Metabolic risk factors and mammographic breast density among Egyptian postmenopausal women with type 2 diabetes mellitus

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Purpose
To evaluate the association of various metabolic risk factors with percent mammographic breast density (PMD), and to assess the advantage of screening mammogram in type 2 diabetes mellitus (T2DM) postmenopausal diabetic women.

Patients and methods
This was a cross-sectional study which included 90 postmenopausal women, who were divided into two groups: group I included 60 patients diagnosed with T2DM and group II included 30 controls.
All participants were subjected to history taking, clinical assessment, fasting serum glucose, glycated hemoglobin, Homeostatic Model Assessment 2-IR calculation, serum lipid profile, and screening mammogram (PMD).

Results
There was significant inverse associations between PMD and weight (P=0.006, 0.022, 0.010), BMI (P=0.003, 0.015, 0.001), and waist circumference (P=0.001, 0.019, 0.001) in cases, control, and total sample, respectively. After adjustment for weight in the total sample, the extremely dense group (breast imaging-reporting and data system D) was only associated with age of menarche (odds ratio, 0.404), while in cases group, breast imaging-reporting and data system D was only significantly associated with waist circumference (odds ratio, 0.756).

Conclusions
PMD levels were not increased in the presence of multiple metabolic risks, pointing to an alternative pathway explaining the increased risk of cancer breast in T2DM postmenopausal women.

Keywords:
insulin resistance, metabolic syndrome, percent mammographic breast density, postmenopause, type 2 diabetes mellitus

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Background

Type 2 diabetes mellitus (T2DM) is a growing health problem worldwide. T2DM is strongly linked to the epidemic of obesity. People with T2DM are constantly at an increased risk for both microvascular and macrovascular complications due to hyperglycemia and the various components of insulin resistance (IR) syndrome. Environmental factors (e.g. overweight, sedentary lifestyle, and unhealthy food) and genetic factors contribute significantly to multiple pathophysiological disorders that affect T2DM glucose homeostasis [1]. DM and its metabolic changes can contribute to cancer development and progression through increased
body weight, prediabetes status, and metabolic syndrome (MetS). Type 2 diabetes is related to a greater risk for several cancers (including colorectal, postmenopausal breast, endometrial, liver, pancreatic, bladder, and non-Hodgkin's lymphoma) [2,3], with the exception of prostate cancer [4].

IR and impaired insulin secretion remain the main defect in T2DM [5,6], in hyperinsulinemia, both endogenous and exogenous, may be related to an increased risk of many cancers [7]. Concerning breast cancer, previous research has proven that IR is associated with increased prevalence of tumors and more aggressive tumor biology [8].

The MetS, also referred to as IR syndrome, is described clinically as having at least three of the following disorders: abdominal adiposity, raised blood pressure, raised fasting plasma glucose, raised triglycerides, and reduced high-density lipoprotein (HDL) cholesterol [9]. Although MetS is known to predict the risk of cardiovascular diseases and type 2 diabetes, late proof recommends that MetS and its components are related

to the risk for many cancers in women, such as postmenopausal breast cancer [10]. Therefore, diabetes and carcinogenesis might be bound together by the same several and interconnected biological mechanisms that connect visceral obesity, prediabetes, and MetS to malignant growth.

Hyperinsulinemia and MetS may affect breast cancer risk through a mechanism related to increased mammographic density. Insulin indirectly promotes breast cancer development, through upregulation and modulation of bioavailability of insulin growth factor-1 and insulin growth factor-2, particularly in the tumor microenvironment. It has been proposed that insulin and insulin growth factor-1 act directly as paracrine and autocrine growth factors for breast cancer cells via the activation of PI3K/AKT/mTOR and RAS/RAF/MAPK signaling pathways [11].

