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Association of mammographic density and benign breast calcifications individually or combined with hypertension, diabetes, and hypercholesterolemia in women ≥40 years of age: a retrospective study

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ABSTRACT

Recent evidence has linked certain mammographic characteristics, including breast calcifications (Bcs) and mammographic density (MD), with atherosclerotic cardiovascular disease risk factors in women, but data are limited and inconsistent. We aimed to evaluate the association of MD and/or Bcs with hypertension, diabetes, and hypercholesterolemia in women ≥40 years of age. Through hospital electronic records, we retrospectively identified mammograms of non-pregnant women aged ≥40 years and without breast cancer and retrieved reports and relevant data. MD and Bcs were recorded; risk factor status was diagnosed based on treatment profile and clinical and laboratory data. In total, 1406 women were included. MD was inversely related to hypertension, diabetes, hypercholesterolemia, triglyceride levels, age, and body mass index (BMI) (p value for trend <0.001). Bcs were positively associated with hypertension, diabetes, hypercholesterolemia, age, BMI, and elevated creatinine (p<0.05). Controlling for age and BMI, MD category A (MD-A) was independently associated with hypercholesterolemia; Bcs were independently associated with diabetes. Combining MD-A with Bcs did not increase the odds significantly. Analysis for additive interactions revealed a significant interaction between MD-A and BMI, increasing the odds of hypertension, and a trend for increased odds of diabetes by adding MD-A and/or Bcs to BMI. Decreased MD and presence of Bcs are associated with hypertension, diabetes, and hypercholesterolemia in women ≥40 years of age. MD-A may represent a new obesity index independently associated with hypercholesterolemia and additive to hypertension risk. Bcs are independently associated with diabetes. Combining MD and Bcs did not improve the odds significantly, which may reflect mechanistic differences.

INTRODUCTION

Recent evidence has linked some breast tissue components as viewed on mammographic

Significance of this study

What is already known about this subject?
⇒ There is an increasing interest in extending the benefits of screening mammography to include cardiovascular disease (CVD) screening and risk stratification.
⇒ Studies favor an association between breast arterial calcifications and CVD and CVD risk factors.
⇒ Few studies examined the association of other breast tissue components including mammographic density (MD) with CVD or CVD risk factors.

What are the new findings?
⇒ We evaluated and compared the associations of MD and benign breast calcifications (Bcs) with hypertension, hypercholesterolemia, and diabetes in women ≥40 years of age.
⇒ Both MD and Bcs were significantly associated with these three risk factors.
⇒ Controlling for age and body mass index (BMI), Bcs were independently associated with 1.4-fold increased odds of diabetes.
⇒ MD category A was independently associated with 1.6-fold increased odds of hypercholesterolemia, and when added to BMI more than doubled the odds of hypertension.
⇒ MD category A is related to increased BMI and parallels its association with the risk factors, and may represent a new obesity index in women ≥40 years of age.

How might these results change the focus of research or clinical practice?
⇒ The additional information gained from the mammogram regarding CVD risk factors may identify opportunities for targeted atherosclerotic CVD risk factor screening, early treatment, and prevention, and add to CVD risk stratification among women ≥40 years of age.

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examinations with atherosclerotic cardiovascular disease (CVD) risk factors in women.[1] Among those, benign breast calcifications (Bcs) are better studied, although data remain limited.[2] However, mammographic examinations report on other breast tissue characteristics that remain underexplored in that regard. In particular, mammographic density (MD), which classifies breast composition according to the amount of fatty and fibroglandular tissue,[3] has been extensively studied in relation to breast cancer risk,[4] but its association with other vital issues related to women's health, particularly CVD health, remains to be explored.

Since a majority of women who are 40 years of age or older undergo mammography annually for screening for breast cancer, further evaluation of mammogram images may provide additional information regarding important CVD risk factors. The additional details may provide insights regarding screening and prevention of CVD risk factors, and CVD risk stratification at no extra cost or radiation, and increase the test yield.[1] In view of the shortage and inconsistency of available data, this study aimed to evaluate the association of MD and Bcs individually and combined with the risk of hypertension, diabetes, and hypercholesterolemia in a large population of women ≥40 years of age. The association of MD and Bcs with other lipid parameters, including triglycerides and high-density lipoprotein cholesterol (HDL-C), was also evaluated.

