Egyptian Journal of Radiology and Nuclear Medicine

RESEARCH Open Access

Evaluation of volumetric breast density as a risk factor for breast carcinoma in pre- and postmenopausal women, its association with hormone receptor status and breast carcinoma subtypes defined by histology and tumor markers

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Abstract

Background: Mammographic breast density is acknowledged as an independent risk factor for breast cancer. Its association with different pathological types and tumors markers is still under evaluation. This study aims to assess the associations of volumetric density grades (VDG) with breast cancer risk in premenopausal and postmenopausal age groups separately. We also aim to assess the association of VDG with hormone receptor status and breast cancer subtypes defined by histology and tumor markers (ER, PR, Her 2-neu and Ki 67).

Results: This retrospective study was done with inclusion of two comparable groups of 185 breast cancer cases and 244 healthy controls. These groups were further divided into pre- and postmenopausal subgroups. Mammograms of the cases and controls were evaluated by fully automated volumetric breast density software-VOLPARA and classified into four VDG. The hormone receptor status and breast cancer subtypes defined by histological features and tumor markers in the various VDG were also evaluated. The risk of developing carcinoma was significantly higher in women with high-density breasts (VDG-c + VDG-d) as compared with low-density breasts (VDG-a + VDG-b) in both premenopausal and postmenopausal subgroups. No significant difference was seen in the histopathological characteristics of breast cancer among various VDG.

Conclusions: Our study suggests positive association between high VDG and risk of cancer in both premenopausal and postmenopausal group of Indian women. The hormone receptor status and breast cancer subtypes defined by histology and tumor markers did not reveal any relation to the grades of breast density.

Background

Mammographic breast density (MBD) is defined as the relative amount of radio-dense fibro-glandular tissue compared with radiolucent adipose tissue. MBD is acknowledged as an established sovereign breast cancer risk factor [1, 2]. Mammographic density is affected by both heritable and acquired factors with 50–60% of the variance being determined by heritable factors [3, 4]. Other determinants including age, body mass index (BMI), reproductive status, hormone replacement therapy and tamoxifen treatment also influence MBD [3, 5]. The augmented risk of breast cancer lasts for more than or equal to 10 years after density assessment in both

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pre- and postmenopausal women [6]. However, increased MBD is known to be coupled with decreased mammographic sensitivity [7].

Breast cancer is a diversified disease; different histological subtypes of breast cancer have specific clinical and imaging features that make their diagnosis and management challenging and influence prognosis of the patients [8–11]. Some of the well-established risk factors for developing breast cancer, such as age, parity, age at first child birth, breast feeding, menopausal status, body mass index, history of hormone therapy and alcohol consumption, have shown associations only with certain histological subtypes, suggesting multifactorial etiology [12–15]. It is still under evaluation whether breast density differentially affects the risk of certain pathological subtypes of breast cancer. Positive association has been found between high MBD and tumor characteristics that are related to grave prognosis, including larger size, higher grade, estrogen receptor (ER) status and lymph node invasion [16–19], which could be explained by delay in diagnosis due to reduced sensitivity of mammography and/or aggressive tumor biology [2].

A number of studies have been performed to establish the association of MBD with breast cancer subtype defined by hormone receptor status with the inconsistent results. Most of the studies have primarily investigated the association between MBD and ER status without addressing to Her-2-neu (H2P) or progesterone receptor (PR) status [20, 21]. Few studies found MBD to be associated with both ER positive and ER negative tumors while other found a lack of correlation between MBD and ER status [16, 22, 23]. Similarly, a small case only study found an association between MBD and PR positivity [24], whereas study by Seo et al. [25] found no correlation between high density and human epidermal growth factor receptor 2 (Her2-neu) status.

Breast density assessment can be done using qualitative or quantitative methods. The qualitative method using Breast Imaging Reporting and Data System (BI-RADS) is based on subjective interpretation and has suboptimal reproducibility. To overcome these issues, quantitative methods have been developed for measuring mammographic density in a quantitative manner. One such quantitative density tool is Volpara (Volpara Solutions, Wellington, New Zealand), which is a commercial fully automated product recently developed to measure volumetric breast density. It is based on computerized algorithm that calculates X-ray attenuation at each pixel and converts the attenuation to estimate the tissue composition by creating a density map. By adding these values in the density map, this tool can measure the fibro glandular tissue volume in each breast and breast density is determined as the percentage of fibro-glandular tissue volume. Mapping of that percentage is used to automatically generate volumetric density grade (VDG) a to d, which corresponds to the BI-RADS density categories, A to D [26]. Only few studies have been conducted on the Indian population to look for the association of breast density and cancer risk, and only one study used an automated mammographic volumetric breast density (VBD) assessment in the Indian population [26].