High percent mammographic breast density (PMD) is an important risk factor for breast cancer [12]. It reflects the composition of breast tissue: dense fibroglandular breast tissue appears light (radiopaque) on mammograms, while fat tissue seems darkish (nondense). Women with a high PMD (75% or more) have a four-fold to six-fold more risk of breast cancer in comparison with women with a low PMD [13]. Abdominal adiposity affects breast density and breast cancer risk in opposite directions with abdominal adiposity associated with low PMD [14].

Mammographic density, considered as a biological marker of cumulative exposure of mammary cells to hormones and other growth factors [15], can interfere with mammogram detection of breast cancer. Reduced mammographic sensitivity to breast cancer in women with very dense breast tissue compared with those with fattier breast tissue has been observed [16].

The aim of this study was to evaluate the association of IR and T2DM with mammographic breast density and to evaluate the role of mammograms in screening for breast cancer in postmenopausal women with type 2 diabetes.

Patients and methods

Study population

This is a cross-sectional study on 90 postmenopausal women recruited from the outpatient clinic at Alexandria Main University Hospital after obtaining a signed informed consent. The study participants were divided into two groups.

Group I: included 60 postmenopausal women with type 2 diabetes for at least 1 year. Eligible women were more than or equal to 50-year olds having no menstrual cycle for at least 2 years.

Group II: included 30 healthy postmenopausal women.

Exclusion criteria included women with T1DM, premenopausal, endocrinal diseases, renal and hepatic diseases, history of breast surgery, history of other malignant diseases, smoking, and alcohol consumption.

All procedures performed were in accordance with the ethical standards of the Faculty of Medicine, Alexandria University and with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

Methodology

The study participants were subjected to history taking: general medical, menstrual, and reproductive history (such as age at menarche, menopausal status, hormone replacement therapy (HRT), and the number of live births, and history of lactation) and breast history (history of breast surgery, breast biopsies, breast augmentation, and malignancy).

Complete clinical examination and determination of anthropometric measures including body weight (kg), height (m), waist circumference (cm), and calculation of BMI (kg/m^2).

Weight and height were measured using a calibrated balancer and a vertical ruler with participants wearing light clothing and no shoes. Height was recorded to the nearest 0.1 cm and weight to the nearest 0.1 kg.

BMI was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2). Waist circumferences were measured at the mid-distance between the iliac crest and the last rib margin with a soft tape while the participant was in a standing position. Measurements were recorded to the nearest 0.1 cm.

Blood pressure was measured from the dominant arm of seated patients with an appropriately sized sphygmomanometer after 5 min of rest in sitting position.

About 10 ml fasting venous blood samples (10–12 h of fasting) were taken from each participant participating

in this study, for measurement of fasting serum glucose, fasting serum insulin level, glycated hemoglobin, total serum cholesterol, HDL cholesterol, low-density lipoprotein cholesterol, and serum triglycerides.

Homeostatic Model Assessment 2-IR (HOMA2-IR) data were calculated using HOMA Calculator, version 2.2.2 (Diabetes Trial Unit, University of Oxford, UK; http://www.dtu.ox.ac.uk/index.php?maindoc_/homa/).

Measurement of mammographic breast density

The mammograms were made for all women in the Department of Radiology at Alexandria University. For each breast, craniocaudal and mediolateral oblique views have been taken. All mammograms were archived, printed, and reviewed by a qualified radiologist with 13 years of experience in accordance with the qualitative method; breast imaging-reporting and data system (BI-RADS, American College of Radiology, Reston, VA), using subjective and semiquantitative assessment suggestions that have been added to the fifth edition to assign an overall breast composition rating on the basis of the densest tissue area to convey the likelihood of lesion obscuration. Hence, though a breast might have an overall density percentage of less than 50%, it is densely collected in one region, with an otherwise surrounding fatty tissue it will be considered heterogeneously dense to convey that this area may obscure cancer. Breast density is classified as almost entirely fat (BI-RADS A), scattered fibroglandular densities (BI-RADS B), heterogeneously dense (BI-RADS C), or extremely dense (BI-RADS D) [17].

