudes between MD and all tumor subtypes, while others suggest that the associations are driven specifically by estrogen receptor (ER)-positive (+) or ER-negative (−) tumors [9–12]. One meta-analysis showed the association between MD and ER + and ER− tumors to be of similar magnitude in case-control and case-only designs, although significant heterogeneity across studies was found [11]. Further, the majority of these studies were conducted in Western settings where women are regularly screened.

The MD distribution and prevalence of tumor subtypes has been shown to vary by race/ethnicity [13–16]; however, little is known about the relationship between MD and clinical features of breast tumors in Asian populations. Asian women are known to have a higher proportion of denser breasts [15, 17–20], tend to have an earlier age at breast cancer onset, and have a higher proportion of HER2-enriched tumors [14, 21] compared to Western women. Replication of studies in diverse populations may provide additional insight into the subtype-specific etiology of breast cancer. The objective of the current study was to comprehensively assess the relationship between MD and molecular tumor markers (ER, PR, HER2, Ki-67, CK5/6, EGFR, and TP53) and clinical characteristics (node, grade, and tumor size) among women with breast cancer in China, where the breast cancer incidence rate, prevalence of known risk factors, screening practices, and MD are thought to be markedly different from those of Western women.

Materials and methods

Study population

The study population includes 2001 invasive breast cancer cases diagnosed and treated at the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (CHCAMS), Beijing, during 2008 to 2016. Eligible cases included those who had a confirmed breast cancer diagnosis, complete ER, PR, and HER2 status, information on established risk factors, and diagnostic mammograms available. A subset of patients diagnosed in each of

these years were randomly selected for MD assessment. The majority of these patients were symptomatic and only a small proportion (< 10%) were detected through physical exams or screening. The distribution of demographic and clinical characteristics of the patients included in this MD evaluation was similar to the overall breast cancer patient population diagnosed at CHCAMS between 2008 and 2016 (N = 10,546, Supplementary Table 1). The project was approved by the CHCAMS Ethics Committee and was exempted from review by the Office for Human Research Protections at the National Institutes of Health because it did not involve interaction with human subjects and/or use of personal identifying information (exempt# 11,751).

Mammographic density (MD)

Images from full-field digital diagnostic mammograms were retrospectively scored for MD by a trained radiologist (EL) using the Breast Imaging Reporting and Data System (BI-RADS) guidelines recommended by the American College of Radiology (5th edition). MD was classified into four categories: A = almost entirely fat, B = scattered fibroglandular densities, C=heterogeneously dense, and D = extremely dense [22]. To assess inter-radiologist variability, a subset of images (n = 144) was independently read by four senior radiologists. The average inter-observer agreement was 0.66 (range of weighted kappa = 0.59–0.70) for BI-RADS four levels and 0.73 (range of kappa = 0.61–0.83) for two levels (non-dense [A + B] and dense [C + D]). We also performed a masked repeated review of 51 randomly selected cases to assess intra-observer variability (EL) and scores did not significantly differ across readings (concordance = 84.7%, p = 0.54).

Clinical characteristics and immunohistochemical (IHC) subtype

Clinical characteristics including nodal status (positive/negative), tumor size (≤ 2 cm/> 2 cm), grade (well [I], moderately [II], and poorly [III] differentiated), and IHC marker status were extracted from pathology reports. ER and progesterone receptor (PR) tumor expression were considered positive for IHC with ≥ 1% nuclear staining. HER2 expression was determined by IHC and fluorescence in situ hybridization (FISH). An IHC score of 3+ or a FISH-positive test result was defined as HER2+. HER2 IHC 2+ cases without FISH data were considered negative. IHC staining data was available for Ki-67 (n = 1530), EGFR (n = 1414), CK5/6 (n = 1463), and TP53 (n = 1307). Ki-67 was considered high if 30% or more of the cells showed nuclear staining. For EGFR and CK5/6, > 1% staining was considered positive. TP53 expression was classified into two categories (negative = 0% and positive > 0%). We used Ki-67 status (low/high) to discriminate luminal A and B and used tumor grade as a surrogate for patients with missing Ki-67 [23]. Molecular subtypes were defined as: luminal A: ER+ or PR+, HER2−, and low Ki-67/histologic grade (I or II); luminal B-HER2+ : ER+ or PR+, and HER2+; luminal B-high proliferative: ER+ or PR+, HER2−, and high Ki-67/histologic grade (III); HER2-enriched: ER−, PR−, and HER2+; and triple-negative (TN)-basal like: ER−, PR−, HER2−, and EGFR+ or CK5/6+. We excluded tumors that stained negative for all five markers due to small sample size (n = 7).