METHODS
Study design and patient population
Women who underwent a mammogram at King Abdullah bin Abdulaziz University Hospital, Riyadh, Saudi Arabia, from March 2017 to March 2020 were retrospectively identified through the hospital database. Participants were considered eligible if they were ≥40 years of age and had determinable blood pressure (BP), cholesterol, or glycemic status from the electronic hospital records. The exclusion criteria were breast cancer, uninterpretable images, and pregnancy. If a participant had multiple mammograms over the years, the most recent or the one with the most complete data of interest was included.

Data collection and diagnostic criteria
For the diagnosis of hypertension, hypercholesterolemia, and diabetes, an electronic search was performed to retrieve participants' medications and relevant investigation results (fasting lipid profile, fasting or random blood sugar (FBS or RBS), and hemoglobin A1c (HbA1c)). For BP data, a manual search for non-emergency, outpatient BP readings was performed. Women's age, height and weight for body mass index (BMI) calculation, and creatinine levels were also recorded. Only results within 1 year of the mammogram date and the closest (if multiple) were included.

Participants were identified as hypertensive if they were receiving antihypertensive medications or their BP reading met the thresholds for hypertension,[5] and normotensive if the untreated BP was <130/80 mm Hg. Hypercholesterolemia was diagnosed if the participant was receiving statin therapy or had a fasting low-density lipoprotein cholesterol (LDL-C) ≥4.9 mmol/L[6]; its absence was indicated by untreated LDL-C level <4.9 mmol/L. Diabetes was diagnosed if the participant was receiving antidiabetic medications

or had at least one FBS, RBS, or HbA1c level meeting the diagnostic criteria for diabetes (FBS ≥7.0 mmol/L, RBS ≥11.1 mmol/L, or HbA1c ≥6.5%),[7] while euglycemia was indicated by untreated euglycemic indices. The records of the participants who were receiving only a small dose of a beta-blocker, ACE inhibitor, angiotensin receptor blocker, metformin, or a glucagon-like peptide-1 receptor agonist were searched for indications. If the indications were other than hypertension or diabetes, they were classified based on their BP and blood sugar index results.

MD category was recorded as defined by the American College of Radiology's Breast Imaging Reporting and Data System (Fifth Edition): category A (MD-A): almost entirely fatty breast tissue; B (MD-B): scattered fibroglandular densities; C (MD-C): heterogeneously dense breast tissue; and D (MD-D): extremely dense.[8] The presence or absence of Bcs was also noted and these were classified according to size as microcalcifications (≤2 mm) and macrocalcifications (>2 mm).[9]

Statistical analysis
All data obtained were recorded on Excel spreadsheets and in SAS 9.4. Continuous variables are reported as mean and SD or median and IQR, as appropriate, while categorical variables are expressed as frequencies with percentages. Statistical significance was defined as $p < 0.05$. Logistic regression adjusted for age and BMI was used to examine the association between major CVD risk factors (BP status, hypercholesterolemia, and diabetes status) and participant characteristics (MD-A vs non-MD-A, and presence of Bcs) in the entire cohort. We then further conducted an analysis adjusted for age and stratified by obesity status (BMI >30 kg/m²). A saturated logistic regression model that included all two-way and three-way interactions between MD, Bcs, and obesity was used to estimate the association in each stratum defined by the combination of these three variables. The results are presented as ORs and their 95% CIs.

RESULTS
Selection of the study participants
In total, 1406 women met the study criteria (figure 1). Among these, 32 were receiving small doses of beta-blockers, ACE inhibitors, or angiotensin receptor blockers for indications other than hypertension (palpitations, coronary artery disease (CAD), or renal disease); they were
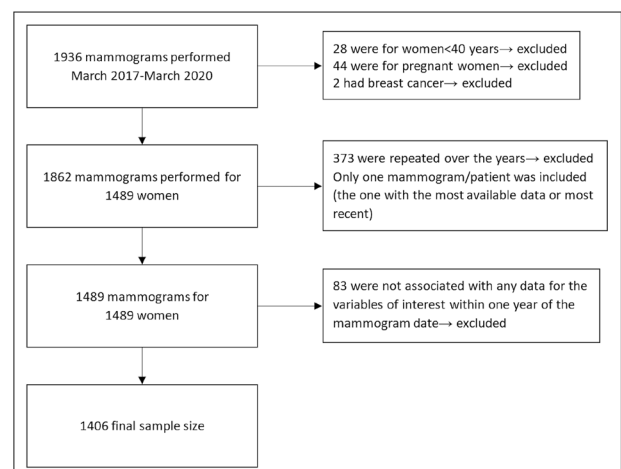

Figure 1 Selection of the study participants.

analyzed according to their BP values. Another 83 were receiving metformin or liraglutide for polycystic ovary syndrome, obesity, or pre-diabetes and were analyzed according to their glycemic parameters. These two groups were evenly distributed among the MD and Bcs categories.

