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Combined Effect of Volumetric Breast Density and Body Mass Index on Breast Cancer Risk

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Abstract

Background: Breast density and body mass index (BMI) are used for breast cancer risk stratification. We evaluate whether the positive association between volumetric breast density and breast cancer risk is strengthened with increasing BMI.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Specifically, the San Francisco Mammography Registry and Mayo Clinic have received institutional review board approval enroll participants, link data, and perform analytic studies. All procedures are Health Insurance Portability and Accountability Act (HIPAA) compliant.

Informed consent: Passive permission to provide data for research is obtained at each mammography visit for all women participating in the San Francisco Mammography Registry. All women presenting for screening at the Mayo Clinic have the option of providing authorization to use their medical records, images and diagnostic information for research; 93% provided authorization.

Methods: The San Francisco Mammography Registry and Mayo Clinic Rochester identified 781 premenopausal and 1850 postmenopausal women with breast cancer diagnosed between 2007 and 2015 that had a screening digital mammogram at least 6 months prior to diagnosis. Up to three controls (N=3535) were matched per case on age, race, date, mammography machine, and state. Volumetric percent density (VPD) and dense volume (DV) were measured with Volpara™. Breast cancer risk was assessed with logistic regression stratified by menopause status. Multiplicative interaction tests assessed whether the association of density measures was differential by BMI categories.

Results: The increased risk of breast cancer associated with VPD was strengthened with higher BMI for both premenopausal ($p_{interaction}$=0.01) and postmenopausal ($p_{interaction}$=0.0003) women. For BMI<25, 25-30, and ≥30 kg/m^2, ORs for breast cancer for a 1 SD increase in VPD were 1.24, 1.65, and 1.97 for premenopausal, and 1.20, 1.55, and 2.25 for postmenopausal women, respectively. ORs for breast cancer for a 1 SD increase in DV were 1.39, 1.33, and 1.51 for premenopausal ($p_{interaction}$=0.58), and 1.31, 1.34, and 1.65 ($p_{interaction}$=0.03) for postmenopausal women for BMI<25, 25-30 and ≥30 kg/m^2, respectively.

Conclusions: The effect of volumetric percent density on breast cancer risk is strongest in overweight and obese women. These associations have clinical relevance for informing prevention strategies.

Keywords

Breast density; mammographic density; breast cancer; body mass index

Introduction

Breast density is one of the strongest and most common risk factors for breast cancer and has the highest population attributable fraction of any common breast cancer risk factor for breast cancer.[1] Many techniques for measuring breast density are used in clinical and research settings, including Breast Imaging Reporting and Data System (BI-RADS) breast density (qualitative assessment), two-dimensional (“area-based”) and three-dimensional (“volumetric”) assessment. Research suggests broadly similar associations with breast cancer risk across measurement techniques.[2-4]

Obesity is a well-established risk factor for postmenopausal breast cancer. Although obesity has been associated with no effect or reduced breast cancer risk among premenopausal women,[5, 6] some literature suggests that obesity is indeed a risk factor for premenopausal breast cancer after adjusting for breast density.[7-10] Both Harris et al.[8] and Boyd et al.[10] found that adjustment for area-based percent density reversed the protective association between obesity and premenopausal breast cancer risk. Kerlikowske et al. [9] also found that body mass index (BMI) measured during the premenopausal period was a risk factor for ten-year breast cancer risk after adjusting for density as assessed by the American College of Radiology’s BI-RADS categories.[11] These findings suggest that overweight and obese women with dense breasts, whether premenopausal or postmenopausal, may have a higher risk of breast cancer than currently appreciated. Three previous studies using area-based breast density have evaluated if the effect of breast density is stronger among women with

high BMI, with two studies finding no evidence of an interaction and the third finding stronger effects of percent density in overweight and obese postmenopausal women.[12]

Volumetric breast density software can be used in the clinical setting for breast cancer risk stratification. Therefore, to optimize risk prediction in the clinical setting, it is important to understand if obesity modifies the effect of volumetric breast density on risk. We assessed if the effect of volumetric breast density on breast cancer risk is modified by obesity in a population of women from two large breast screening cohorts.