Since extremely dense breast can affect mammographic screening through the masking effect of the underlying pathologies it is considered as a standalone risk factor for breast cancer [18]. This study focused on extremely dense breast referred to BI-RADS D versus BI-RADS A/B/C; this description has been used in other studies [19].

Statistical analysis [20]

Data were fed to the computer and analyzed using IBM SPSS software package, version 20.0. (IBM Corp., Armonk, New York, USA) [21]. Qualitative data were described using number and percent. The Kolmogorov–Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, SD, and median. χ^2 test for categorical variables was used to compare between different groups. Fisher's exact or Monte Carlo correction for χ^2 when more than 20% of the cells have an expected count of less than 5 and Student's t test for normally distributed quantitative variables, to compare between two studied groups. Mann–Whitney test for abnormally distributed quantitative variables, to compare between two studied groups. Regression to detect the most independent/affecting factor for dense cases. Significance of the obtained results was judged at the 5% level.

Results

Table 1 shows the comparison between the two studied groups according to different parameters. The mean age of group I (diabetic postmenopausal women) was 57.55±6.31 years, while the mean age of group II was 55.93±5.86 years with no significant difference in age between patients with cases and controls.

Statistically, there was a statistically significant difference in the age of menarche, parity, hypertension, height, weight, BMI, waist circumference, fasting plasma glucose, glycated hemoglobin, fasting insulin, HOMA2-IR, and lipid profile between the two studied groups, while there was no statistical significant difference in the age of postmenopause, HRT, history of lactation, history of breast surgery, and family history of breast cancer as shown in Table 1.

As regards the duration of diabetes, 32 cases had diabetes for less than 10 years, while 28 cases had diabetes for more than 10 years. The mean of duration was 11.97±6.71 years. The number of cases treated by metformin was three, 10 by sulfonylurea, 24 by metformin and sulfonylurea, 14 by metformin and insulin, nine by premixed insulin, while no one was off treatment as shown in Table 2.

Comparison between the two studied groups according to breast density

The number of women with BI-RADS A was 13 cases and nine controls; BI-RADS B was 14 cases and 14 control; BI-RADS C was 22 cases and three controls, BI-RADS D was 11 cases and four controls (Fig. 1).

Statistically there was a significant difference in breast density of diabetic postmenopausal women (cases) compared with nondiabetic postmenopausal women (control) (P=0.023) (Fig. 2).

However, there was no statistically significant difference between both groups on classifying the breast density as BI-RADS A/B/C versus BI-RADS D (extremely dense breast).

Table 1 Comparison between the two studied groups according to different parameters

	Cases (*N*=60)	Control (*N*=30)	*P*
Age (years)	57.55±6.31	55.93±5.86	0.244
Hypertension	38 (63.3)	12 (40)	0.036*
Blood pressure			
Systolic	140.0±15.68	124.7±12.24	<0.001*
Diastolic	92.42±9.32	79.83±6.36	<0.001*
Age at menarche (years)	13.03±1.54	12.33±1.24	0.033*
Age postmenopause (years)	48.43±4.22	48.20±4.22	0.805
Number of children	4 (0–8)	3 (2–5)	0.006*
HRT	5 (8.3)	1 (3.3)	0.659
History of lactation	50 (83.3)	24 (80)	0.697
History of BC surgery	1 (1.7)	2 (6.7)	0.257
Family history of BC	6 (10)	3 (10)	1.000
Height (m)	1.61±0.06	1.54±0.04	<0.001*
Weight (kg)	82.97±14.37	66.03±8.18	<0.001*
BMI (kg/m^2)	32.04±5.73	27.80±3.60	<0.001*
Waist circumference	111.5±9.79	95.9±4.39	<0.001*
FBG	225.0±74.12	87.27±9.92	<0.001*
Fasting insulin	13.4 (5.37–52.70)	6.43 (2.9–13.8)	<0.001*
HbA1C	10.15±1.71	5.46±0.37	<0.001*
Total cholesterol	223.3±53.76	194.87±50.46	0.016*
TG	145.5 (72–332)	115 (51–219)	0.015*
HDL	38.9±4.83	44.13±10.21	0.012*
LDL	155.5 (110–300)	150 (61–159)	0.003*
HOMA index	2.02 (0.84–23.26)	0.80 (0.39–1.79)	<0.001*
Breast density			
BI-RADS A	13 (21.7)	9(30)	0.023*
BI-RADS B	14(23.3)	14(46.7)	
BI-RADS C	22(36.7)	3(10)	
BI-RADS D	11(18.3)	4(13.3)	