Baseline characteristics of the participants

The baseline characteristics of the study population are displayed in table 1. The mean age was 53.8 years. Overall, 8.9% had MD-A, and 38.8%, 47.7%, and 4.6% had MD-B, MD-C, and MD-D, respectively. Bcs were detected in 20%. Approximately 55.3% and 38.6% had stage 1 and stage 2 hypertension, respectively. Hypercholesterolemia was observed in 48.1% of patients and 32.3% had diabetes. The results of HDL-C and triglycerides are displayed.

Relationship between MD and Bcs and the studied variables

The relationship between MD and Bcs and the studied variables is shown in table 1. Significant negative trends were detected between MD category and participants' age, BMI, hypertension, hypercholesterolemia, diabetes, and mean triglyceride level (p<0.001). Those in the lowest MD category (MD-A) were older and had greater BMI and risk factor prevalence (hypertension: 69.9%, hypercholesterolemia: 65.4%, and diabetes: 43.6%). There was no significant difference in HDL-C (mean or <1.3 mmol/L), hypertriglyceridemia (triglycerides ≥2 mmol/L), or creatinine level between the four MD categories.

In the case of Bcs, the presence of any Bcs was associated with increasing age (p<0.001), BMI (p=0.043), hypertension (p=0.008), hypercholesterolemia (p=0.016), diabetes (p<0.001), elevated creatinine (p<0.001), and mean triglyceride level (p=0.021), but not triglycerides ≥2 mmol/L or HDL-C measures. When Bcs were stratified according to size, significant positive trends for increased prevalence of hypertension (p=0.012), hypercholesterolemia (p=0.010), and diabetes (p<0.001) with increasing Bcs size were detected. Bcs were more prevalent in women with MD-D. A significant positive trend between increasing MD and Bcs was detected (p=0.006). The distribution of MD and/or Bcs per obesity status in the study population and the distribution of the studied risk factors among participant characteristics and among all participants with the same risk factor are shown in figure 2.

The evaluation of the association of MD and/or Bcs with the studied risk factors after adjustment for BMI and age is shown in figure 3. Neither MD-A nor Bcs individually or combined was independently associated with hypertension risk. Conversely, the odds of hypercholesterolemia were significantly increased in women with MD-A (OR 1.60, 95% CI 1.00 to 2.54, p=0.048), and the presence of any Bcs independently increased the odds of diabetes (OR 1.4, 95% CI 1.01 to 1.94, p=0.043).

Evaluation for additive interactions between MD-A and/or Bcs with obesity

Further assessment for additive interactions between MD-A and/or Bcs with obesity on the odds of the three risk factors, with adjustment for age, is shown in figure 4. Compared with non-obese women with non-MD-A densities and no

Bcs (the reference), obese women with non-MD-A densities and no Bcs (obese only) had significantly increased odds of hypertension (OR 2.09, 95% CI 1.6 to 2.74, p<0.001). The addition of MD-A to obesity increased the odds of hypertension significantly more than obesity alone (OR 5.37 compared with 2.09, p=0.005). The addition of calcification to obesity did not increase the odds of hypertension compared with obesity only (OR 2.27 compared with 2.09, p=0.686). Conversely, the addition of both Bcs and MD-A to obesity decreased the odds of hypertension compared with MD-A and obesity, although this was statistically insignificant (OR 5.09 compared with 5.37, p=0.949).

With regard to hypercholesterolemia, obese women with non-MD-A densities and no Bcs (obese only) had increased odds for dyslipidemia compared with the reference (OR 1.36, 95% CI 1.01 to 1.84, p=0.041). The addition of MD-A to obesity increased the odds of hypercholesterolemia compared with the reference (OR 2.22, 95% CI 1.20 to 4.11, p=0.011) but not compared with obesity only (OR 2.22 compared with 1.36, p=0.115). Neither the addition of Bcs nor Bcs and MD-A was associated with a significant increase in the odds of hypercholesterolemia compared with the reference.

In the case of diabetes, the odds of all four comparisons were significantly higher than the reference, with a tendency for a graded increase. However, compared with the odds of obesity only, the addition of MD-A to obesity did not significantly increase the odds of diabetes (OR 2.80 compared with 2.59, p=0.797). Conversely, the addition of Bcs or Bcs and MD-A to obesity resulted in trends for increased odds of diabetes compared with obesity only (OR 3.56 compared with 2.59, p=0.129 and OR 5.02 compared with 2.59, p=0.362, respectively), but they did not reach statistical significance.