Methods

Study Population

Cases and controls were sampled from the San Francisco Mammography Registry (SFMR) and the Mayo Clinic Breast Screening practice. Each study has institutional ethics approvals and is described briefly below and in detail elsewhere.[2]

San Francisco Mammography Registry (SFMR)

The SFMR is a diverse, multi-facility mammography screening registry that collects demographic, risk factor, and mammography data from breast screening facilities in the San Francisco Bay Area. Cancer outcomes are obtained annually through linkage to the California Cancer Registry (CCR), which pulls from the Northern and Southern California Surveillance Epidemiology and End Results (SEER) programs. Passive permission to provide data for research is obtained at each mammography visit for all women. The SFMR has collected raw “for processing” digital mammograms from Hologic-Selenia since 2006 from four facilities, and only women from these facilities were eligible for the nested case-control study. Women with a breast cancer diagnosis (invasive cancer or ductal carcinoma in situ) between January 2007 and 2015, and a screening full-field digital mammogram (FFDM) at least 6 months prior to diagnosis were included as cases. Two controls without breast cancer were matched to each case on age, date of earliest mammogram, race/ethnicity, mammography facility, and mammography unit.

Mayo Clinic, Rochester, Breast Screening Practice

The Mayo Clinic, Rochester, has collected and stored raw FFDM images acquired with Hologic-Selenia units since April 2008. Women presenting for breast screening at the Mayo Clinic who reside in the tri-state area of MN, IA and WI, were eligible for inclusion in the Mayo case-control study. Previous studies have shown that women presenting for routine screening mammography who reside in the tri-state area are likely to return to Mayo to receive their diagnosis and primary treatment for breast cancer.[13] Thus, breast cancers were identified through linkage to the Mayo Clinic Tumor Registry. All women presenting for screening have the option of providing authorization to use their medical records, images and diagnostic information for research; 93% provided authorization. Women residing in the tri-state area who were diagnosed with breast cancer at Mayo with a FFDM screening exam at least 6 months prior to diagnosis were included as cases. Three controls from the screening practice without breast cancer were matched on age, race / ethnicity, date and

mammography unit of earliest mammogram, state of residence and date of last mammogram.

Mammogram Selection

A total of 2912 cases and 6538 controls from the SFMR and Mayo Clinic were eligible for inclusion in the analysis. For cases, we selected the earliest available mammogram between 6 months and 5.5 years prior to the cancer diagnosis. Forty-five cases (1.5%) had no mammograms within 5.5 years of diagnosis; therefore, the most recent mammogram outside 5.5 years was used (mean years prior to diagnosis = 6.3). For matched controls, we selected the mammogram from the date closest to the case mammogram included; we excluded 29 controls (0.4%) that had no images within 365 days of the case mammogram. We excluded 168 cases and 246 controls with missing data on BMI and 8 cases and 16 controls with unknown menopause status. The total sample included 781 premenopausal and 1868 postmenopausal cases, and 1730 premenopausal and 4298 postmenopausal controls. The mean time from mammogram to case diagnosis was 3.1 (SD: 1.4) years.

Covariate Data

Demographic and risk factor data were self-reported on a clinical questionnaire at each mammography visit. BMI was calculated from self-reported height and weight (SFMR) or was obtained from the medical record closest to the time of mammogram (Mayo) [median(range) days between BMI and mammogram: 2 (0-364)]. Covariates used for analysis include age, BMI, race/ethnicity, menopause status, age at first birth, parity, first-degree family history of breast cancer and current use of postmenopausal hormone therapy (HT). Menopause status was classified according to the complex definition in Phipps et al. (2010),[14] whereby women who were <55 years or self-reported as premenopausal and not on HT were classified as premenopausal, and women who were ≥55 years, self-reported as postmenopausal, or self-reported HT use were classified as postmenopausal. BMI was calculated as normal weight (<25 kg/m^2), overweight (25-29 kg/m^2), and obese (≥30 kg/m^2). Given previous literature suggesting that very obese women (≥35 kg/m2) may represent a population of women at high risk, [15] we also included a four category classification of BMI including the ≥35 kg/m^2 category for postmenopausal women; sample size prohibited this classification in premenopausal women. Age at first birth and parity were combined, with levels for nulliparous (no births), age at first birth ≤30 years, and age at first birth >30 years.