Qualitative data were described using *n* (%) and compared using c^2 test. Normally quantitative data were expressed in mean±SD and was compared using Student's *t* test, while abnormal quantitative data were expressed using median (minimum–maximum) and compared using Mann–Whitney test. BC, breast cancer; BI-RADS, breast imaging-reporting and data system; FBG, fasting blood glucose; HbA1C, glycated hemoglobin; HDL, high-density lipoprotein; HOMA, Homeostatic Model Assessment; HRT, hormone replacement therapy; LDL, low-density lipoprotein; TG, triglycerides. *Statistically significant at *P* value less than or equal to 0.05.

According to this study, postmenopausal women with BI-RADS D (extremely dense breasts) had lower BMIs than those with BI-RADS A/B/C. Also, the BI-RADS D group (extremely dense breast) had earlier menarche, less live birth, and history of HRT use than the BI-RADS A/B/C groups. Statistically, there was no significant relation between BI-RADS A/B/C and BI-RADS D groups regarding age, duration of diabetes, type of treatment, and age of menopause.

Also, there was a statistically significant inverse relationship between breast density and age of menarche for cases, control, and total sample ($P<0.001$, $P=0.005$, $P<0.001$) respectively, but there was no significant relation between breast density and age of menopause for cases, control, and total sample (Fig. 3).

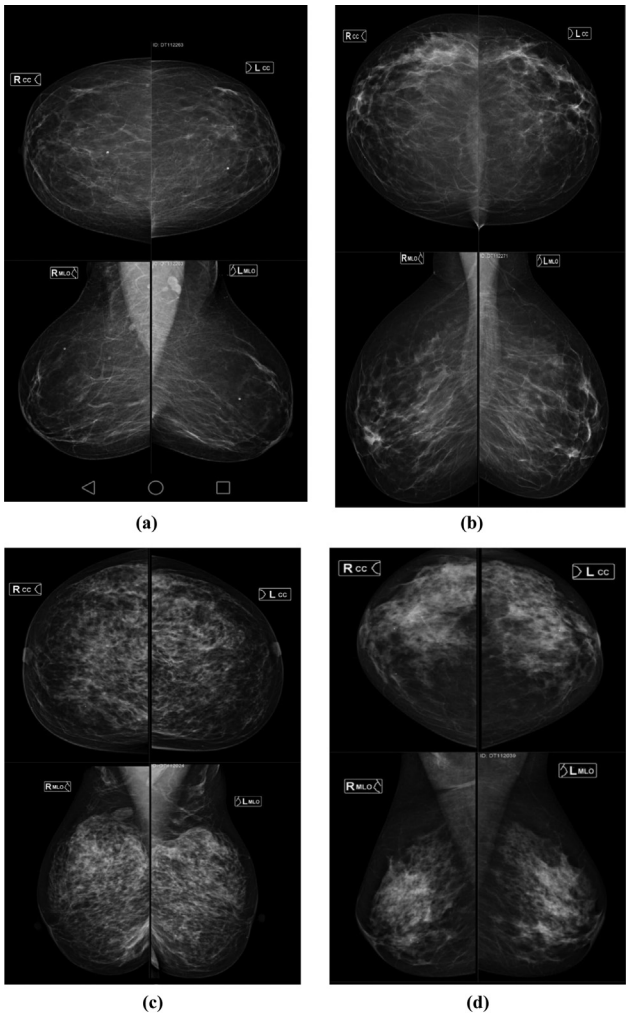
There was a statistically significant positive relationship between history of hormonal replacement therapy and the extremely dense breast group (BI-RADS D) for cases and total sample ($P=0.039$, 0.006), but it was insignificant for the control group ($P=0.133$). However, there was no relationship between breast density and history of