DISCUSSION

The results of this study show that in women ≥40 years of age, both MD and Bcs can be linked to the risk of hypertension, diabetes, and hypercholesterolemia, but with variable associations and strengths. A significant inverse trend between MD category and the three risk factors was observed, with women falling in the lowest category or MD-A having the highest prevalence. After adjustments for BMI and age, MD-A was independently associated with a 1.6-fold increase in the odds of hypercholesterolemia. No independent association was observed with hypertension or diabetes. Similarly, the presence of any Bcs was associated with an increased prevalence of the three risk factors, with a graded increase with increased Bcs size. Controlling for BMI and age, Bcs were independently associated with a 1.4-fold increase in the odds of diabetes.

Analysis for additive interactions detected more than doubling of the odds of hypertension by the addition of MD-A to obesity compared with obesity only and a statistically insignificant increase in the odds of hypercholesterolemia. The addition of Bcs to MD-A and obesity did not further increase the odds of hypertension or hypercholesterolemia significantly. Conversely, the addition of MD-A, Bcs, or both to obesity resulted in a tendency for a graded increase in the risk of diabetes; however, this did not reach statistical significance, which may be due to the

Table 1 Baseline characteristics of the study population per MD and Bcs status

Variable	All (N=1406)	MD					Bcs			Bcs*			
		A	B	C	D	P value	None	Any	P value	None	Micro	Macro	P value
Age (years)						<0.001			<0.001				<0.001
n (%)		125 (8.9)	545 (38.8)	671 (47.7)	65 (4.6)		1125	281		1125	243	32	
Mean (SD)	53.8 (8.0)	57.5 (8.8)	55.6 (8.1)	52.2 (7.3)	48.3 (5.9)		53.3 (7.8)	55.9 (8.4)		53.3 (7.8)	55.2 (8.4)	60.3 (7.2)	
Range	40.2–89.0	41.3–89.0	40.2–86.1	40.2–79.3	40.5–66.7		40.2–89.0	40.8–79.3		40.2–89.0	40.8–79.3	45.5–79.3	
BMI (kg/m²)						<0.001			0.043				0.054
n	1372	123	528	656	65		1097	275		1097	238	32	
Mean (SD)	32.2 (6.7)	35.8 (8.7)	33.5 (6.4)	30.9 (6.1)	26.8 (4.4)		32.0 (6.7)	32.9 (6.8)		32.0 (6.7)	33.0 (6.8)	31.9 (6.6)	
Range	14.7–81.5	21.6–75.5	15.7–55.6	14.7–81.5	18.8–40.1		14.7–81.5	19.1–55.1		14.7–81.5	19.1–55.1	22.2–47.0	
HTN													
Stage 1†, n (%)	760/1374 (55.3)	86/123 (69.9)	327/536 (61.0)	322/652 (49.4)	25/63 (39.7)	<0.001	589/1100 (53.5)	171/274 (62.4)	0.008	589/1100 (53.5)	142/237 (59.9)	23/31 (74.2)	0.012
Stage 2‡, n (%)	531/1374 (38.6)	69/123 (56.1)	248/536 (46.3)	201/652 (30.8)	13/63 (20.6)	<0.001	406/1100 (36.9)	125/274 (45.6)	0.008	406/1100 (36.9)	104/237 (43.9)	17/31 (54.8)	0.006
Hypercholesterolemia§, n (%)	571/1188 (48.1)	68/104 (65.4)	246/476 (51.7)	241/558 (43.2)	16/50 (32.0)	<0.001	439/948 (46.3)	132/240 (55.0)	0.016	439/948 (46.3)	110/206 (53.4)	19/29 (65.5)	0.010
DM¶, n (%)	399/1234 (32.3)	48/110 (43.6)	187/493 (37.9)	159/577 (27.6)	5/54 (9.3)	<0.001	290/986 (29.4)	109/248 (44.0)	<0.001	290/986 (29.4)	87/213 (40.8)	19/30 (63.3)	<0.001
HDL-C (mmol/L)						0.268			0.553				0.306
n	1145	94	459	542	50		914	231		914	197	29	
Mean (SD)	1.34 (0.32)	1.32 (0.33)	1.33 (0.30)	1.35 (0.34)	1.40 (0.38)		1.34 (0.32)	1.33 (0.35)		1.34 (0.32)	1.33 (0.37)	1.31 (0.27)	
Range	0.56–3.09	0.70–2.48	0.72–3.09	0.56–2.78	0.78–2.22		0.56–2.72	0.72–3.09		0.56–2.72	0.72–3.09	0.85–2.05	
<1.3, n (%)	557/1145 (48.6)	47/94 (50.0)	224/459 (48.8)	266/542 (49.1)	20/50 (40.0)	0.558	443/914 (48.5)	114/231 (49.4)	0.811	443/914 (48.5)	99/197 (50.3)	13/29 (44.8)	0.954
TG (mmol/L)						<0.001			0.021				0.048
n	1146	95	459	542	50		915	231		915	197	29	
Mean (SD)	1.24 (0.66)	1.35 (0.60)	1.32 (0.71)	1.17 (0.62)	1.11 (0.71)		1.22 (0.63)	1.33 (0.77)		1.22 (0.63)	1.34 (0.79)	1.37 (0.65)	
Range	0.27–5.70	0.35–4.24	0.35–4.78	0.27–5.70	0.30–3.99		0.30–4.78	0.27–5.70		0.30–4.78	0.27–5.70	0.35–3.30	
≥2, n (%)	118/1146 (10.3)	11/95 (11.6)	59/459 (12.9)	42/542 (7.7)	6/50 (12.0)	0.076	91/915 (9.9)	27/231 (11.7)	0.436	91/915 (9.9)	23/197 (11.7)	4/29 (13.8)	0.336
Cr (µmol/L)						0.102			0.607				0.640
n	1151	100	459	539	53		915	236		915	204	27	
Median (IQR)	56.0 (49.0–63.0)	56 (48–62.5)	56 (50–64)	55 (48–62)	54 (50–60)		56 (49–63)	54 (49–63)		56 (49–63)	55 (49–63)	52 (49–60)	
Range	28.0–275.0	33–122	32–180	28–275	31–83		28–275	31–180		28–275	31–165	40–180	
>90, n (%)	16/1151 (1.4)	3/100 (3.0)	8/459 (1.7)	5/539 (0.9)	0/53 (0.0)	0.052	7/915 (0.8)	9/236 (3.8)	<0.001	7/915 (0.8)	8/204 (3.9)	1/27 (3.7)	<0.001
Bcs													
Any n (%)	281 (20.0)	16 (12.8)	101 (18.5)	148 (22.1)	16 (24.6)	0.006							