Breast Density Measurement

BI-RADS breast density was assessed by radiologists as part of routine clinical practice. In addition, raw (“for processing”) FFDM images were available at both sites and Volpara™ (Version 1.5.3, Matakina Technology, New Zealand) software was run on all four views for cases and controls. Volpara™ is a fully-automated software that measures volumetric breast density on FFDM images. The Volpara proprietary algorithm identifies an area of the breast that is entirely fatty tissue and uses this reference point to estimate the thickness of dense tissue at each pixel in the image, not including the skin.[16] Estimates of dense breast volume (DV) are obtained by summing the estimated dense tissue across all pixels in the breast image and estimated total breast volume is determined by multiplying the estimated

breast area by the breast thickness. Volumetric percent density (VPD) is obtained by dividing the estimated DV from the total breast volume, and nondense volume (NDV) is obtained by subtracting DV from total breast volume. We measured breast density on the cranio-caudal (CC) and medio-lateral oblique (MLO) views for both left and right breasts for each woman. The estimates from all 4 views were averaged to obtain the final density values.

Statistical Methods

Characteristics of the cases and controls by menopause status are summarized by frequency and percentage or median and interquartile ranges. We used unconditional logistic regression models, stratified by menopause status and adjusted for matching factors and family history of breast cancer, age at first birth / parity, and HT (postmenopausal models only). Sensitivity analyses comparing conditional and unconditional models, and using log-transformed density values found similar results, therefore simpler models were used for interpretability. Models for DV and NDV were mutually adjusted. We fit interaction terms between BMI categories [<25 (normal weight), 25-30 (overweight) and >30 (obese) kg/m2] with each density measure [VPD, DV and NDV (per standard deviation)] and used interaction p-values to test whether association of density measures was differential by BMI categories. Ordinal trend tests, assuming a linear effect with increasing BMI categories, were used to assess whether odds ratios for the effect of density measures showed evidence of monotonic trends across BMI categories. Analyses were conducted in SAS 9.4.

Results

Characteristics of cases and controls by menopause are reported in Table 1. Cases had greater VPD and DV than controls among both premenopausal (VPD: 14.9% vs. 12.0%, DV: 74.1 cm^3 vs. 64.4 cm^3) and postmenopausal women (VPD: 6.8% vs. 6.1%, DV: 53.4 cm^3 vs. 48.0 cm^3)(all p-values<0.001). There were no significant differences in unadjusted NDV between cases or controls for premenopausal or postmenopausal women. Cases had a higher proportion of women with heterogeneously or extremely dense breasts than controls for both premenopausal and postmenopausal women.

Higher BMI was associated with decreased VPD and increased DV for both premenopausal and postmenopausal women (Table 2). The median VPD was 16.6%, 8.9% and 5.1% and DV was 62.4, 68.5, and 68.1 cm^3 for normal, overweight, and obese premenopausal women, respectively. Similar trends were seen for postmenopausal women, who had 8.8%, 5.3% and 4.3% VPD, and 42.6, 48.4 and 55.7 cm^3 DV, respectively. Non-dense volume increased with BMI: the median NDV was 397.9, 811.2, and 1297.8 cm^3 for premenopausal, and 514.3, 883.4, and 1310.9 cm^3 for postmenopausal normal, overweight, and obese women, respectively.