Table 2 Distribution of the studied cases according to duration of diabetes and antidiabetic medications

	Cases (*N*=60)
Duration (years)	10 (1–30)
≤10	32 (53.3)
>10	28 (46.7)
Treatment	
No treatment	0
OHD	
Met only	3 (5)
SU	10 (16.7)
Met+SU	24 (40)
Met+insulin (premixed)	14 (23.3)
Insulin (premixed)	9 (15)

OHD, oral hypoglycemic drugs; SU, sulfonylurea. Qualitative data were described using *n* (%). Abnormal quantitative data were expressed using median (minimum–maximum).

Figure 1



Visual assessment of breast density on mediolateral oblique and craniocaudal mammograms, with density rated according to the fifth-edition BI-RADS categories: (a) 62-year old, diabetic, postmenopausal women with BI-RADS A (entirely fatty) breasts; (b) 54-year old, diabetic, postmenopausal women with BI-RADS B (fibroglandular) breasts; (c) 65-year old, diabetic, postmenopausal women with BI-RADS C (heterogeneously dense) breasts; and (d) 53-year old, diabetic, postmenopausal women with BI-RADS D (extremely dense) breasts. BI-RADS, breast imaging-reporting and data system.

lactation, history of breast surgery, and family history of breast cancer for cases, control, and total sample. There was no relation between BI-RADS A/B/C versus BI-RADS D groups as regards hypertension for cases, control, and total sample.

Postmenopausal women, whose mammograms were BI-RADS A/B/C, had a significantly higher BMI (P=0.003, 0.015, 0.001 in cases, control, and total sample) and waist circumference (P=0.001, 0.019, 0.001 in cases, control, and total sample) compared with postmenopausal women with extremely dense mammograms (BI-RADS D) as shown in Fig. 4.

Mammographic breast density had a statistically significant positive relation to both fasting insulin (P=0.038) and HOMA index (P=0.044) in the control group, but not for cases group and total sample.

A multivariable adjusted model showed that extremely dense cases for total sample (n=90) was only associated with the age of menarche (odds ratio, 0.404; 95% confidence interval, 0.179–0.910), while in cases (T2DM) group (n=60), extremely dense breast was only significantly associated with waist circumference (odds ratio, 0.756; 95% confidence interval, 0.584–0.978) (Table 3).

Discussion

In this study of the relationships between breast density and each component of MetS, an inverse association between mammographic breast density, weight, BMI, and waist circumference was identified.

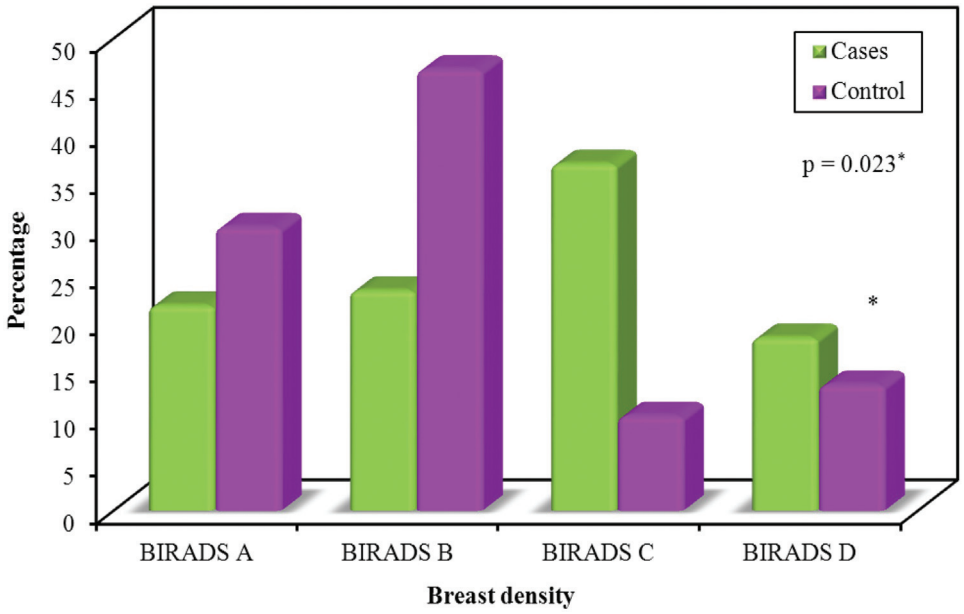
The inverse association between waist circumference and breast density remained statistically significant after adjusting the weight. This inverse association is consistent with findings from other studies such as Conroy *et al.* [22], Woolcott *et al.* [23], Pollán *et al.* [24], and Kim *et al.* [19].