Risk factors

Risk factors were extracted from medical records and included age at diagnosis (< 45 years [reference], 45–55 years, > 55 years), body mass index (BMI) (underweight/normal: < 25

[reference], overweight: 25–30, obese: > 30 kg/m^2), family history of breast cancer (yes/no), and reproductive factors including age at menarche, age at menopause, menopausal status (premenopausal/post-menopausal), parity (nulliparous/parous), and breastfeeding history (yes/no). BMI categories underweight/normal were combined due to the small number (n = 26, 1.5%) of underweight women.

Statistical analysis

Differences in the distribution of each risk factor and tumor feature by BI-RADS density categories were assessed using one-way analysis of variance (ANOVA) for continuous variables or Chi square tests for categorical variables. Cumulative logistic regression using the CLOGIT function was used to evaluate the relationships between MD (outcome variable) and each risk factor or tumor feature with the adjustment for age and BMI (Supplementary Table 2). Multinomial logistic regression models were used to test associations between MD and tumor subtype (outcome variable) with the adjustment for confounders. BI-RADS categories A and B were combined in the final multinomial model as the “non-dense” group due to a small number of women with almost entirely fatty breasts (n = 147, 7.4%). Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated comparing each tumor subtype to the luminal A subtype. Variables that were significantly associated with MD in the age and BMI adjusted model were included in the final model (menopausal status (premenopausal [reference] vs. postmenopausal), parity (nulliparous [reference] vs. parous), and nodal status (positive vs. negative [reference]). Breastfeeding was significant in the age and BMI adjusted model, but its inclusion did not change the results and therefore, was eliminated from the final model due to additional missing data (n = 424, 21%). Analyses were also stratified by menopausal status and BMI to determine if the association between MD and molecular subtype varied by these factors. In the BMI stratified models, we additionally adjusted for BMI as a continuous covariate to reduce residual confounding by BMI within strata, and the results were similar (Supplementary Table 3). We also conducted a sensitivity analysis excluding IHC HER2 2+ cases with missing FISH data. The results were also similar and therefore we included HER2 2+ with missing FISH data in the final models. All p values presented are two-sided. Analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

Results

The final analysis included 2001 Chinese women diagnosed with breast cancer between 2008 and 2016. The mean age at diagnosis was 51.7 years (SD = 10.7) and the average BMI was 24.7 kg/m^2 (SD = 3.8). The distribution of BI-RADS categories was as follows: 7.4% (A, almost entirely fat), 24.2% (B, scattered fibroglandular densities), 49.4% (C, heterogeneously dense), and 19.0% (D, extremely dense). As expected, MD significantly decreased with increasing age and BMI (Table 1, Supplementary Figure 1). In the model adjusted for age and BMI, women with extremely dense breasts were more likely to be premenopausal, nulliparous, and never breast feeders, compared to women with “non-dense” breasts (BI-RADS: A & B) (Supplementary Table 2). Regarding MD in relation to tumor characteristics, higher MD was associated with EGFR expression, and negative nodal status.

In the age- and BMI-adjusted models, MD was not significantly associated with any other tumor features examined (Supplementary Table 2).

Table 2 shows the associations between MD and molecular subtype adjusting for age, BMI, menopausal status, parity, and nodal status. Chinese women with extremely dense breasts were more likely to have HER2-enriched tumors compared to luminal A tumors (OR: 1.81, 95% CI 1.08–3.06, $p = 0.03$), and a significant trend across density categories was observed (OR_{trend}: 1.44, $p_{trend} < 0.01$). The associations were similar among pre-menopausal (OR: 1.63, 95% CI 0.76–3.48, $p = 0.21$) and post-menopausal women (OR: 2.03, 95% CI 0.94–4.38, $p = 0.07$) (Table 3). In contrast, the analysis stratified by BMI showed that the association for the HER2-enriched subtype with extremely dense breasts was only seen among women with BMI < 25 kg/m^2 (OR: 2.43, 95% CI 1.24–4.76, $p \leq 0.01$), but not among overweight/obese women (OR: 0.98, 95% CI 0.38–2.52, $p = 0.96$) (Table 4).

TN-basal-like patients also tended to have higher MD (OR_{trend}: 1.26 (0.94–1.67), $p_{trend} = 0.12$); however, the association was not significant. Interestingly, the association was stronger among overweight/obese women (OR: 1.62, 95% CI 0.94–2.79, $p = 0.08$) (Table 4).