VPD, DV, and BI-RADS density were positively associated with breast cancer risk in premenopausal women, and there was clear evidence of an interaction for VPD ($p_{interaction}$=0.01), but not DV ($p_{interaction}$=0.58) or BIRADS density ($p_{interaction}$=0.44) (Table 3). The effect of VPD increased strongly with increasing BMI (p_{trend}=0.007) with odds ratios (OR) for breast cancer risk for a 1 SD increase in VPD among normal weight,

overweight, and obese women of 1.24 (95% CI: 1.1-1.4), 1.65 (95% CI: 1.3-2.1) and 1.97 (95% CI: 1.3-3.0) respectively. For DV, a 1 SD increase corresponded to ORs of 1.39 (95% CI: 1.2-1.5), 1.33 (95% CI: 1.2-1.5) and 1.51 (95% CI: 1.2-1.8), and for BI-RADS, ORs of 1.33 (95% CI: 1.1-1.6), 1.50 (95% CI: 1.1-2.0), and 1.68 (95% CI: 1.2-2.4) for normal weight, overweight and obese women, respectively, though neither interaction was statistically significant (Table 3).

Similar effects were seen in postmenopausal women, however the association between breast density and cancer risk differed significantly with increasing BMI for VPD ($p_{interaction}$=0.0003), DV ($p_{interaction}$=0.03) and BI-RADS breast density ($p_{interaction}$=0.09) (Table 3). ORs for breast cancer risk for a 1 SD increase in VPD were 1.20 (95% CI: 1.1-1.3), 1.55 (95% CI: 1.3-1.9), 2.25 (95% CI: 1.6-3.2) (p_{trend}=0.0001) and for a 1 SD increase in DV were 1.31 (95% CI: 1.2-1.4), 1.34 (95% CI: 1.2-1.5), 1.65 (95% CI: 1.4-1.9) (p_{trend}=0.01) for normal weight, overweight, and obese women, respectively. ORs corresponding to a per category increase in BI-RADS were 1.29 (95% CI: 1.1-1.4), 1.49 (95% CI: 1.3-1.7) and 1.59 (95% CI: 1.3-1.9) (p_{trend}=0.03). (Table 3).

There were no statistically significant differences in the effect of NDV on risk by BMI category for premenopausal or postmenopausal women. Among postmenopausal women, a 1 SD increase in NDV was associated with reductions in breast cancer risk in women in the lowest two BMI categories, with ORs of 0.77 (95% CI: 0.7-0.9), 0.80 (95% CI: 0.7-0.9), and 0.92 (95% CI: 0.8-1.0) for normal weight, overweight and obese women, respectively, though the interaction was not statistically significant (Table 3).

Discussion

We found that higher VPD was associated with increased premenopausal and postmenopausal breast cancer risk, and that this effect was substantially strengthened in overweight and obese women in both menopausal groups. The increased risk of breast cancer with higher DV and BI-RADS breast density was also strengthened in overweight and obese postmenopausal women. These results suggest that overweight and obese women with elevated breast density are at increased breast cancer risk compared to overweight and obese women without elevated breast density.

Previous research evaluating differences in the effect of breast density on breast cancer risk by adiposity have used two-dimensional density assessment and have had mixed findings. Two of three studies found no effect modification by BMI in premenopausal and postmenopausal women.[12, 17, 18] One study of postmenopausal Chinese women found that breast cancer risk for women with >75% vs. <10% area-based density was 9.5-fold greater for women with BMI >=26.7 kg/m^2, compared with 3.5-fold in women with BMI<26.7 kg/m^2.[18] A subsequent paper hypothesized that these findings were due to decreased image contrast as a result of increased compressed breast thickness in overweight women, leading to an underestimate of breast density.[19] While it is difficult to directly compare our study given different classification of BMI and area-based vs. volumetric breast density measures, our study finds similarly high breast cancer risks among overweight and obese women with high volumetric percent density.