In this study, we aim to-

1. Assess the associations of VDG with breast cancer risk in premenopausal and postmenopausal age groups separately.
2. Assess the association of VDG with hormone receptor status and breast cancer subtypes defined by histology and tumor markers (ER, PR, Her 2-neu and Ki 67).

Methods

Patient selection

This retrospective study in case–control layout was conducted at the Breast Imaging unit of Radiodiagnosis department of our Institute from January 2019 to December 2020. The study was approved by our Institution Ethics committee. All women who had come for screening or diagnostic mammography were included in the study. Women who had undergone mastectomy for breast cancer and had come for surveillance mammography of contralateral breast were also included in the study. Pregnant, lactating women and those with large or bilateral breast lesions were excluded from the study to avoid false density estimation. Women with a history of breast conservation surgery, radiotherapy, chemotherapy or hormonal therapy were also excluded for the same reason. Institute ethics committee waived off the requirement for written informed consent as our study was retrospective in nature.

These patients underwent standard 2D imaging and DBT as a single procedure at the same breast compression on a Digital Mammography Unit (GE Healthcare Senographe Essential 54020/CESM1/SenoClaireA.6) using automatic exposure controls (AECs) called automatic optimization of parameters (AOP). It uses information from the leading part of the detector to vary the scan velocity dynamically, thus adjust anode/filter combinations, peak kilovoltage and target signal-to-noise ratio based on the thickness of compressed breast. Digital mammography was performed in two views: the craniocaudal (CC) and medio-lateral oblique (MLO) view and tomosynthesis in one view (MLO). Additional views were taken when required. Ultrasound was done whenever

required on Supersonic AIXPLORER Multiwave Version 12.2.0808USG scanner.

Volumetric breast density (VBD) assessment

Quantitative volumetric assessment was done by using software Volpara Density (Imaging software version 3.3.2, Volpara Algorithm version Number1.5.4.0, Wellington, New Zealand). Volpara works by selecting a reference point of known breast composition, such as fatty breast tissue just anterior to the chest wall. Then, it works backward and calculates the attenuation at each pixel appertaining to the reference pixel. It calculates the types of tissue that must have been present between the pixel and the x-ray source. Then, the volume of fibro glandular tissue in cubic centimeters, the volume of breast tissue in cubic centimeters and their ratio are obtained to acquire quantitative VBD. The volumetric density grade (VDG) is the VBD threshold at various levels and was determined automatically in each case and was noted. VBD of less than 3.5% is VDG-a, 3.5–7.4% is VDG-b, 7.5–15.5% is VDG-c, and ≥ 15.5% to VDG-d. (Fig. 1)

As per the presentation, mammographic and ultrasonographic findings in each case, BI-RADS assessment category was assigned. Two hundred and fifty-six masses with suspicious features were identified, and underwent trucut biopsy and their pathological findings were available to us for analysis. Out of these 256 lesions, 193 came out to be malignant. We could not get accurate demographic data (like age at menarche, age at first child birth and menopausal status) in 8 of the histologically confirmed cases of malignancy, hence excluded them from study. Remaining 185 patients with biopsy proven malignancy and complete demographic details constituted the "case group." Two hundred and forty-seven women with no suspicious lesion on mammogram or ultrasound constituted the comparison group. Out of these, three