Discussion

Mammographic density is a strong and well-established risk factor for breast cancer; however, its association with intrinsic tumor subtypes remains unclear and inconsistent [9, 10, 12, 24–28]. In addition, few studies have evaluated the relationships between MD and tumor characteristics in Asian populations. In our large study of Chinese breast cancer patients with comprehensive pathology and risk factor data, we found that higher MD was associated with the HER2-enriched subtype, compared to the luminal A subtype. These findings may explain the elevated proportion of HER2+ cancers in previously reported studies among Asian women [14, 21].

The association between MD and molecular subtypes has been inconsistently observed in the literature, which may reflect differences in study populations, power, MD assessment, marker measurement, subtype classification, and adjustment for covariates. A smaller case-control study conducted in a Korean population using a quantitative measure of MD did not observe associations between MD and breast cancer risk by tumor marker-defined subtypes [10]. In contrast, an association between higher MD and the HER2-enriched subtype was reported in Chinese women, although the association was only observed when MD was estimated by BI-RADS and not by a density analysis software (DAS) [29]. The association of higher MD with the HER2-enriched subtype was also reported in a recent study using both quantitative and BI-RADS MD measurements in a North American population of 457 breast cancer patients, although in that study MD was only associated with the HER2-enriched subtype using volumetric breast density (OR: 1.06, 95% CI 1.01–1.12, per percentage point increase), and not BI-RADS density [24]. Interestingly, we found that the association between higher MD and the HER2-enriched subtype was only seen in women with normal BMI, whereas the association for the TN-basal-like subtype was stronger in overweight or obese women. Previous studies demonstrated that the association between obesity and breast cancer risk varied by menopausal status and molecular subtypes [30],

suggesting complex mechanisms underlying obesity and breast cancer development. For example, tumor-associated stromal cells, including adipocytes, fibroblasts, and immune cells, showed distinct distributions, activities, and interactions [31, 32], which sustain a proinflammatory and transforming tumor microenvironment (TME). Alterations in numerous processes, such as inflammation, hormone signaling, extracellular matrix, and cell metabolism, are associated with obesity-related TME, which might confound or mask the associations between MD and breast cancer subtypes. Although the exact mechanisms remain unclear, these findings may explain the inconsistent associations observed between MD and tumor subtypes in previous studies that were conducted in populations with different BMI distributions.

Our observed association between higher MD and HER2+ subtypes in Asian women is interesting since we and others have previously reported a higher proportion or incidence of HER2-enriched breast cancer in Asian American and indigenous Asian women compared with Caucasians [14, 21]. Though the overall breast cancer incidence rates are lower, we previously found that Asian Americans at ages 40–69 years had the highest incidence rates for HER2-enriched breast cancer among all ethnic groups using Surveillance, Epidemiology, End Results (SEER) data [14]. Similar results were seen in our previous analysis of Malaysian breast cancer patients in Sarawak [21]. The reasons for the observed increase in risk of developing HER2-enriched tumors among Asian women remain unclear since the etiologic factors for this specific subtype are largely unknown. Our findings demonstrating that Asian breast cancer patients with elevated MD have an increased likelihood of the HER2-enriched subtype suggest that MD may partially explain the high frequency of the HER2-enriched subtype among Asian women.

Potential biological explanations between MD and tumor subtypes are not well understood. A previous study found upregulation of pSTAT3 in patients with high MD and patients with HER2+ breast tumors [33], suggesting a possible link between HER2 and STAT signaling pathways in the molecular basis of MD. MD reflects relative proportions of epithelial and stromal tissues in comparison with adipose tissues in the breast [34]. Prior studies have found histologic features, such as terminal duct lobular unit (TDLU) involution to be correlated with MD. For example, lower extent of TDLU involution was associated with higher MD [35–37] and increased breast cancer risk [34, 35], suggesting that MD reflects a higher amount of “at-risk” epithelium. In addition to changes that are specific in breast epithelium, high MD is also associated with molecular changes in stromal cells. The interaction between tumor and stromal cells is bidirectional and the constant cross-talk between tumors and its microenvironment is believed to significantly contribute to tumor phenotypes and cancer outcomes [38]. Studies have shown that high MD is associated with a complex pattern of upregulation and downregulation of extracellular matrix proteins and architectural remodeling in the breast, which may lead to DNA damage and mutations that promote certain breast cancer subtypes [39, 40]. Alternatively, distinct genomic profiles in tumors may stimulate the proliferation of epithelium and alter the stromal composition, which in turn leads to increased MD. For example, a recent study reported that HER2 signaling activated chemokine production and immune cell infiltration of the breast cancer TME [41], and increased immune cell populations such as macrophages, dendritic cells, and B lymphocytes, as well as programmed cell death protein 1 (PD-1) expression were

observed in both epithelium and stroma of patients with high MD [42]. In a breast cancer study conducted in Poland, we previously observed that extratumoral microenvironment gene expression was associated with mammographic density [43]. Future genomic studies in Asian women evaluating mutations and gene expression levels in both tumor tissue and surrounding stroma in relation to MD are needed to better understand the molecular mechanisms underlying high MD and the tumor subtypes it promotes, such as HER2-enriched.