Differences between our study and previous research may reflect differences in area-based and volumetric assessment, or the potential that the two measurement types capture different underlying entities of breast density.[20-22] Inverse associations between BMI and dense area have been commonly reported,[8, 23-25] whereas studies of DV, including ours, show positive associations with BMI.[26-28] The reason for these opposing associations on area-based measures is unclear but is thought to be due to distortions of dense and fat tissue from the projection of a three-dimensional to a two-dimensional image. Consequently, in our study women with both high BMI and high DV may represent a population not previously identified in previous research using two-dimensional assessment. For example, where previously an obese woman may have been classified with low dense breast area, in our study she may be classified as having high DV. Alternatively, the volumetric measurement may truly capture a different underlying entity of breast density.[20-22]

We found that increased risk with increasing BMI was stronger for VPD than DV, suggesting that it is not only the amount of dense tissue that is relevant but the microenvironment of the surrounding breast. If both DV and NDV provide independent information about breast cancer risk, it is not surprising that VPD, which incorporates both measures, is the most strongly associated with risk. Indeed, we found that the positive association of DV on breast cancer risk was substantially strengthened when adjusted for NDV, and that NDV was protective for breast cancer even after adjustment for DV and BMI. This finding is consistent with previous research using area-based measures of breast density.[29-32] Biologically, the protective effect of NDV may be explained by increased breast involution in fat tissue, vitamin-D3 induced growth regulation of the epithelium, or decreased extracellular matrix stiffness that leads to reduced cancer risk.[33] However, the protective effect of NDV may also be dependent on obesity. A recent study found that mammary fat tissue in obese women had increased myofibroblasts compared to lean women, which contributes to extracellular matrix stiffness and can promote carcinogenesis.[34] Though we did not find significantly different associations of NDV by BMI on risk, the OR's trended towards greater protection of NDV in women with BMI<30 kg/m^2, lending some support to the hypothesis that NDV in obese women may have different cellular properties that promote carcinogenesis.

The biological mechanism supporting the stronger effect of DV in postmenopausal women with high BMI is unclear. One potential explanation is that the inflammatory effects of adiposity are mediated through increases in DV, which would explain the positive association between obesity and DV in our study. Obesity is associated with hyperinsulinemia, increased circulating adipokines and inflammatory markers that may upregulate cellular proliferation, and postmenopausal obesity is associated with increased circulating estrogens from adipose tissue.[35] These biological effects of adiposity may contribute to increased DV on the causal pathway to breast cancer risk, explaining why obese women who had higher DV had the highest risk of breast cancer. Studies looking at weight change and breast density have had mixed findings, with some suggesting that weight gain is associated with increased dense tissue,[35, 36] though the only study to use DV found inverse associations with weight gain.[37] Further research is needed to evaluate the biological mechanisms by which NDV and DV are associated with breast cancer risk in both obese and non-obese women.

Our findings have strong clinical implications, as breast density is increasingly used for risk prediction in clinical settings. Breast cancer risk models, including the Breast Cancer Surveillance Consortium (BCSC) model,[38] incorporate BI-RADS breast density assessment into 5- and 10-year breast cancer risk prediction, and a recent study suggests that adding volumetric density to these models increases the ability to stratify risk.[39] In fact, our study shows that the interaction between BMI and density measures was detected only using the volumetric measures among premenopausal women, noting the importance of this more precise and complementary density assessment to assessing joint associations with other risk factors in the risk models. Volumetric breast density will be progressively incorporated into risk prediction, and as such, our results are timely as they inform additional risk due to the interaction between BMI and volumetric density that may allow further risk stratification for primary and secondary prevention. A total of 18% of premenopausal and 24% of postmenopausal controls in our study were overweight or obese and had a DV above the mean, representing a high clinical and public health relevance.

Our study is the first to report a stronger effect of volumetric breast density in overweight and obese women, and benefits from a large sample of premenopausal and postmenopausal women with raw FFDM images. Our limitations include the use of self-reported BMI and menopausal status. While our use of broad categories of BMI should mitigate substantial misclassification, misclassification of menopause status is possible. However, misclassification of menopause would likely be non-differential, leading to an underestimate of the interaction effects in both pre- and postmenopausal women.