This inverse association is confusing with the positive relationship between abdominal adiposity and breast cancer, independent of BMI [25,26]. This confusing impact is explained by the fact that the effects of abdominal adiposity on the risk of breast cancer may not be due to breast density but by other alternative pathways [27].

We found a nonstatistically significant positive association between mammographic breast density and hyperglycemia. This finding is consistent with Kim *et al.* [19]. A modest inverse association between mammographic breast density and hyperglycemia was determined in the Study of Women's Health Across the Nation (SWAN) [22]. Only those with MetS had a lower mean mammographic breast density, although the association between hyperglycemia and the MetS was not statistically significant. They concluded that although hyperglycemia may be related to the risk of breast cancer, the effects of hyperglycemia on the risk of breast cancer are not mediated by an increase in mammographic breast density [22].

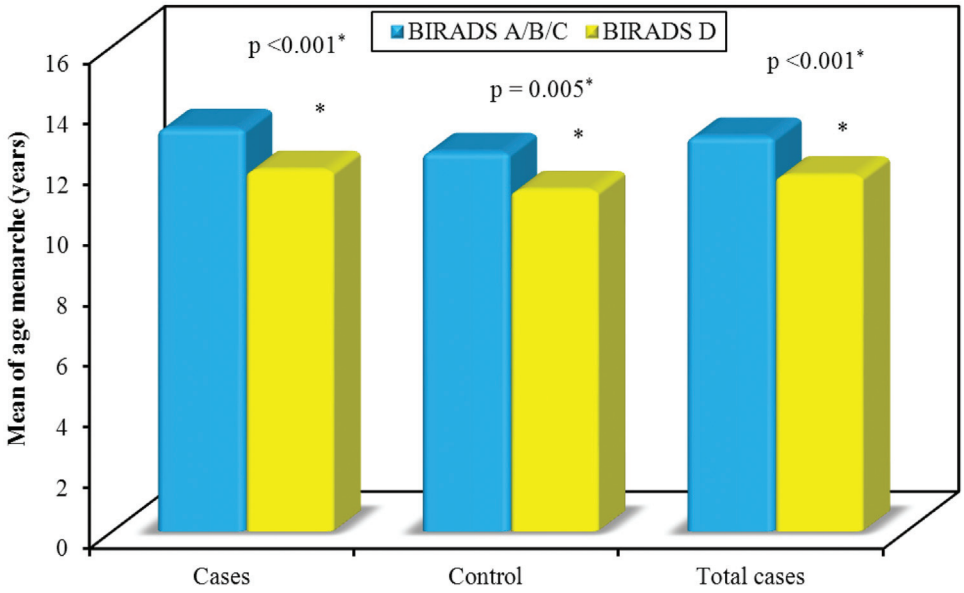
Moreover, Sellers *et al.* [28] in a cross-sectional analysis using data from the large Minnesota Breast Cancer

Figure 2



Comparison between the two studied groups according to breast density.