As expected, age, BMI, and several reproductive factors such as parity and menopausal status were associated with MD in our study. Consistent with results from studies conducted in Germany and Sweden, we did not see associations of MD with most molecular markers such as ER, PR, and Ki-67 [44, 45]. Our results suggest that the MD-HER2 association is very specific, which is unlikely driven by estrogen response, proliferation, or tumor aggressiveness as indicated by TP53 status and tumor grade.

The strengths of this study include access to a large sample of uniquely unscreened Asian women who have historically been understudied for breast density, a comprehensive evaluation of IHC markers, the collection of key exposures related to MD, and the validation of MD measurement by multiple experienced radiologists. However, our study is not without limitations. First, our sample is not representative of all breast cancer populations in China. Second, the proportion of patients having fatty breasts was low, which may have limited the power to detect MD associations. In addition, BI-RADS measurements are categorical and known to be subjective, and therefore we cannot rule out the possibility of misclassification between BI-RADS categories or bias from radiologist readings. However, prior studies have demonstrated reasonable correlations between BI-RADS density measures and automated quantitative metrics [46, 47]. Further, we had good inter- and intra-rater agreement, suggesting the BI-RADS measurement was not significantly biased.

In summary, we found that women with higher MD were more likely to have the HER2-enriched tumor subtype in a study population of Chinese breast cancer cases. Our findings may partially explain the higher proportion of HER2+ cancers observed in Asian women. Further studies using quantitative MD measurements to confirm the association between MD and HER2 expression in breast cancer patients and to evaluate the role of MD in the etiology of HER2-enriched breast cancer among Asian populations are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

This work was supported by the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Division of Cancer Epidemiology and Genetics.

Abbreviations

MD	Mammographic density

ER+	Estrogen receptor-positive
ER−	Estrogen receptor-negative
PR+	Progesterone receptor-positive
PR−	Progesterone receptor-negative
CHCAMS	Chinese Academy of Medical Sciences and Peking Union Medical College
BI-RADS	Breast Imaging Reporting and Data System
IHC	Immunohistochemical
FISH	Fluorescence in situ hybridization
BMI	Body mass index
ANOVA	Analysis of variance
OR	Odds ratio
CI	Confidence interval
SD	Standard deviation
DAS	Density analysis software
SEER	Surveillance, Epidemiology, and End Results
TDLU	Terminal duct lobular involution

References

1. Boyd NF, Guo H, Martin LJ et al. (2007) Mammographic density and the risk and detection of breast cancer. N Engl J Med 356:227–236 [PubMed: 17229950]
2. McCormack VA, dos Santos Silva I (2006) Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Prev Biomark 15:1159–1169
3. Yaghjyan L, Colditz GA, Collins LC et al. (2011) Mammographic breast density and subsequent risk of breast cancer in postmenopausal women according to tumor characteristics. J Natl Cancer Inst 103(15):1179–1189. 10.1093/jnci/djr225 [PubMed: 21795664]
4. Eriksson L, Czene K, Rosenberg L et al. (2012) The influence of mammographic density on breast tumor characteristics. Breast Cancer Res Treat 134:859–866. 10.1007/s10549-012-2127-0 [PubMed: 22710708]
5. Phipps AI, Buist DS, Malone KE et al. (2012) Breast density, body mass index, and risk of tumor marker-defined subtypes of breast cancer. Ann Epidemiol 22:340–348 [PubMed: 22366170]
6. Eriksson L, Hall P, Czene K et al. (2012) Mammographic density and molecular subtypes of breast cancer. Br J Cancer 107:18–23 [PubMed: 22644308]
7. Yang W-T, Dryden M, Broglio K et al. (2008) Mammographic features of triple receptor-negative primary breast cancers in young premenopausal women. Breast Cancer Res Treat 111:405–410 [PubMed: 18026834]
8. Chen J-H, Hsu F-T, Shih H-N et al. (2009) Does breast density show difference in patients with estrogen receptor-positive and estrogen receptor-negative breast cancer measured on MRI? Ann Oncol 20:1447–1449 [PubMed: 19654204]

