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# Low density mammography is associated with increased carotid intima-media thickness in middle aged premenopausal women

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## Abstract

**Objectives:** As the hormonal status of women does influence both mammographic breast density and atherosclerosis, the aim of the study was to evaluate the association between breast density on mammography and carotid intima-media thickness (CIMT).
**Methods:** Two-hundred premenopausal women with mammographic breast density of one (n=100) or four (n=100) were selected for this cross-sectional study. CIMT was measured according to the guidelines of Mannheim Consensus. The correlation between mammographic breast density and CIMT was assessed.
**Results:** Mean age was 45.9±3.4 years and 45.8±3.2 years in the groups with mammographic density of 1 and 4, respectively, which showed no significant difference. CIMT correlated with age with a Pearson Correlation Coefficient of 0.470 ($p<0.001$). CIMT was significantly higher in women with ACR-mammographic density of 1 ($p<0.001$).
**Conclusion:** Women with mammographic breast density of 1 revealed a higher CIMT. Further studies evaluating breast density and CIMT in pre- and postmenopausal women and assessing simultaneously the serum hormone level could give more information about the cause and effect of this correlation.

**Keywords:** Carotid Intima-Media Thickness, Mammography, Breast Density, Atherosclerosis.

## Introduction

Atherosclerosis is one of the major causes of mortality and there has always been interest to find efficient screening tools for earlier and easier detection. If a positive correlation can be shown between mammographic findings and cardiovascular risk, screening mammography could simultaneously be used as a screening tool for atherosclerosis. Breast arterial calcification (BAC) seen on mammography is one of the issues recently evaluated as an indicator for the presence of coronary calcifications.[1-4] Women with BACs have a higher cardiovascular risk than those without calcifications up to a summarized OR of 2.6.[4,5] Trimboli et al., reviewed existing evidence on the relation between BACs and coronary artery disease and reported a relative risk of 1.8 for myocardial infarction and a hazard ratio of 1.44 for cardiovascular death in women with BAC on mammography. Also, a positive correlation was seen between BAC and diabetes and hyperlipidemia, two major risk factors for atherosclerosis.[4] In women with pre-existing cardiovascular disease, the presence of breast calcifications was associated with hazard ratio of 1.79 for cardiovascular death.[6]

Breast parenchymal density is also reported in mammograms and is in close relation to menopausal status and serum hormone levels,[7,8] but a correlation between breast density and atherosclerosis is not evaluated until now. Mammographic density is associated with higher levels of serum progesterone, estrogen and sex-hormone binding globulin in premenopausal

women.[8] After menopause, with the decline of serum hormone levels, breast density decreases obviously. More than 70% of patients between 40 and 49 years old have dense breasts in contrast to only 36% of women in their 70s.[7] As the hormonal milieu of women is assumed to have influence on both, i.e., breast density and atherosclerosis, the aim of our study was to evaluate the association between mammographic breast density and atherosclerosis. To our knowledge, there is only one study addressing the correlation between breast parenchymal density and atherosclerosis, showing increased cardiometabolic risk in patients with low density breasts.[6] Carotid Intima-Media Thickness (CIMT) is strongly associated with atherosclerosis in other body regions and is often used as a measure of atherosclerosis.[9]

## Objectives

To determine the risk of cardiovascular disease, we used CIMT in our study as an indicator for the presence of atherosclerosis and assessed its' correlation with mammographic density in premenopausal women.

## Methods

To determine the sample size, a pilot study was performed and a median CIMT of 0.518 ± 0.030 mm for women with an ACR breast density of 1 and a median of 0.590 ± 0.048 mm for women with ACR breast density of 4 was calculated. With α=0.01 and β=0.01, a sample size of 15 for each group was calculated. As no similar studies were available to calculate the sample size, we preferred to increase the number to 100 women for each group to achieve more significant results. Premenopausal women between 40 and 50 years old who were referred for screening mammography were included in this cross-sectional study. Mammography was performed (Planmed, Sophie) and women with breast density of 1 and 4 (according to the American College of Radiology Breast Density Classification) were selected for the study.[10] The density was assessed by one radiologist. Written informed consent was taken and history and physical examination and lab data including blood sugar and lipid profile was obtained. Women with the following major cardiovascular risk factors were excluded: High LDL cholesterol, cigarette smoking, blood pressure ≥ 140/90 mmHg or on anti-hypertensive medication, HDL cholesterol < 40 mg/dL, diabetes mellitus, family history of premature CHD, and BMI>30 kg/$m_2$.[11] Ultimately, 100 women with breast density of 1 and 100 women with breast density of 4 were included. Color-Doppler Ultrasound was performed by a second radiologist who was blinded to the results of the mammogram. Ultrasound was performed with B-mode, 7-12 MHz probe (WS80A Samsung) from the end-diastolic far wall distance in the distal 2 centimeters of both common carotid arteries, according to the Mannheim Carotid Intima-Media Thickness and Plaque Consensus.[12,13] Measurement was done automatically with a minimum of 150 points.

### Statistical analysis

The continuous variables were expressed as the mean± SD, and the categorical variables were presented as a percentage and frequency. For assessing the correlation between CIMT and age, Pearson correlation coefficient and linear regression analysis and to compare the two groups, t-test was used. All statistical analyses were performed with SPSS (version 20.0, SPSS Inc, Chicago, IL, USA). A "P-value" less than 0.05 was considered significant.

### Ethical considerations

The study protocol was designed according to the revised guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of our institution (approval number: 5755). All participants signed an informed consent form.