Figure 3



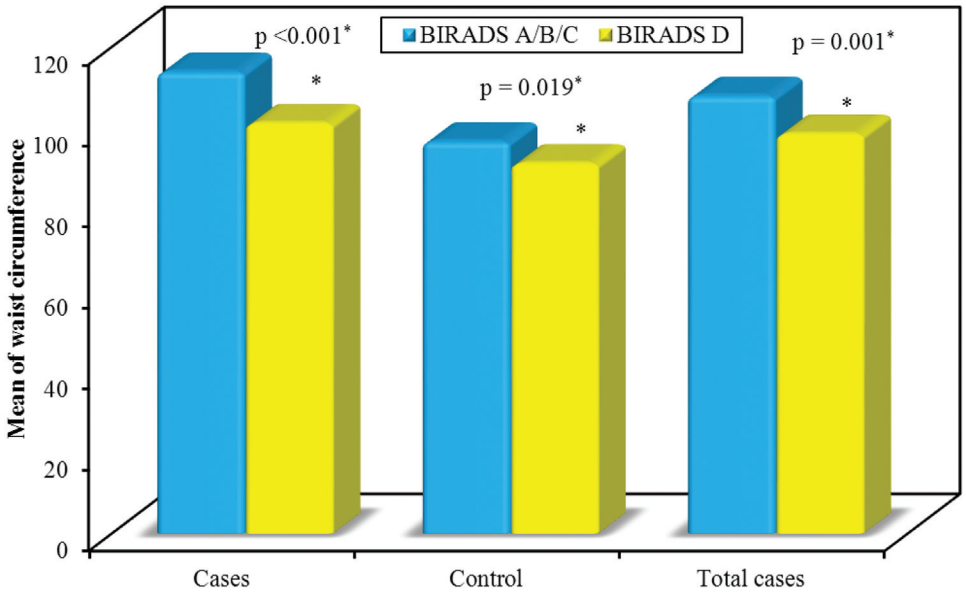
Relationship between breast density and age at menarche (years) for cases, control, and total groups.

Family Study did not show a difference in percent density by diabetes status in BMI-adjusted models in premenopausal or postmenopausal Caucasian women.

In this study, we could not find an association between breast density and neither fasting insulin nor HOMA index. Several studies as Diorio *et al.* [29], Sellers *et al.* [28], Conroy *et al.* [22] have demonstrated that mammographic density does not relate to IR indicators (diabetes status, fasting glucose, or C-peptide levels) after adjustment for overall adiposity.

On the other hand, Kim *et al.* [19] observed a significant association of fasting glucose and HOMA-IR with dense breast in both premenopausal and postmenopausal women, and this association remained significant after adjustment for potential confounders, supporting the hypothesis that IR, a modifiable risk factor, can increase the risk of breast cancer through high mammographic breast density, and is associated with more aggressive and a higher tumor recurrence rate [8,30,31].

Figure 4



Relationship between breast density and waist circumference for cases, control, and total groups.

Table 3 Univariate and multivariate analyses for parameters affecting extremely dense cases for total sample (*N*=90)

Extremely dense for total sample	Univariate		Multivariate[a]	
	P	OR (95% CI)	*P*	OR (95% CI)
Age at menarche (years)	0.005*	0.403* (0.214–0.757)	0.029*	0.404* (0.179–0.910)
Number of children	0.003*	0.439* (0.256–0.752)	0.580	0.808 (0.380–1.719)
HRT	0.005*	13.27* (2.168–81.25)	0.063	15.71 (0.863–286.17)
BMI (kg/m^2)	0.003*	0.764* (0.64–0.914)	0.065	0.788 (0.613–1.015)
Waist circumference	0.005*	0.901* (0.837–0.969)	0.872	0.991 (0.893–1.101)

CI, confidence interval; HRT, hormone replacement therapy; OR, odd's ratio. [a]All variables with *P* value less than 0.05 was included in the multivariate. *Statistically significant at *P* value less than or equal to 0.05.