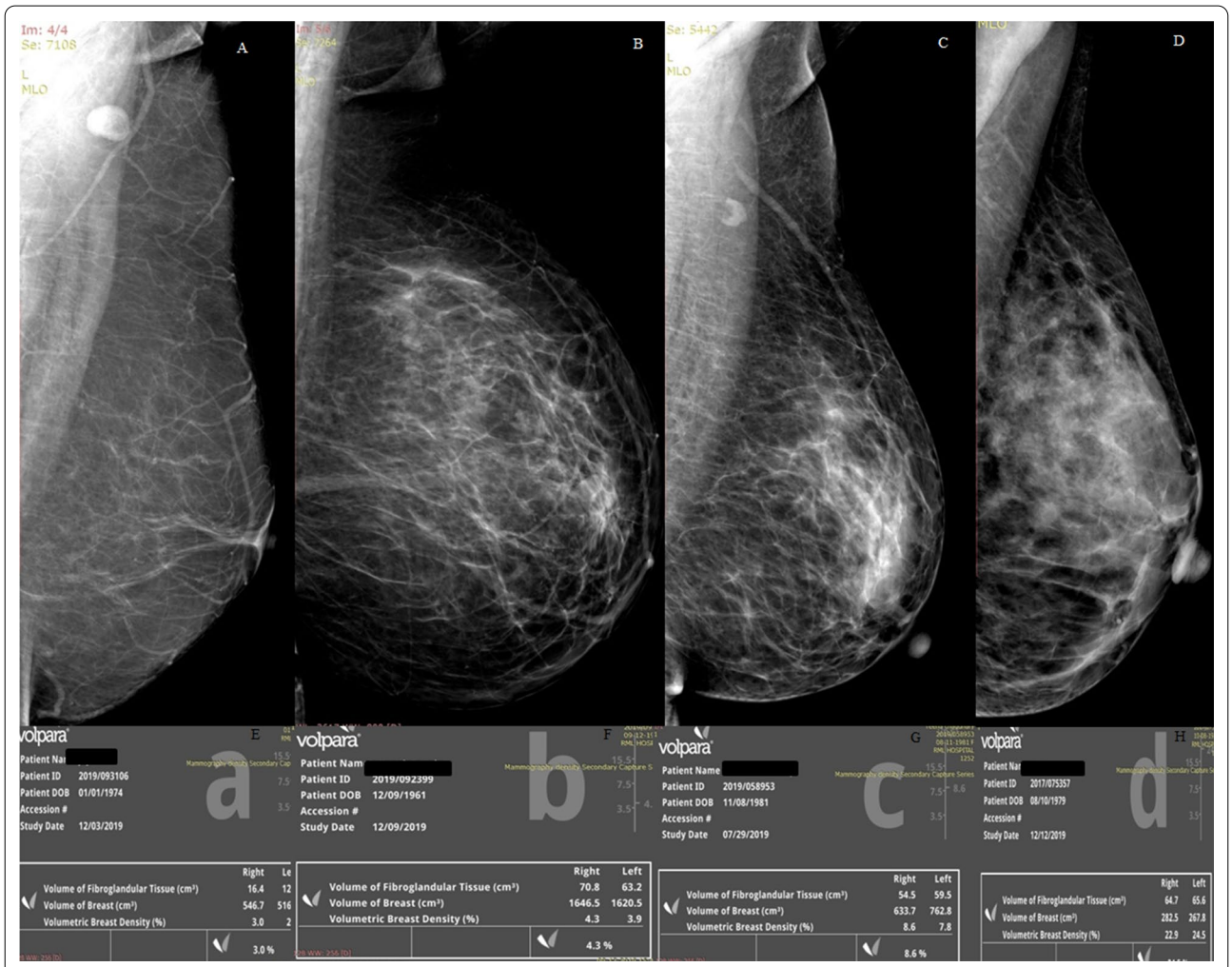

Fig. 1 Medio-lateral oblique views of mammograms showing different Volpara density grades with quantitative volumetric density values: **A**, **E** Grade a (3.0%), **B**, **F** Grade b (4.3%), **C**, **G** Grade c (8.6%) and **D**, **H** Grade d (24.5%)

females had undergone hysterectomy for various reasons, hence excluded from the study. Remaining 244 women with negative mammogram and ultrasound constituted the "control group."

Since menopause is an event which has major influence on the changes in breast tissue, both the groups (cases and controls) were reevaluated after dichotomizing the study subjects (185 cases + 244 controls) into "premenopausal" and "postmenopausal" subgroups. "Menopause" was defined as the time when the woman had missed menses for 12 consecutive months in absence of any physiological, surgical or medical condition that may cause bleeding to stop. A total of 188 women were enrolled in premenopausal (79 cases + 109 controls) and 241 (106 cases + 135 controls) in postmenopausal subgroups.