The p value was based on the Jonckheere–Terpstra or Cochran-Armitage trend test for continuous and binary variables. For categorical variables with more than two levels, the p value was based on analysis of variance, Kruskal-Wallis test, χ² test, or Fisher's exact test, or Fisher's exact test as appropriate.
*6 (0.4%) participants had both microcalcification and macrocalcification and were excluded from this analysis. For the dichotomized level of calcification, the p value was based on two levels, χ² test or Fisher's exact test was used.
†BP ≥130/80 mm Hg or on treatment.
‡BP ≥140/90 mm Hg or on treatment.
§fasting low-density lipoprotein cholesterol ≥4.9 mmol/L or on treatment.
¶FBS ≥7, RBS ≥11.1, or HbA1c ≥6.5, or on treatment.
Bcs, breast calcifications; BMI, body mass index; BP, blood pressure; Cr, creatinine; DM, diabetes mellitus; FBS, fasting blood sugar; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; MD, mammographic density; RBS, random blood sugar; TG, triglycerides.

Nonobese n=579 (42.2%)					Obese n=793 (57.8%)				
Patient characteristics	N (%) of total study population	Risk factor	N (%) among patient characteristics	N (%) among risk factor	Patient characteristics	N (%) of total study population	Risk factor	N (%) among patient characteristics	N (%) among risk factor
Nonobese Non MD-A No Bcs	446 (32.5)	Hypertension	175/437 (40.0)	175/742 (23.6)	Obese Non MD-A No Bcs	544 (39.7)	Hypertension	325/534 (60.9)	325/742 (43.8)
		Hypercholesterolemia	140/369 (37.9)	140/553 (25.3)			Hypercholesterolemia	227/464 (48.9)	227/553 (41.0)
		Diabetes	68/390 (17.4)	68/389 (17.5)			Diabetes	174/472 (36.9)	174/389 (44.7)
Nonobese + MD-A	31 (2.3)	Hypertension	11/31 (35.5)	11/742 (1.5)	Obese + MD-A	76 (5.5)	Hypertension	63/75 (84.0)	63/742 (8.5)
		Hypercholesterolemia	13/25 (52.0)	13/553 (2.4)			Hypercholesterolemia	44/64 (68.8)	44/553 (8.0)
		Diabetes	7/28 (25.0)	7/389 (1.8)			Diabetes	33/68 (48.5)	33/389 (8.5)
Nonobese + Bcs	98 (7.1)	Hypertension	48/95 (50.5)	48/742 (6.5)	Obese + Bcs	161 (11.7)	Hypertension	108/158 (68.4)	108/742 (14.6)
		Hypercholesterolemia	44/82 (53.7)	44/553 (8.0)			Hypercholesterolemia	76/140 (54.3)	76/553 (13.7)
		Diabetes	25/86 (29.1)	25/389 (6.4)			Diabetes	75/146 (51.4)	75/389 (19.3)
Nonobese + MD-A + Bcs	4 (0.3)	Hypertension	2/4 (50.0)	2/742 (0.3)	Obese + MD-A + Bcs	12 (0.9)	Hypertension	10/12 (83.3)	10/742 (1.3)
		Hypercholesterolemia	1/3 (33.3)	1/553 (0.2)			Hypercholesterolemia	8/10 (80.0)	8/553 (1.4)
		Diabetes	1/2 (50.0)	1/389 (0.3)			Diabetes	6/10 (60.0)	6/389 (1.5)