9. Holm J, Eriksson L, Ploner A et al. (2017) Assessment of breast cancer risk factors reveals subtype heterogeneity. Cancer Res 77:3708–3717. 10.1158/0008-5472.CAN-16-2574 [PubMed: 28512241]
10. Shin J, Lee JE, Ko HY et al. (2018) Association between mammographic density and tumor marker-defined breast cancer subtypes: a case-control study. Eur J Cancer Prev 27:239–247. 10.1097/CEJ.0000000000000353 [PubMed: 28957821]
11. Antoni S, Sasco AJ, dos Santos Silva I, McCormack V (2013) Is mammographic density differentially associated with breast cancer according to receptor status? A meta-analysis. Breast Cancer Res Treat 137:337–347 [PubMed: 23239150]
12. Sartor H, Zackrisson S, Elebro K et al. (2015) Mammographic density in relation to tumor biomarkers, molecular subtypes, and mode of detection in breast cancer. Cancer Causes Control 26:931–939. 10.1007/s10552-015-0576-6 [PubMed: 25860114]
13. Carey LA, Perou CM, Livasy CA et al. (2006) Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 295:2492–2502 [PubMed: 16757721]
14. Clarke CA, Keegan THM, Yang J et al. (2012) Age-specific incidence of breast cancer subtypes: understanding the black-white crossover. J Natl Cancer Inst 104:1094–1101. 10.1093/jnci/djs264 [PubMed: 22773826]
15. del Carmen MG, Halpern EF, Kopans DB et al. (2007) Mammographic breast density and race. Am J Roentgenol 188:1147–1150 [PubMed: 17377060]
16. Rajaram N, Mariapun S, Eriksson M et al. (2017) Differences in mammographic density between Asian and Caucasian populations: a comparative analysis. Breast Cancer Res Treat 161:353–362. 10.1007/s10549-016-4054-y [PubMed: 27864652]
17. Nie K, Su M-Y, Chau M-K et al. (2010) Age- and race-dependence of the fibroglandular breast density analyzed on 3D MRI. Med Phys 37:2770–2776. 10.1118/1.3426317 [PubMed: 20632587]
18. Sung H, Ren J, Li J et al. (2018) Breast cancer risk factors and mammographic density among high-risk women in urban China. NPJ Breast Cancer 4:3 10.1038/s41523-018-0055-9 [PubMed: 29423438]
19. Nazari SS, Mukherjee P (2018) An overview of mammographic density and its association with breast cancer. Breast Cancer 25:259–267. 10.1007/s12282-018-0857-5 [PubMed: 29651637]
20. Heller SL, Hudson S, Wilkinson LS (2015) Breast density across a regional screening population: effects of age, ethnicity and deprivation. Br J Radiol 88:20150242 10.1259/bjr.20150242 [PubMed: 26329467]
21. Horne HN, Beena Devi CR, Sung H et al. (2015) Greater absolute risk for all subtypes of breast cancer in the US than Malaysia. Breast Cancer Res Treat 149:285–291. 10.1007/s10549-014-3243-9 [PubMed: 25537643]
22. D'Orsi CJ, Sickles EA, Mendelson EB, Morris EA et al. (2013) ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. American College of Radiology, Reston
23. Sisti JS, Collins LC, Beck AH et al. (2016) Reproductive risk factors in relation to molecular subtypes of breast cancer: results from the nurses' health studies. Int J Cancer 138:2346–2356. 10.1002/ijc.29968 [PubMed: 26684063]
24. Edwards BL, Atkins KA, Stukenborg GJ et al. (2017) The association of mammographic density and molecular breast cancer subtype. Cancer Epidemiol Biomark Prev 26:1487–1492. 10.1158/1055-9965.EPI-16-0881
25. Vachon C, Tamimi R, Chen Y-Y et al. (2016) Abstract IA22: mammographic density: a risk factor for all breast cancers or only specific subtypes? Cancer Epidemiol Prev Biomark 25:IA22 10.1158/1538-7755.DISP15-IA22
26. Razzaghi H, Troester MA, Gierach GL et al. (2013) Association between mammographic density and basal-like and luminal A breast cancer subtypes. Breast Cancer Res BCR 15:R76 10.1186/bcr3470 [PubMed: 24008056]
27. Yaghjyan L, Tamimi RM, Bertrand KA et al. (2017) Interaction of mammographic breast density with menopausal status and postmenopausal hormone use in relation to the risk of aggressive breast cancer subtypes. Breast Cancer Res Treat 165:421–431. 10.1007/s10549-017-4341-2 [PubMed: 28624977]

