

Mammographic Breast Density as a Predictor of Radiological Findings Requiring Further Investigation

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ABSTRACT: **Background:** High density breast mammography has been associated with a greater risk for breast cancer and an increased likelihood of false negative results.

Objectives: To assess whether the degree of mammographic breast density correlates with increased risk for the presence of radiographic findings requiring further histological investigation.

Methods: Included in the study were 2760 consecutive screening mammograms performed in a large volume, early detection mammography unit. All mammograms were complemented by high resolution ultrasound and interpreted by a single expert radiologist. Breast density (BD) was evaluated using a semi-quantitative 5 grade scale and grouped into low breast density (LBD) and high breast density (HBD) mammograms. Demographic and all relevant obstetric, personal and family history of breast cancer data were recorded.

Results: Of the 2760 mammograms 2096 (76%) were LBD and 664 (24%) were HBD. Mean age of the LBD and HBD groups was 59 ± 10.5 and 50.9 ± 9.3 years respectively ($P = 0.001$). Breast density significantly correlated with presence of mammographic findings requiring further histological assessment (8.7% and 12.3% for LBD and HBD respectively, $P < 0.01$). In women younger than 60 years in whom histological assessment was required due to these findings, malignant pathology was significantly more prevalent in the HBD group (2.3% and 4.1% respectively, $P = 0.03$). Age, parity, patient history and HBD were identified as independent risk factors for any pathological mammographic finding.

Conclusions: Highly dense mammography, aside from being an indicator of higher risk for breast cancer, appears to be associated with a significantly higher incidence of findings that will prompt further investigation to achieve a definite diagnosis.

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2011). Timely diagnosis of breast malignancy depends highly on adequate imaging and recognition of the apparent breast pathology. Breast density is a key factor affecting the radiographic appearance of the breast, which changes with age and correlates with the ratio between the fatty and glandular parenchymal components of the breast. Women younger than 35 years display dense breast tissue on mammography in 65% of cases, compared to only 20–15% of cases in women older than 65 [1]. High breast density (BD) has been shown to be associated with increased risk for breast cancer both as an independent factor and as an obscuring element masking the radiographic pathological findings and delaying time of the diagnosis [2-9].

As a result, some breast cancers escape detection by mammography screening [10,11]. This has raised intense debate as to the role of complementary screening methods such as breast sonography, magnetic resonance imaging (MRI) or 3D-tomography in patients shown to have high BD.

The association between breast density and the need for further radiological and/or surgical assessment was previously described by Carney and colleagues [12]. However, although age > 60 years and heterogeneously/extremely dense breasts correlated with higher likelihood of requiring biopsy and/or surgical consult in one patient subpopulation, no further data were recorded as to whether a surgical intervention/biopsy was performed and the histologic results of those procedures, if performed.

The aims of this study were to analyze the data from our experience in a large tertiary medical center, identify a possible correlation between the degree of mammographic density and the presence of any finding requiring further histologic investigation (tissue biopsy or surgical intervention), and assess correlation with specific histological diagnoses.

PATIENTS AND METHODS

The study included 2760 screening mammograms performed during 1 year (2004–2005) in a high volume early detection

Breast cancer is the most common malignant disease afflicting women worldwide, comprising a sixth of all female cancers (according to the World Health Organization,

mammography unit within a large tertiary university-affiliated medical center. All mammograms were complemented by high resolution ultrasound performed and interpreted by a single expert breast radiologist. Breast density was evaluated in all mammograms using a semi-quantitative 5 grade scale [13] and grouped into low density (1–3, LBD) and high density (4–5, HBD) mammograms.

All demographic and additional relevant obstetric as well as family and personal history of breast cancer data were entered into a database. Test results were entered as normal or as the presence of any of the following: lump (cystic or solid), distorted tissue architecture or density [14], and suspicious calcifications. The study protocol was approved by the Sheba Medical Center institutional review board.

Statistical analysis was performed using SAS 9.2. Chi-square test was used for categorical variables. Odds ratios (OR) and 95% confidence interval (CI95%) were calculated for each of the compared variables. Subjects with missing data were excluded in the subsequent analysis. *P* value < 0.05 was considered statistically significant. Sub-analysis was performed for the > 60 year old patient group. Multivariate logistic regression was used to identify independent risk factors for any pathological mammographic finding.