Figure 2 Distribution of MD-A and/or Bcs per obesity status in the study population and distribution of the studied risk factors among participant characteristics and among all participants with the same risk factor. The presence of MD-A and/or Bcs, although more commonly observed among obese women, represented <10% and <20% of the non-obese and obese populations, respectively. Bcs, benign breast calcifications; MD-A, mammographic density A.

small number of participants with this cluster. These findings add to the value of the mammogram in women's health and support personalized patient–provider discussions of the mammogram findings[1] beyond breast cancer risk. If Bcs or reduced MD, particularly MD-A, is detected, screening for CVD risk factors, if not already attempted, should take place and closer follow-up and intensification of healthy lifestyle changes should be advised.

Association of MD-A with the studied CVD risk factors

In this study, we evaluated the associations of MD from a metabolic perspective, while most previous literature
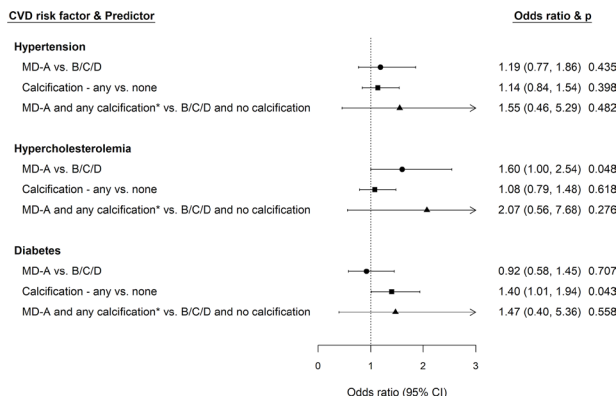

Figure 3 OR for the studied risk factors per mammographic density and breast calcifications with adjustment for body mass index and age. *n is only 16 for hypertension, 13 for hypercholesterolemia, and 12 for diabetes mellitus. CVD, cardiovascular disease; MD, mammographic density; MD-A, almost entirely fatty breast tissue; MD-B, scattered fibroglandular densities; MD-C, heterogeneously dense breast tissue; MD-D, extremely dense.
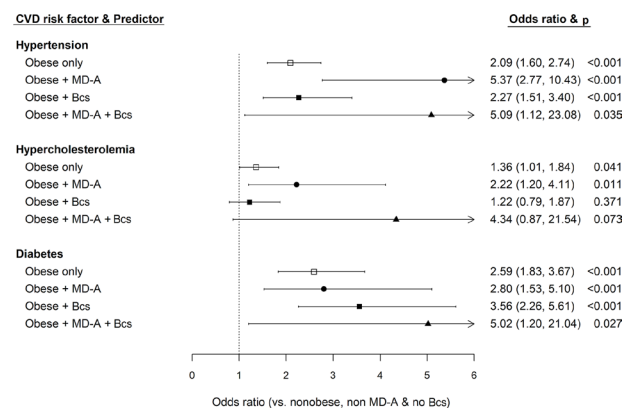
reported from a breast cancer risk point of view.[10 11] We observed that MD-A was closely related to increased BMI, and both were related in a similar manner to the studied risk factors. This parallel relationship of MD-A and BMI with the risk factors suggests that MD-A or increased breast adiposity may represent a new non-anthropometric obesity or body fat distribution index[12–14] that can be linked to atherosclerotic risk factors among women. Although obesity contributes directly to incident CVD risk factors, it is the regional body fat distribution, which is often sex-related, that is largely responsible for the observed differences in risk profiles.[15 16] Breast adipose tissue is an endocrine organ that secretes adipokines, cytokines, chemokines, and growth factors.[17] Women with increased body fat exhibit greater breast inflammation with higher levels of circulating metaboinflammatory factors,[11] and greater expression of