The ER, PR and Her2-neu status was derived from core biopsies or postoperative specimens and were available for 127 patients. Based on these hormone receptor status, breast carcinomas were classified into three groups-luminal type (ER+, PR+, Her2±), Her2 positive (ER−, PR−, Her2+) and triple-negative breast cancers (ER−, PR−, Her2−) as these cancer groups have therapeutic and prognostic implications. Ki67 index scoring was performed in clinically low-stage luminal like carcinomas (like in T_1N_0 disease) as only in those cases it could have changed the treatment plan. Cases with > 14% positive nuclei were classified as high Ki-67 expression, and those with < 14% were classified as low Ki-67 expression. It was available only for 14 patients. Hence, further classification of luminal type breast carcinomas into Luminal A and Luminal B was not done.

Statistical analysis

It was carried out on SPSS Version 21.0 statistical Analysis Software. Cross-tab and frequency were used to calculate different parameters among cases and controls and t-test to estimate mean and SD. Mann–Whitney U test was used to compare different parameters between cases and controls. Nonparametric-one sample test was applied for comparison between premenopausal and postmenopausal subgroups. Pearson's correlation coefficient was measured to find out difference in the distribution of VDG among cases and controls. Bivariate Pearson correlation was measured to look for association between different VDG types and occurrence of carcinoma in premenopausal and postmenopausal women. Chi-square test was applied to evaluate the relation between VDG versus hormone receptor status and breast cancer subtypes defined by histology and tumor markers.

Results

A total of 185 biopsy proven breast cancer patients constituted the "case" group and compared with a group of 244 "controls." Cross-tab and frequency were used to calculate different parameters among cases and controls and t-test to estimate mean and SD. The mean age of control group was 48.7 ± 10.1 years and that of case group was 50.3 ± 11.02 years. The mean age at menarche in control group was 13.4 ± 0.92 years and that of case group was 13.4 ± 0.76 years. The mean age at first child birth in control group was 20.9 ± 6.7 years and that of case group were 20.7 ± 5.97 years. Premenopausal status was seen in 42.7% of controls and 44.6% of cases. Nulliparity was observed in 6.5% of controls and 5.9% of cases. Exclusive breast feeding was present in 80.3% of controls and 80.0% of cases. All the aforementioned factors were compared in cases and controls by using Mann–Whitney U test. We found no significant difference in distribution of subjects in the two groups and thus the two groups were comparable. (Table 1)

Among the controls, most common breast density type was VDG-b (45.49%) followed by VDG-c (25%), VDG-d (17.21%) and VDG-a (12.29%). Among the cases, the frequency of VDG-c (57.83%) was the highest, followed by VDG-d (26.48%). For computation of correlation, VDG-a and VDG-b were amalgamated together to form low-density breasts (LDB), and VDG-c and VDG-d as high-density breasts (HDB). Pearson's correlation coefficient was measured and significant difference was found in the distribution of VDG among cases and controls, i.e., more controls had VDG-a ($P = 0.009$) and VDG-b ($P = 0.002$) while more cases had VDG-c density ($P = 0.015$). Distribution of VDG-d among the two groups was insignificant (P 0.065).

Table 1 Clinical and demographic profile of case and control groups

Variables	Cases ($n = 185$)	Controls ($n = 244$)
Menopausal status-		
Premenopausal	79	109
postmenopausal	106	135
Age (mean + SD)	50.3 + 11.02 years	48.7 + 10.1 years
Age at menarche (mean + SD)	13.4 + 0.76 years	13.4 + 0.92 years
Age at first childbirth (mean + SD)	20.7 + 5.97 years	20.9 + 6.7 years
Parity		
Nulliparous	11	16
Parous	174	228
Exclusive breast feeding		
Present	148	196
Absent	37	48

Similarly more controls had LDB whereas more cases had HDB with Odd's ratio (OR-2; 95% CI) ($P=0.005$ each). (Table 2)

Among premenopausal women, VDG-c was most commonly seen (in 38.29%) followed by grade d (in 31.91%). VDG-b was seen in 27.65% and VDG-a in 2.1% of premenopausal population. In other words, high-density breasts were present in 70.20% and low density in 29.80% of this group. In postmenopausal subgroup VDG-c was again the most common entity (39.83%) followed by grade b (36.09%). VDG-d and VDG-a was noted in 12.86% and 11.20% of these women. Or, we can say, high density was present in 52.69% and low density in 47.29% of the postmenopausal subgroup. Nonparametric-one sample test was applied and significant difference was found in the distribution of VDG-a ($P=0.014$) and VDG-b ($P=0.042$) between premenopausal and postmenopausal subgroups, i.e., more postmenopausal women had VDG-a and VDG-b type densities. Distribution of VDG-c and VDG-d among the two subgroups was insignificant ($P=0.211$ and 0.646, respectively) (Table 3).