RESULTS

Over the period of 1 year 2760 screening mammograms were performed. Mean overall age was 56 years (± 10.7) and 71% were post-menopausal. Group demographic characteristics are presented in Table 1. Of the 2760 mammograms 2096 (76%) were LBD and 664 (24%) HBD. The mean age of the patients in both groups was 59 ± 10.5 years and 50.9 ± 9.3 years respectively (*P* = 0.001). Group and subgroup structure is presented in Figure 1. A total of 1459 mammographic findings were detected in 1272 women (46.0%). LBD and HBD significantly correlated with the presence of mammographic findings requiring histological assessment: 8.7% and 12.3% respectively, OR 1.54, CI95% 1.17–2.03, *P* = 0.002. Thus, in the HBD group the incidence of a solid lump (9%) and suspicious calcifications (4.4%) were significantly higher compared to the LBD group (6.6% and 1.8% respectively, *P* = 0.001 and *P* = 0.0002). Tissue irregularity did not differ significantly between the HBD and LBD groups (3.3% and 2.7% respectively, *P* = NS). Tissue histology revealed malignant pathology in 74 patients in the LBD group and 30 patients in the HBD group (3.5% and 4.5% respectively, OR 1.29, *P* = NS).

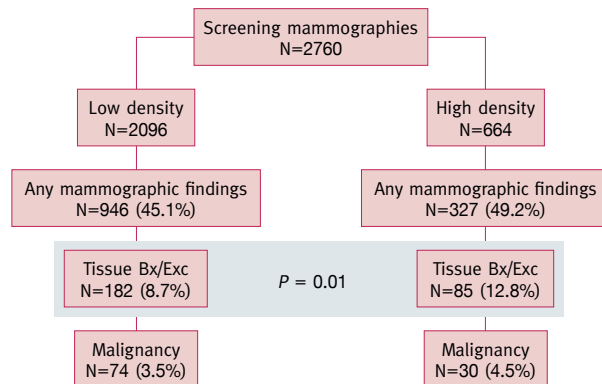
High risk non-malignant breast pathologies (atypical ductal hyperplasia and lobular carcinoma in situ) were more frequent in the HBD group (1.05% vs. 0.33% in concordance, OR 3.18, CI95% 1.11–9.10, *P* = 0.03). Malignant findings of invasive breast cancer (IDC/ILC) did not differ significantly between breast density groups. Occurrence of ductal carcinoma in situ

Table 1. Baseline characteristics of study population by age group

	Overall	Age < 60	Age ≥ 60
N	2760	1824	936
Age (years)	56.0 (10.7)	68.1 (6.3)	49.9 (6.5)
Mean mammographic density	2.7 (1.1)	2.9 (1.1)	2.2 (0.9)
Unknown cases	0 (0%)	0 (0%)	0 (0%)
Age at menarch (years)	13.0 (1.7)	13.0 (1.4)	13.2 (1.4)
Unknown cases	75 (2.7%)	45 (2.5%)	30 (3.2%)
Parity			
No. of pregnancies	3.6 (2.1)	3.5 (1.9)	4.0 (2.5)
Parous	2571 (93.2%)	1699 (93.1%)	872 (93.1%)
Nulliparous	141 (5.1%)	104 (5.7%)	37 (4.0%)
Unknown cases	48 (1.7%)	21 (1.2%)	27 (2.9%)
Age at first pregnancy (years)	24.9 (4.3)	25.2 (4.3)	24.1 (4.2)
Unknown cases	340 (12.3%)	217 (11.9%)	123 (13.1%)
Age at menopause (years)	48.9 (4.7)	47.9 (7.7)	50.0 (4.4)
Use of HRT	592 (21.4%)	313 (37.7%)	279 (29.8%)
Unknown cases	1 (0%)	1 (0%)	0 (0%)
Family history of breast cancer (%)	738 (26.7%)	519 (28.5%)	219 (23.4%)
Unknown cases	0 (0%)	0 (0%)	0 (0%)
Personal history of breast cancer (%)	637 (23.1%)	351 (19.2%)	286 (30.6%)
Unknown cases	0 (0%)	0 (0%)	0 (0%)

Data presented as mean (standard deviation) or n (%)
HRT = hormone replacement therapy

Figure 1. Overall association of breast density in screening mammographies with mammographic findings

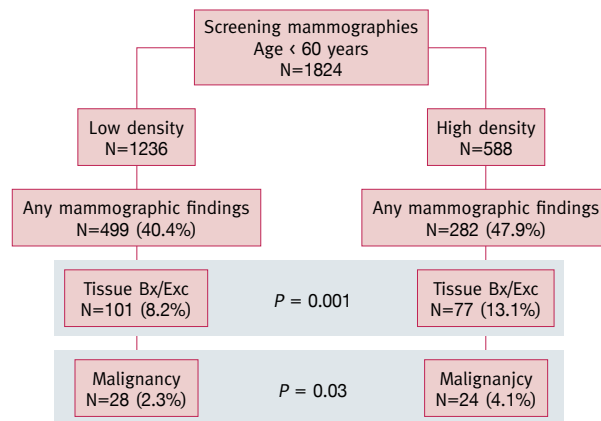


Dens = density, Bx = biopsy, Exc = excision

(DCIS) was more prevalent in the HBD group (3.6% vs. 1.2%, OR 3.10, CI95% 1.76–5.47, *P* = 0.0001).