Figure 4 OR of the studied risk factors per MD-A and/or Bcs added to obesity, with adjustment for age. Bcs, benign breast calcifications; CVD, cardiovascular disease; MD-A, mammographic density A.

adipogenic and proinflammatory genes is detected in the breast adipose tissue of obese women compared with non-obese women.[18]

Limited available evidence has focused on the association of MD with the metabolic syndrome cluster[10 19–23] rather than individual CVD risk factors. Inconsistencies in the results are noted, likely due to the small number of participants,[10 21 24] inclusion of variable age groups (premenopausal,[22] post-menopausal,[21] or both[19]), and multiple ethnicities.[10 24] However, available data, in similar-aged populations, have hinted of an inverse association between MD and metabolic syndrome, particularly atherogenic lipid profiles, which supports our observations. In a cross-sectional study from Thailand involving 713 women ≥40 years of age, an inverse association between metabolic syndrome and per cent MD was noted, and after controlling for BMI the inverse association remained with triglycerides.[23] Tehranifar et al,[24] in a study involving 191 women 40 years of age or older, found that only a history of hypercholesterolemia was inversely associated with per cent density and dense area. Having multiple metabolic conditions was also associated with lower density. In another study by the same group, however, no association between BMI-adjusted per cent density and metabolic syndrome or its components was detected in a similar-aged population, apart from HDL-C, which was associated with increased density.[10] Conversely, in a study involving 364 premenopausal Chilean women, no association between metabolic syndrome and absolute dense volume was found; however, triglycerides were related to higher absolute dense volume.[20] In the largest study to date, involving 73,974 Korean women, metabolic syndrome and its components were associated with dense breasts (MD-D) in premenopausal women, while in both premenopausal and postmenopausal women high blood glucose and insulin resistance were positively associated with dense breasts.[22] Our findings on MD have validity; the distribution of MD categories[25–27] in this study and the inverse relation between MD and age and BMI[25 27–29] are consistent with the available literature. Further, the registered prevalence of the studied risk factors is in keeping with reports from Saudi Arabia and the world.[5 30 31] The relation between MD-A and the three risk factors is in harmony with what is anticipated from its established association with BMI.

The observed association of MD-A with hypercholesterolemia confirms earlier reports hinting at an association.[23 24] The stronger association in the case of hypercholesterolemia compared with the other risk factors may be explained by the fact that hypercholesterolemia is a classic characteristic of obesity[32] and is the most common obesity-related comorbidity, followed by hypertension and diabetes.[33] It is well established that changes in body fat depots significantly impact plasma lipoprotein composition and concentrations.[32] The independent association of MD-A with hypercholesterolemia suggests that MD-A may increase cholesterol levels through metabolic pathways that are not related to obesity. Evidence from bariatric surgery studies has shown that the metabolic effects of bariatric surgery on the breast parenchyma and MD are independent of absolute BMI reduction, suggesting the existence of such pathways.[34] While no similar mammographic data exist for comparison, the independent association of hypercholesterolemia with other obesity indices supports our findings.[35]

In the case of hypertension, the significant additive interaction between MD-A and BMI is in accordance with other investigators' observations that the combination of obesity indices and BMI yields the highest risk of incident hypertension compared with each measure alone.[36 37] Unlike waist circumference,[14] however, MD provided an additive but not independent association with hypertension. Conversely, on the other end of the spectrum, increased gluteofemoral adiposity decreases metabolic disease prevalence.[14 38] It may be postulated that MD-A is an intermediate between the two other phenotypes. Breast adipose-derived stem cells exhibit greater immunomodulatory and antioxidative capabilities than their abdominal counterparts.[39] There are no comparisons with gluteofemoral adipose cells at present. The association of MD-A with hypertension and hypercholesterolemia adds to the present knowledge of the differences in obesity-associated hypertension and hypercholesterolemia in men and women, which is of immense clinical importance.[40 41]