In premenopausal and postmenopausal subgroups, malignancy was present in 42.02% and 43.98% of the study population. In premenopausal subgroup, women with VDG-c had maximum number of carcinoma cases (40 out of 72, i.e., 55.5%) followed by VDG-d (29 out of 60, i.e., 48.33%) and VDG-b (10 out of 52, i.e., 19.2%). Only 4 premenopausal women had VDG-a, but none of them had breast carcinoma (zero out of 4). In postmenopausal subgroup, women with VDG-c had highest number of carcinoma cases (67 out of 96, i.e., 69.79%) followed by VDG-d (20 out of 31, i.e., 64.51%), VDG-b (18 out of 87, i.e., 20.68%) and VDG-a (1 out of 27, i.e., 0.03%). Bivariate Pearson correlation was measured and no significant difference was found between different VDG types and occurrence of carcinoma in premenopausal ($P=0.228$) or postmenopausal women ($P=0.297$).

Table 3 Difference in distribution of different volumetric density grades in premenopausal and postmenopausal women

VDG	Menopausal status	*P* value
A	Premenopausal	0.014
	Postmenopausal	
B	Premenopausal	0.042
	Postmenopausal	
C	Premenopausal	0.211
	Postmenopausal	
D	Premenopausal	0.646
	Postmenopausal	

In premenopausal subgroup, women with HDB (VDG-c plus VDG-d) had more number of carcinoma cases (69 out of 132, i.e., 52.27%) compared with LDB (VDG-a plus VDG-b) (10 out of 56, i.e., 17.85%). Similarly, in postmenopausal subgroup, women with HDB had more number of carcinoma cases (87 out of 127, i.e., 68.50%) compared with LDB (19 out of 114, i.e., 16.66%). Chi-square test was applied and statistically significant difference was found between HDB and risk of developing carcinoma in both premenopausal and postmenopausal subgroups with OR = 2.98 and 2.63, respectively, with 95% CI, ($P<0.001$ and $P=0.003$, respectively).

In the present study, the infiltrating ductal carcinoma was the most common histopathological type, ($n=175$, 94.59%) followed by malignant phyllodes (1.0%, $n=2$). Invasive lobular carcinoma, mucinous carcinoma, invasive papillary carcinoma, DCIS, carcino-sarcoma, primary lymphoma of breast, neuroendocrine tumor and Paget's disease were equally distributed in 0.5% cases ($n=1$ for each). Out of 175 cases of infiltrating ductal carcinoma ($n=175$), maximum cases were seen in

Table 2 Distribution of different volumetric density grades in case and control groups in premenopausal, postmenopausal and all age groups

VDG	Group	Premenopausal	Postmenopausal	All age groups	*P* value
A	Case	0	1	1	0.009
	Control	4	26	30	
B	Case	10	18	28	0.002
	Control	42	69	11	
C	Case	40	67	107	0.015
	Control	32	29	61	
D	Case	29	20	49	0.819
	Control	31	11	42	
Total	Case	79	106	185	0.065
	Control	109	135	246	

Table 4 Risk of carcinoma in different VDG in premenopausal and postmenopausal age groups

VDG	Premenopausal	*P* value	Postmenopausal	*P* value
A	0	0.228	1	0.297
B	10		18	
C	40		67	
D	29		20	
Total	79		106	

VDG-c ($n=104$) followed by VDG-d ($n=45$), VDG-b ($n=25$). Only one woman who had VDG-a type breast had malignancy and it was infiltrating ductal carcinoma. Malignant phyllodes was seen in only 2 cases and both the cases belonged to breasts with VDG-d. Chi-square test was applied and no statistically significant difference in distribution of VDG was found among different histological types ($P=0.312$) (Table 4).