In summary, we found that the effect of volumetric breast density on breast cancer risk was higher in overweight and obese compared with normal weight women, suggesting the potential to further stratify women for targeted primary and secondary prevention. Future research should confirm this finding and investigate biological mechanisms by which obesity and volumetric density interact to increase breast cancer risk.

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Table 1.

Characteristics of study sample by menopause and case status.

	Premenopausal		Postmenopausal	
	Control (n=1730)	*Case (n=781)*	*Control (n=4298)*	*Case (n=1868)*
	N (%)			
Age				
<45 Years	780 (45.1)	371 (47.5)	31 (0.7)	10 (0.5)
45 to 64 Years	950 (54.9)	410 (52.5)	2289 (53.3)	1005 (53.8)
≥65 Years	NA	NA	1978 (46.0)	853 (46.7)
Body Mass Index (BMI)				
Normal (<25 kg/m^2)	1062 (61.4)	518 (66.3)	2025 (47.1)	828 (44.3)
Overweight (25-29 kg/m^2)	382 (22.1)	172 (22.0)	1293 (30.1)	573 (30.7)
Obese I (≥30 kg/m^2)	286 (16.5)	91 (11.7)	980 (22.8)	467 (25.0)
Race				
Caucasian	1271 (73.5)	561 (71.8)	3582 (83.3)	1514(81.1)
Asian	362 (20.9)	176 (22.5)	536 (12.5)	274 (14.7)
Black	28 (1.6)	18 (2.3)	77 (1.8)	42 (2.3)
Hispanic	69 (4.0)	26 (3.3)	103 (2.4)	38 (2.0)
Family Histoiy of Breast Cancer				
No	1455 (84.7)	571 (74.3)	3402 (79.2)	1313 (71.0)
Yes	263 (15.3)	198 (25.7)	892 (20.8)	537 (29.0)
Unknown	12	12	4	18
Age at First Birth / Parity				
Nuiiiparous	515 (29.8)	277 (35.5)	976 (22.7)	504 (27.0)
<30 Years	623 (36.0)	210 (26.9)	2703 (62.9)	1080 (57.8)
>30 Years	592 (34.2)	294 (37.6)	619 (14.4)	284 (15.2)
Current Hormone Therapy				
No	1724 (100)	736 (100)	3536 (83.1)	1412 (80.0)
Yes	NA	NA	717 (16.9)	354 (20.0)
Unknown	6	45	45	102
BI-RADS breast density				
a	110 (7.3)	21 (3.2)	853 (22.1)	229 (14.1)
b	440 (29.2)	138 (20.8)	1686 (43.7)	716 (44.0)
c	678 (45.0)	318 (48.0)	1118 (29.0)	563 (34.6)
d	279 (18.5)	186 (28.1)	198 (5.1)	119 (7.3)
Unknown	223	118	443	241
	Median (IQR)			
Age, years	45.0 (6.3)	45.0 (6.0)	63.4 (14.0)	63.0 (13.4)
Volumetric Percent Density, %	12.0 (11.3)	14.9 (11.2)	6.1 (5.2)	6.8 (5.8)
Dense Volume, *cm^3*	64.4 (43.4)	74.1 (53.8)	48.0 (29.0)	53.4 (32.9)
Nondense Volume, *cm^3*	552.4 (547.8)	538.1 (505.6)	766.5 (610.6)	777.3 (655.8)

Table 2.

Distribution of volumetric breast density by BMI category in premenopausal (n=1,730) and postmenopausal (n=4,298) controls.