The association of MD-A with diabetes was less pronounced. Obesity and obesity indices have strong associations with diabetes[42]; in this study, however, we did not detect an independent association between diabetes and MD-A and only a trend for increased odds of diabetes was observed by the addition of MD-A to obesity. This may be due to the fact that diabetes, unlike the other studied risk factors, has a dual effect on MD, causing both reduced and increased MD,[43] thereby compromising the significance of the association. Increases in MD have been linked to diabetes per se,[22 44] its complications,[45] and insulin therapy.[43]

Association of Bcs with the studied CVD risk factors

Although we evaluated benign Bcs in general, which may have various etiologies,[9] women with diabetes tend to develop breast arterial calcifications (BACs), which involve the medial layer of the arterioles.[1 46] The observed predictors of Bcs in this study and the independent association with diabetes are in accordance with current literature on BACs.[1] While all major CVD risk factors have been linked to the development/presence of arterial calcifications, diabetes appears to be the most important predisposing factor,[47] which is in accordance with the study findings.

The present evidence of the association of BACs with CVD risk factors is indirectly derived from studies evaluating its association with CVD and reproductive factors in addition to CVD risk factors.[48 49] A recent meta-analysis involving studies that assessed the association of BACs with CAD found that BACs were positively associated with diabetes, hypertension, and hypercholesterolemia. When only good-quality studies were included, the association with hypercholesterolemia became insignificant.[48] In another meta-analysis, when good-quality and multivariable adjusted studies were included, ORs of 1.56 (95% CI 1.32 to 1.83) and 1.73 (95% CI 1.39 to 2.15) were detected for diabetes, respectively. No independent association with hypertension or hypercholesterolemia was observed.[49] Our results are in accordance with these meta-analyses and support them. This study, however, directly assessed the association of Bcs with the risk factors and was not subject to the methodological heterogeneity and selection bias that may occur from the inclusion of variable studies

in meta-analyses.[48 49] Additionally, to the best of our knowledge, Bcs have never been evaluated in comparison with or in addition to MD.

Association of MD-A and Bcs combined with risk factors

We observed no further increase in the odds of the risk factors by the addition of Bcs to MD-A and obesity, except for a tendency for increased odds of diabetes. While this may be due to the small number of participants with these characteristics, asynergy in the mechanisms behind the association of MD-A and Bcs with the risk factors is another potential explanation. The increased prevalence of Bcs in women with increased MD supports this theory.

The association of adiposity with the three studied risk factors is well established. Obesity contributes directly to the occurence of hypertension, diabetes, and dyslipidemia,[16] and it may be speculated that a similar association occurs in the case of MD-A. Conversely, the association of arterial calcifications with CVD risk factors varies. Although hypertension, hypercholesterolemia, and diabetes have been associated with arterial calcifications, this relation is not consistent across all vascular beds and for men and women.[50] In the case of BACs, an association with diabetes is reported but not with obesity, hypertension, or dyslipidemia.[49] At the molecular level, the pathogenesis of arterial calcifications involves multiple biological pathways including those related to inflammation, apoptosis, disruptions of calcium phosphate homeostasis, extracellular matrix degeneration, and genetic aberrations, and the initial drivers remain unclear.[46] Similarly, obesity has a complex pathogenesis and exhibits heterogeneity in the pathways and mechanisms by which it leads to adverse health outcomes.[16] While some overlap in the pathways of adiposity and arterial calcifications may exist, their effects/associations with the studied risk factors remain distinct. It may be that the association of MD-A with hypertension and hypercholesterolemia is a causal one emanating from its relation to obesity, while Bcs are a consequence of the inflammatory state commonly associated with insulin resistance and diabetes.[47] The observed tendency for increased odds of diabetes by the addition of both Bcs and MD-A to obesity is likely due to its strong association with both obesity[42] and Bcs.[47]

CONCLUSION

We found that both MD and Bcs are significantly associated with atherosclerotic CVD risk factors. In particular, MD-A was independently associated with hypercholesterolemia and additive to BMI increasing hypertension risk and may represent a new obesity index in women. Bcs were independently associated with diabetes. These findings have clinical value. Since a majority of women above 40 years of age undergo mammography annually for breast cancer screening, additional information gained from the mammogram may identify opportunities for targeted atherosclerotic CVD risk factor screening, early treatment, and prevention, and add to CVD risk stratification among them.

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