The ER, PR and Her2-neu receptor status was available for 127 patients out of 185 cases of cancer breast. ER, PR and Her2 positivity was noted in 43.30% ($n=55$), 42.51% ($n=54$) and 29.82% ($n=38$) of the cases, respectively. Out of the total ER+ cases, maximum were from VDG-c ($n=29$, 52.72%) followed by VDG-d ($n=18$, 32.72%), VDG-b ($n=7$, 12.72%) and VDG-a ($n=1$, 1.8%). Similarly, PR+ status was most commonly seen in VDG-c ($n=25$, 46.29%) followed by VDG-d ($n=21$, 38.9%), VDG-b ($n=7$, 12.9%) and VDG-a ($n=1$, 1.8%). Her 2 neu expression was most commonly seen in VDG-c ($n=26$, 68.4%) followed by VDG-d ($n=8$, 21%), and VDG-b ($n=4$, 10.5%). It was absent in the only case seen in VDG-a. Chi-square test was applied and no statistically significant difference in distribution of VDG was found as compared to hormone receptor status ($P=0.263$ for ER, $P=0.197$ for PR and $P=0.75$ for Her2-neu). High Ki-67 expression (>14%) was noted in 11 patients and low Ki-67 expression (<14%) was seen in 3 patients.

Based on the hormone receptor status, breast carcinomas were classified into three groups—Luminal type ($n=59$, 46.45%), Her2 positive ($n=31$, 24.4%) and Triple-Negative Breast cancers ($n=37$, 29.13%). Ki-67 index was available for 14 patients. Luminal type breast cancer was most commonly distributed in VDG-c ($n=30$ or 50.8%) followed by VDG-d ($n=20$, i.e., 33.9%), VDG-b ($n=8$ or 13.55%) and VDG-a ($n=1$ or 1.6%). Similarly, Her2 positive breast cancer was most commonly seen in VDG-c ($n=23$, i.e., 74.2%) followed by VDG-d ($n=5$ or 16.12%) and VDG-b ($n=3$, i.e., 9.6%). TNBC was most commonly seen in VDG-c ($n=22$, i.e., 59.4%) followed by VDG-d ($n=10$ or 27.02%) and VDG-b ($n=5$ or16.12%). Only one carcinoma case was present in VDG-a and that was luminal like. Chi-square test was applied and no statistically significant difference in distribution of VDG was found as compared to hormone receptor groups ($P=0.903$ for TNBC, $P=0.237$ for Her 2 positive tumors and $P=0.867$ for Luminal type cancers).

Discussion

MBD is a radiographic depiction of dense fibro-glandular tissue in the breast in comparison to fatty tissue. Wolfe was the first to describe and classify breast density on mammogram and to put forward the association between different parenchymal patterns and breast cancer risk [18]. Since then, several studies have acknowledged MBD as an individualistic risk factor for breast cancer with an inverse relationship to mammographic sensitivity [19–21].

In the present study, we found that statistically significant proportion of controls had LDB, VDG-a and VDG-b. Similarly, more cases had HDB and VDG-c. Distribution of VDG-d among the two groups was not statistically significant. These findings were in accordance with the previous study which revealed that dense mammographic patterns (>50%) were seen in 16.3% of control subjects and 26.7% of cases [28].

Proportion of HDB in premenopausal group was much higher as compared to the postmenopausal subgroup. These findings correlated well with study by Attam et al. [27] Distribution of LDB in pre and postmenopausal women was statistically different, i.e., more postmenopausal women had LDB. Difference in the distribution of HDB among the two subgroups was insignificant (Table 5).

In the present study, statistically significant difference was found between high-density breasts and risk of developing carcinoma in both premenopausal and postmenopausal subgroups with OR = 2.98 and 2.63, respectively, with 95% CI, *(P* < 0.001 and $P=0.003$, respectively). These results are similar to those of previous study which had shown that the increased risk of breast cancer associated with VDG was found in both premenopausal (*P interaction* = 0.01) and postmenopausal *(P interaction* = 0.0003) women and it gets strengthened with higher BMI [28]. Other study suggests that the risk of breast cancer increases with the rise of volumetric density grade (VDG) in postmenopausal women ($P<0.001$)

Table 5 Risk of carcinoma in HDB and LDB in premenopausal and postmenopausal age groups

VDG	Premenopausal	*P* value	Postmenopausal	*P* value
LDB (A + B)	0 + 10 = 10	< 0.001	1 + 18 = 19	0.003
HDB (C + D)	40 + 29 = 69		67 + 20 = 87	