28. Krishnan K, Baglietto L, Stone J et al. (2017) Mammographic density and risk of breast cancer by tumor characteristics: a case-control study. BMC Cancer 17:859 10.1186/s12885-017-3871-7 [PubMed: 29246131]
29. Ji Y, Shao Z, Liu J et al. (2018) The correlation between mammographic densities and molecular pathology in breast cancer. Cancer Biomark. 10.3233/CBM-181185
30. Neuhouser ML, Aragaki AK, Prentice RL et al. (2015) Overweight, obesity, and postmenopausal invasive breast cancer risk: a secondary analysis of the women's health initiative randomized clinical trials. JAMA Oncol 1:611–621. 10.1001/jamaoncol.2015.1546 [PubMed: 26182172]
31. Iyengar NM, Gucalp A, Dannenberg AJ, Hudis CA (2016) Obesity and cancer mechanisms: tumor microenvironment and inflammation. J Clin Oncol 34:4270–4276. 10.1200/JCO.2016.67.4283 [PubMed: 27903155]
32. Lengyel E, Makowski L, DiGiovanni J, Kolonin MG (2018) Cancer as a matter of fat: the crosstalk between adipose tissue and tumors. Trends Cancer 4:374–384. 10.1016/j.trecan.2018.03.004 [PubMed: 29709261]
33. Radenkovic S, Konjevic G, Gavrilovic D et al. (2019) pSTAT3 expression associated with survival and mammographic density of breast cancer patients. Pathol Res Pract 215:366–372. 10.1016/j.prp.2018.12.023 [PubMed: 30598340]
34. Ginsburg OM, Martin LJ, Boyd NF (2008) Mammographic density, lobular involution, and risk of breast cancer. Br J Cancer 99:1369–1374. 10.1038/sj.bjc.6604635 [PubMed: 18781174]
35. Ghosh K, Hartmann LC, Reynolds C et al. (2010) Association between mammographic density and age-related lobular involution of the breast. J Clin Oncol 28:2207–2212. 10.1200/JCO.2009.23.4120 [PubMed: 20351335]
36. Gierach GL, Patel DA, Pfeiffer RM et al. (2016) Relationship of terminal duct lobular unit involution of the breast with area and volume mammographic densities. Cancer Prev Res 9:149–158. 10.1158/1940-6207.CAPR-15-0282
37. Ghosh K, Vierkant RA, Frank RD et al. (2017) Association between mammographic breast density and histologic features of benign breast disease. Breast Cancer Res 19:134 10.1186/s13058-017-0922-6 [PubMed: 29258587]
38. Sherratt MJ, McConnell JC, Streuli CH (2016) Raised mammographic density: causative mechanisms and biological consequences. Breast Cancer Res 18:45 10.1186/s13058-016-0701-9 [PubMed: 27142210]
39. Sawada Y, Tamada M, Dubin-Thaler BJ et al. (2006) Force sensing by mechanical extension of the Src family kinase substrate p130Cas. Cell 127:1015–1026. 10.1016/j.cell.2006.09.044 [PubMed: 17129785]
40. Mouw JK, Yui Y, Damiano L et al. (2014) Tissue mechanics modulate microRNA-dependent PTEN expression to regulate malignant progression. Nat Med 20:360–367. 10.1038/nm.3497 [PubMed: 24633304]
41. Triulzi T, Forte L, Regondi V et al. (2019) HER2 signaling regulates the tumor immune microenvironment and trastuzumab efficacy. Oncoimmunology 8:e1512942 10.1080/2162402X.2018.1512942 [PubMed: 30546951]
42. Huo CW, Hill P, Chew G et al. (2018) High mammographic density in women is associated with protumor inflammation. Breast Cancer Res 20:92 10.1186/s13058-018-1010-2 [PubMed: 30092832]
43. Sun X, Gierach GL, Sandhu R et al. (2013) Relationship of mammographic density and gene expression: analysis of normal breast tissue surrounding breast cancer. Clin Cancer Res 19:4972–4982. 10.1158/1078-0432.CCR-13-0029 [PubMed: 23918601]
44. Gabrielson M, Chiesa F, Paulsson J et al. (2016) Amount of stroma is associated with mammographic density and stromal expression of oestrogen receptor in normal breast tissues. Breast Cancer Res Treat 158:253–261. 10.1007/s10549-016-3877-x [PubMed: 27349429]
45. Fasching PA, Heusinger K, Loehberg CR et al. (2006) Influence of mammographic density on the diagnostic accuracy of tumor size assessment and association with breast cancer tumor characteristics. Eur J Radiol 60:398–404. 10.1016/j.ejrad.2006.08.002 [PubMed: 17030108]
46. Lee HN, Sohn Y-M, Han KH (2015) Comparison of mammographic density estimation by Volpara software with radiologists' visual assessment: analysis of clinical-radiologic factors affecting

discrepancy between them. Acta Radiol 56:1061–1068. 10.1177/0284185114554674 [PubMed: 25338836]