Analysis of the impact of breast density on mammographic findings in women younger than 60 years is presented

Figure 2. Association of breast density in screening mammographies with mammographic findings in women younger than 60 years



Dens = density, Bx = biopsy, Exc = excision

In Figure 2, LBD and HBD significantly correlated with the presence of mammographic findings requiring histological assessment (8.2% and 13.8% respectively, OR 1.69, CI95% 1.24–2.32, $P = 0.001$). Core needle biopsy or surgery was performed revealing malignant pathology in 28 patients in the LBD group and 24 patients in the HBD group (2.3% and 4.1% respectively, OR 1.84, CI95% 1.05–3.20, $P = 0.03$). In women younger than 60 years malignant findings of invasive breast cancer (IDC/ILC) did not differ significantly between breast density groups. Occurrence of ductal carcinoma in situ (DCIS) was more prevalent in the HBD group (3.2% vs. 0.8%, OR 4.09, CI95% 1.89–8.86, $P = 0.0003$).

Multivariate logistic regression pointed to HBD as an independent risk factor for any pathological mammographic finding. Other identified independent risk factors include patient age, the age at menarche and at first birth, parity, and personal and family history.

DISCUSSION

In recent years there has been a growing awareness of the clinical significance of high breast density in both the medical community and the general population. Legislation requiring physicians to inform patients of the limitations of screening mammography in women with HBD has been passed in 19 U.S. states* and similar efforts are on their way in Canada and other countries. In this study we investigated the association between breast density and pathological findings requiring further investigation (e.g., breast masses, microcalcifications)

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in a large cohort of screening mammographies performed in a single tertiary center and assessed by a single expert breast radiologist. Our results showed that highly dense breasts had a significantly larger proportion of solid lumps and suspicious calcifications. Women with denser breast tissue had a higher probability of requiring further investigational procedures such as core needle biopsy or excisional surgical biopsy. Furthermore, in the group of women younger than 60, higher breast cancer rates were noted in the HBD group (OR 1.84, CI95% 1.05–3.20, $P = 0.03$). These findings correspond to the study published by Tescic and colleagues [15] who analyzed a multi-center cohort of 52,752 women who had undergone a screening mammography. Their results showed increased risk for breast cancer (OR 1.9, 95%CI 1.3–2.8) among women with dense breasts compared to women with non-dense breasts. A recent similar study by Park and co-authors [16] tested the prognostic value of high volumetric breast density on the risk of breast cancer. An association was found in postmenopausal women ($n=1076$, $P < 0.001$) but not in premenopausal women.

In our cohort, DCIS was the only tumor subtype significantly correlating to mammographic breast density in both the general and the younger age group (OR 3.10 and OR 4.09, respectively). Bertrand et al. [17] recently published their findings on the effect of mammographic breast density on breast tumor subtype based on data pooled from six studies that included a total of 10,613 women who underwent screening mammography. Similar to our results, their study found a difference in the association of mammographic density with DCIS for women aged < 55 years compared with those aged ≥ 55 . The researchers noted that younger women with high mammographic density had increased risk of DCIS.

Few studies have investigated the association between high risk non-malignant breast pathologies (such as atypical ductal hyperplasia, atypical lobular hyperplasia and lobular carcinoma in situ) and mammographic breast density. The statistically significant association between high mammographic breast density and presence of such lesions in the histological specimens described in the present study may explain the high risk phenotype attributed to high breast density.

The optimal imaging for highly dense breast remains a matter of debate. Modalities such as MRI and automated 3D breast sonography have been used separately or combined with image analysis segmentation algorithms in assessment of the breast [18–22]. This increased risk for invasive procedure due to suspicious findings must be considered when evaluating the cost-effectiveness of new complementary imaging modalities for women with high breast density [23–25].

CONCLUSIONS

The results of our study further emphasize the need to regard high breast density as an independent risk factor for breast disease, associated with a significantly increased incidence of

findings that will prompt further investigation to achieve a definite diagnosis. Due to the lower sensitivity of mammography in patients with highly dense parenchyma, it is likely that the true incidence of non-malignant findings is even higher.

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