Table 6 Association of different pathological types of breast carcinoma, hormone receptor status and hormone receptor groups in different density grades

Groups	VDG a ($n=1$)	VDG b ($n=28$)	VDG c ($n=107$)	VDG d ($n=49$)	Total	*P* value
Infiltrating ductal carcinoma	1	25	104	45	175	0.312
Invasive lobular carcinoma	0	0	1	0	1	
Malignant phyllodes	0	0	0	2	2	
Mucinous carcinoma	0	0	0	1	1	
Primary lymphoma of breast	0	1	0	0	1	
DCIS	0	0	1	0	1	
Paget's disease	0	0	0	1	1	
Neuroendocrine tumor	0	1	0	0	1	
Invasive papillary carcinoma	0	0	1	0	1	
Carcino-sarcoma	0	1	0	0	1	
Ki 67[#]						
≤ 14	1	0	1	1	3	
>14	0	1	5	5	11	
ER*	1	7	29	18	55	0.263
PR*	1	7	25	21	54	0.197
Her 2-neu*	0	4	26	8	38	0.75
Hormone receptor groups						
Triple-negative	0	5	22	10	37	<0.001
Her2 positive	0	3	23	5	31	0.237
Luminal	1	8	30	20	59	0.867

[#] Available in 14

*Available in 127

only. Risk of breast cancer in these women was significantly high in VDG 4 compared with VDG 1/2 regardless of body mass index [29].

These findings differ from previously published articles which describe increased risk only in premenopausal women. Attam et al. [27] found 3.8 times risk of developing breast cancer in Premenopausal women with breast density of 50% or more as compared to women with breast density of $<10\%$. (OR = 3.86; 95% CI 1.4–10.1). Koshi et al. [30] also found that in premenopausal women, the odds of having breast cancer was significantly higher for Grade 3 and 4 breasts (odds ratio—3.03 and 3.09, respectively) as compared with Grade 1 and 2 breasts. In postmenopausal women with mammographically dense breast, no such increase in risk was established.

In the present study, most common histopathological type was infiltrating ductal carcinoma. The ER, PR and Her2 status was available for 127 masses out of 185 cases of cancer breast. Based on the hormone receptor status, breast carcinomas were classified into three hormone receptor groups. Luminal type was most commonly seen. No statistically significant difference in distribution of VDG was found as compared to different histological types, hormone receptor status or hormone receptor groups. These findings support the results of previous studies [30–32]. However, there are controversies regarding these results as some studies have suggested that percent mammographic density is positively associated with both luminal A and triple-negative breast cancer [33], while others found more strong association with Her2neu tumors when compared with Luminal A tumors [34].

The strengths of our study are quantitative breast density measurements and presence of comparison groups (cases and controls, premenopausal and postmenopausal) but there are few limitations, viz., small sample size and lack of long term follow-up of controls and non-evaluation of BMI (Table 6).

Conclusion

Our study suggests positive association between high VBD and risk of cancer in both premenopausal and postmenopausal group of Indian women. The hormone receptor status and breast cancer subtypes defined by histology and tumor markers did not reveal any relation to the grades of breast density. This can be explained by the fact that breast cancer is a multifactorial disease which results from a strong interplay between genetic and environmental factors through different pathways.

Abbreviations
MBD: Mammographic breast density; BMI: Body mass index; ER: Estrogen receptor; PR: Progesterone receptor; H2P: Her-2neu; BI-RADS: Breast Imaging Reporting and Data System; VDG: Volumetric density grade; VBD: Volumetric breast density; LDB: Low-density breasts; HDB: High-density breasts.

Acknowledgements
We thank Mrs. Suchita Rai, our Mammography Technologist, for her dedication and tireless efforts to get excellent quality Mammograms for patients' and our benefit.

Authors' contributions
NS conceptualized the project and wrote the manuscript. PJ collected the data. AG helped in data collection and manuscript writing. JM helped in data collection. DS helped in manuscript writing and proof read the manuscript. All authors read and approved the final manuscript.

Funding
No funding was obtained for this study.

Availability of data and materials
The datasets used during the current study can be made available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Waived off by the Institute Ethics Committee.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 16 February 2022 Accepted: 25 March 2022
Published online: 05 April 2022

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