The lack of association between mammographic breast density and lipid profile, especially raised triglycerides or low HDL cholesterol, observed in our study is consistent with Tamburrini *et al.* [32], Conroy *et al.* [22], Kim *et al.* [19].

In our study, women with BI-RADS D (extremely dense breasts) had lower BMIs than those with BI-RADS A/B/C. Also, they had earlier menarche and fewer live births than the BI-RADS A/B/C group. These results were consistent with Conroy *et al.* [22] and Kim *et al.* [19].

Interestingly, we observed a lack of association between breast density and duration of diabetes. In Sanderson *et al.* [33], study, postmenopausal women with a history of diabetes exceeding 10 years had higher breast density than women who have less than 10 years of diabetes. In agreement with this study, there was no effect on the use of insulin or oral antidiabetic medications on mammographic breast density, which can be attributed to the small sample size.

We found an inverse association between parity and breast density inconsistent the results of Yaghjyan *et al.* [34]. The inverse association could be explained by biological changes in the breast tissue during a full-term pregnancy, which leads to changes in permanent gene expression, making them less susceptible to hormonal influences and carcinogenesis [35,36]. As a result, the effect of estrogen on breast cell proliferation could be less prominent in parous women than in nulliparous women leading to less density.

However, in Gapstur *et al.* [37] study, there was no relationships of parity with percentage of breast density in Hispanic women. It may be due to the very low proportion of nulliparous women (≤4%).

In this study, we observed an inverse relationship between age at menarche and breast density. Women with extremely dense breasts with or without MetS had an early age of menarche. However, the age of menopause in relation to breast

density did not show any effect. In agreement with our results, the inverse association was seen in El-Bastawissi *et al*. [38], and de Stavola *et al*. [39]. In contrast, Heng *et al*. [40] found no association between the age of menarche and breast density. These findings are consistent with the possibility that hormonal or reproductive events may have less influence in obese women, whose circulating hormone levels may be influenced by conversion in peripheral adipose tissue.

According to the effect of hormonal replacement therapy on breast density, we found that the use of HRT increased breast density among postmenopausal women. These findings are consistent with Gapstur *et al*. [37], Titus-Ernstoff *et al*. [41], and Kelemen *et al*. [42].In this study, we could not find a relationship between family history of breast cancer and breast density. However, studies such as de Stavola *et al*. [39] and Gapstur *et al*. [37] have not shown an effect of family history of breast cancer on breast density, which is likely due to the limited power to detect a weak association.

The relationship between IR, MetS, and mammographic density remained unclear. Many studies have demonstrated that results vary by ethnicity. A number of studies such as del Carmen *et al*. [43] and Chen *et al*. [44] have shown the relation between breast density and race.

There are several limitations to this study. First, breast density was assessed by a conventional subjective and semiquantitative method (BI-RADS), which is the most current tool of mammographic density estimate. Compared with the aforementioned method, an automated quantitative tissue density software has been developed to provide more precise results as regards the association between mammographic density and breast cancer, but it is expensive, time consuming, and still yields inaccuracies as it uses three-dimensional volumetric models on two-dimensional images and still does not reflect the recent modifications described in the BI-RADS fifth edition [45]. Hence, BI-RADS is still considered to be reliable and disclosed a high intraradiologist percent agreement [46,47]. Furthermore, we only focused on the extremely dense breast of BI-RADS D class.

Second, this study is a cross-sectional analysis, it is possible that we were unable to observe the hypothesized positive association between MetS or its components and mammographic breast density, because we did not evaluate the most relevant etiologic time period.

Conclusion

In conclusion, we do not support the theory that IR, T2DM, and metabolic abnormalities increase breast cancer risk via increasing mammographic breast density or the amount of dense breast tissue among postmenopausal women, but rather through other pathways.

In addition, we would like to point to the great value of breast cancer screening by mammogram in postmenopausal women with MetS, since they have less dense breast tissue and could gain benefit from PMD as a screening tool.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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