	N	Volumetric Percent Density (VPD)	Dense Volume (DV)	Nondense Volume (NDV)
Premenopausal Controls		*Median (IQR)*		
Body Mass Index (BMI)				
Normal (<25 kg/m^2)	1062	16.6 (10.4)	62.4 (41.9)	397.9 (278.5)
Overweight (25-29 kg/m^2)	382	8.9 (6.0)	68.5 (51.9)	811.2 (395.0)
Obese (≥30 kg/m^2)	286	5.1 (3.0)	68.1 (37.3)	1297.8 (753.7)
Postmenopausal Controls				
Body Mass Index (BMI)				
Normal (<25 kg/m^2)	2025	8.8 (7.1)	42.6 (28.8)	514.3 (366.7)
Overweight (25-29 kg/m^2)	1293	5.3 (3.1)	48.4 (28.0)	883.4 (437.6)
Obese (≥30 kg/m^2)	980	4.3 (1.8)	55.7 (26.1)	1310.9 (702.7)

Table 3.

Breast cancer risk (odds ratios [OR], 95% confidence intervals [CI]) by volumetric breast density and body mass index.

		Volumetric Percent Density (VPD)	Dense Volume (DV)	Non-Dense Volume (NDV)	BI-RADS
	Cases/ Controls	*OR (95% CI) for 1 SD Increase*	*OR (95% CI) for 1 SD Increase*	*OR (95% CI) for 1 SD Increase*	*OR (95% CI) for 1 Unit Increase*
Premenopausal (n=2,511)					(n=2,170 with BIRADS)
<25 kg/m²	518/1062	1.24 (1.1,1.4)	1.39 (1.2,1.5)	0.74 (0.6,1.0)	1.33(1.1,1.6)
25-29 kg/m²	172/382	1.65 (1.3, 2.1)	1.33 (1.2,1.5)	0.72 (0.5,1.0)	1.50(1.1,2.0)
≥30 kg/m²	91/286	1.97 (1.3, 3.0)	1.51 (1.2,1.8)	0.86 (0.7,1.1)	1.68(1.2,2.4)
p, interaction *		0.01	0.58	0.56	0.44
p, ordinal **		0.0007	0.68	0.52	0.12
Postmenopausal (n=6,166)					(n=5,482 with BIRADS)
<25 kg/m²	828/2025	1.20 (1.1,1.3)	1.31 (1.2,1.4)	0.77 (0.7, 0.9)	1.29(1.1,1.4)
25-29 kg/m²	573/1293	1.55 (1.3,1.9)	1.34 (1.2,1.5)	0.80 (0.7, 0.9)	1.49(1.3,1.7)
≥30 kg/m²	467/980	2.25 (1.6, 3.2)	1.65 (1.4,1.9)	0.92 (0.8,1.0)	1.59(1.3,1.9)
p, interaction *		0.0003	0.03	0.12	0.09
p, ordinal **		0.0001	0.01	0.07	0.03
Postmenopausal (n=6,166)					(n=5,482 with BIRADS)
<25 kg/m²	828/2025	1.20 (1.1,1.3)	1.31 (1.2,1.5)	0.77 (0.7, 0.9)	1.29(1.1,1.4)
25-29 kg/m²	573/1293	1.54 (1.3,1.9)	1.35 (1.2,1.5)	0.80 (0.7, 0.9)	1.49(1.3,1.7)
30-34 kg/m²	274/586	2.19 (1.4, 3.3)	1.53 (1.3,1.9)	0.88 (0.7,1.1)	1.66(1.3,2.1)
≥35 kg/m²	193/394	2.85 (1.4, 5.6)	1.81 (1.4, 2.3)	0.93 (0.8,1.1)	1.55 (1.2, 2.0)
p, interaction *		0.0005	0.05	0.33	0.15
p, ordinal **		<0.0001	0.01	0.32	0.01

CI=confidence interval; SD=standard deviation; VPD= volumetric percent density; DV= dense volume; NDV=non-dense volume.

Logistic regression models were adjusted for age, study site, race, family history of breast cancer, parity / age at first birth, and hormone replacement therapy (postmenopausal only). DV models were additionally adjusted for NDV; NDV models were additionally adjusted for DV.

1 SD Increase for VPD (6.4%), DV (34.1 cm^3), NDV (508.0 cm^3)

* p-value for interaction between BMI categories and continuous VPD, DV or NDV (per 1 SD).

** p-ordinal tests for trend in the OR's by BMI category.