47. Singh T, Sharma M, Singla V, Khandelwal N (2016) Breast density estimation with fully automated volumetric method: comparison to radiologists' assessment by BI-RADS categories. Acad Radiol 23:78–83. 10.1016/j.acra.2015.09.012 [PubMed: 26521687]

Table 1

Clinical characteristics and breast cancer risk factors by BI-RADS density category

	Density (BI-RADS)					
	Fatty and scattered glandular dense (*n* = 632)		Heterogeneously dense (*n* = 988)		Extremely dense (*n* = 381)	
	n	%	*n*	%	*n*	%
Molecular subtype						
Luminal A	338	53.5	449	45.5	184	48.3
Luminal B-high proliferative	126	19.9	225	22.8	80	21.0
Luminal B-HER2+	80	12.7	169	17.1	51	13.4
HER2-enriched	57	9.0	76	7.7	47	12.3
TN-basal type	31	4.9	69	7.0	19	5.0
Age at diagnosis (years)						
Mean. SD	58.9	9.8	50.1	9.4	43.8	7.4
<45	48	7.6	326	33.0	228	59.8
45–55	174	27.5	401	40.6	135	35.4
>55	410	64.9	261	26.4	18	4.7
BMI						
Mean, SD	25.9	4.0	24.4	3.6	23.3	3.2
<25	249	44.5	514	61.9	271	77.0
25–30	229	40.9	269	32.4	65	18.5
>30	82	14.6	48	5.8	16	4.6
Age at menarche (years)						
Mean, SD	14.9	2.1	14.6	1.9	14.2	1.7
< 12	146	25.6	261	30.3	130	36.4
12–14	225	39.4	345	40.1	148	41.5
> 14	200	35.0	255	29.6	79	22.1
Menopausal status						
Premenopausal	208	36.7	438	51.1	243	68.6
Postmenopausal	359	63.3	420	49.0	111	31.4
Age at menopause (years)						
Mean, SD	50.0	3.9	49.8	4.0	48.6	4.4

	Density (BI-RADS)					
	Fatty and scattered glandular dense (*n* = 632)		Heterogeneously dense (*n* = 988)		Extremely dense (*n* = 381)	
	n	**%**	***n***	**%**	***n***	**%**
<50	91	14.4	495	50.1	314	82.4
>50	541	85.6	493	49.9	67	17.6
Family history of breast cancer						
No	524	91.6	794	92.2	319	90.1
Yes	48	8.4	67	7.8	35	9.9
Breastfeeding						
No	61	11.9	123	16.3	78	25.2
Yes	452	88.1	632	83.7	231	74.8
Parity						
Nulliparous	9	1.6	28	3.3	44	12.6
Parous	558	98.4	824	96.7	305	87.4
Grade						
Grade I/II	390	69.2	600	67.4	230	67.7
Grade III	174	30.9	290	32.6	110	32.4
Tumor size						
<2 cm	144	39.9	218	42.2	75	35.9
>2 cm	217	60.1	299	57.8	134	64.1
Node						
Negative	282	51.0	466	55.4	199	56.9
Positive	271	49.0	375	44.6	151	43.1
ER						
Negative	129	20.4	192	19.4	86	22.6
Positive	503	79.6	796	80.6	295	77.4
PR						
Negative	137	21.7	214	21.7	79	20.8
Positive	495	78.3	773	78.3	301	79.2
HER 2						
Negative	495	78.3	743	75.2	283	74.3
Positive	137	21.7	245	24.8	98	25.7

	Density (BI-RADS)					
	Fatty and scattered glandular dense (*n* = 632)		Heterogeneously dense (*n* = 988)		Extremely dense (*n* = 381)	
	n	**%**	***n***	**%**	***n***	**%**
Kl-67						
Negative	267	63.0	464	55.2	154	58.1
Positive	157	37.0	377	44.8	111	41.9
EGFR						
Negative	300	75.2	558	72.9	171	68.7
Positive	99	24.8	208	27.2	78	31.3
CK56						
Negative	372	90.5	701	88.2	228	88.7
Positive	39	9.5	94	11.8	29	11.3
TP-53						
Negative	182	49.6	327	46.3	115	49.2
Positive	185	50.4	379	53.7	119	50.9

BI-RADS: Breast Imaging Reporting and Data System (fatty and scattered glandular dense = categories A & B, heterogeneously dense = C, extremely dense = D); TN: triple negative; BMI: body mass index; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor 2; EGFR: epidermal growth factor receptor; CK56: cytokeratin 5/6; OR: odds ratio; 95% CI: 95% confidence interval

Table 2

Associations between BI-RADS mammographic density and molecular subtype among 2001 Chinese women with breast cancer

	Fatty and scattered glandular dense (*n* = 632)		Heterogeneously dense (*n* = 988)		Extremely dense (*n* = 381)	
	n	**OR (95% CI)**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
Subtype						
Luminal A	971	Ref.	Ref.		Ref.	
Luminal B-high proliferative	431	Ref.	1.14(0.85-1.52)	0.38	0.99(0.66-1.47)	0.95
Luminal B-HER2+	300	Ref.	1.40(1.01-1.96)	0.05	0.96(0.60-1.52)	0.85
HER2-enriched	180	Ref.	1.01 (0.67-1.51)	0.98	1.81 (1.08-3.06)	0.03
TN-basal like	119	Ref.	1.55 (0.95-2.52)	0.08	1.20(0.60-2.40)	0.61

Modeling tumor subtype as the outcome variable and BI-RADS density as the explanatory variable (fatty and scattered glandular combined as the reference group); models were adjusted for age, BMI, menopausal status, parity, and nodal status

BI-RADS: Breast Imaging Reporting and Data System (fatty and scattered glandular dense = categories A & B, heterogeneously dense = C, extremely dense = D); HER2: human epidermal growth factor 2; TN: triple negative; OR: odds ratio; 95% CI: 95% confidence interval

Table 3

Associations of BI-RADS density and breast cancer subtype stratified by menopausal status (n = 1779)

Premenopausal (n = 889)						
	Heterogeneously dense			Extremely dense		
	n	OR (95% Cl)	p value	n	OR (95% Cl)	p value
Subtype						
Luminal A	292	Ref.		171	Ref.	
Luminal B	78	1.76(1.01-3.07)	0.05	40	1.44(0.75-2.75)	0.27
HER2-enriched	35	1.07 (0.56-2.04)	0.85	27	1.63(0.76-3.48)	0.21
TN	33	1.57 (0.80-3.08)	0.19	5	0.75 (0.24-2.34)	0.62
Postmenopausal (n = 890)						
	Heterogeneously dense			Extremely dense		
	n	OR (95% CI)	p value	n	OR (95% CI)	p value
Subtype						
Luminal A	291	Ref.		75	Ref.	
Luminal B	78	1.21 (0.77-1.90)	0.40	10	0.58(0.26-1.28)	0.18
HER2-enriched	27	0.73 (0.41-1.31)	0.29	16	2.03 (0.94-4.38)	0.07
TN	24	0.84 (0.35-2.02)	0.69	10	1.09(0.38-3.15)	0.87

Modeling tumor subtype as the outcome variable and BI-RADS density as the explanatory variable (fatty and scattered glandular combined as the reference group); models were adjusted for age, BMI, parity, and nodal status

BI-RADS: Breast Imaging Reporting and Data System (Minimally Dense = categories A & B, heterogeneously dense = C, extremely dense = D); HER2: human epidermal growth factor 2; TN: triple negative; OR: odds ratio; 95% CI: 95% confidence interval

Table 4

Associations of BI-RADS density and breast cancer subtype stratified by BMI (*n* = 1743)

	Almost entirely fatty/minimally fatty		Heterogeneously dense			Extremely dense		
	n	**OR (95% CI)**	***n***	**OR (95% CI)**	***p* value**	***n***	**OR (95% CI)**	***p* value**
BMI < 25 (*n* = 1034)								
Subtype								
Luminal A	176	Ref.	353	Ref.		188	Ref.	
Luminal B	29	Ref.	38	1.45(0.89–2.37)	0.13	38	1.04(0.57–1.92)	0.90
HER2-enriched	28	Ref.	37	0.79 (0.44–1.39)	0.41	37	2.43 (1.24–4.76)	<0.01
TN	16	Ref.	34	1.01 (0.51–2.00)	0.97	8	0.48(0.18–1.30)	0.15
BMI >25 (*n* = 709)								
Subtype								
Luminal A	234	Ref.	217	Ref.		55	Ref.	
Luminal B	39	Ref.	59	1.40(0.86–2.29)	0.18	11	1.02 (0.46–2.26)	0.97
HER2-enriched	26	Ref.	21	0.68(0.35–1.34)	0.27	8	0.98 (0.38–2.52)	0.96
TN	12	Ref.	20	1.67(0.74–3.75)	0.21	7	2.57 (0.85–7.78)	0.10

Modeling tumor subtype as the outcome variable and BI-RADS density as the explanatory variable (Fatty and Scattered Glandular combined as the reference group); models were adjusted for age, parity, menopausal status, and nodal status

BI-RADS: Breast Imaging Reporting and Data System (minimally dense = categories A & B, heterogeneously dense = C, extremely dense = D); HER2: human epidermal growth factor 2; TN: triple negative, OR: odds ratio; 95% CI: 95% confidence interval