## Results

Two-hundred women were included in the study. Mean age was 45.9±3.4 years and 45.8±3.2 years in the groups with breast density of 1 and 4, respectively, showing no significant difference (p<0.614). The distribution of patients according to age is shown in a histogram [Figure 1]. CIMT correlated with age with a Pearson correlation coefficient of 0.470 (p<0.001). The linear regression model showed a significant linear correlation between age and CIMT:

CIMT ($10^{-5}$m) = 1.051 × age (year) + 7.375 (p<0.001)

CIMT in the right and left carotid arteries was compared using paired t-test. Mean CIMT was 55.54±7.51 on the right side and 55.72±7.58 on the left, showing no significant difference. Mean CIMT was 57.75±7.90 in women with breast density 1 and 53.50±6.16 in those with breast density 4, showing a significantly higher CIMT in women with low breast density (p<0.001). This difference was evident in both right and left carotid arteries. Details are shown in Table 1.

**Table 1.** Intima-media thickness of right and left carotid arteries in women with mammographic breast density of one and four

| | ACR[a] breast density 1 n=100 | ACR breast density 4 n=100 | P value |
|---|---|---|---|
| Right CIMT [b] in $mm^{-2}$ (mean±SD [c]) | 57.67±7.83 | 53.40±6.56 | <0.001 |
| Left CIMT in $mm^{-2}$ (mean±SD) | 57.83±8.27 | 53.60±6.17 | <0.001 |
| Mean CIMT in $mm^{-2}$ (mean±SD) | 57.75±7.90 | 53.50±6.16 | <0.001 |

a: ACR; American College of Radiology, b: CIMT; Carotid Intima-Media Thickness, c: SD; Standard Deviation.

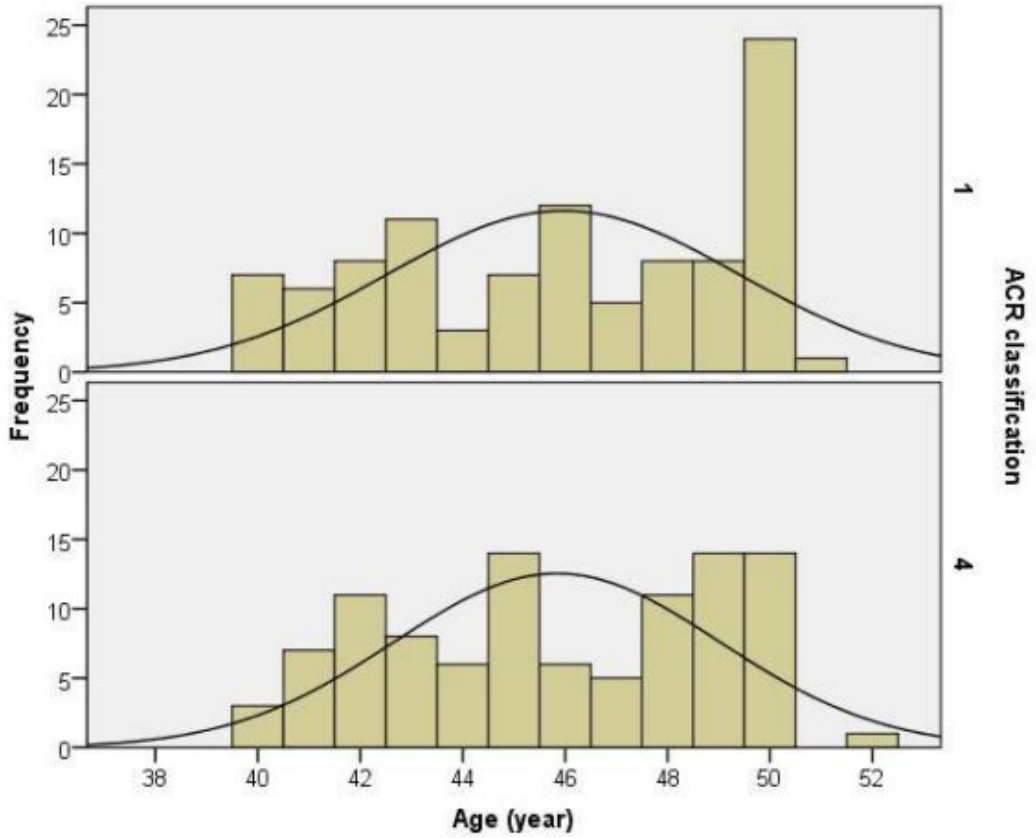


**Figure 1.** Histogram showing age distribution in both groups

## Discussion

Breast density on mammography is related to several factors, such as age, number of pregnancies, menopausal status and serum hormone levels.[6,7,14] Use of hormone replacement therapy in postmenopausal women is associated with increased breast density.[7,15] Johanssen et al. reported a significant correlation between mammographic breast density and serum estradiol level in postmenopausal women.[16] Similarly, Mauro Secco et al. reported a strong positive correlation between breast density and serum estradiol and FSH level in pre- and postmenopausal women.[14] In a recent study on more than 1000 women, breast density was associated with all endogenous plasma hormones, including progesterone, estrogen, corticoids and androgens.[8] According to these findings, the hormonal milieu seems to have a major role in determining breast composition.

The correlation between sex-hormones and atherosclerosis is less understood. The effect of sex-hormones on atherosclerosis is commonly regarded as an unquestioned reality, but existing data are indefinite. Vaidya et al showed that an "androgenic milieu" (higher testosterone and DHEA) is associated with decreased distensibility of the carotid artery in postmenopausal women. In contrary, the 5-year follow up of more than two-thousand men and women, revealed no consistent association between serum androgen concentration and subclinical measures of atherosclerosis in longitudinal analysis.[17] Celestino et al observed only a positive association between intima-media thickness and FSH, but not with Estradiol and Testosterone.[18] The study of Ouyang et al., showed a positive correlation between CIMT and serum testosterone (and not estradiol) in postmenopausal women.[15] To our knowledge, there is no

published meta-analysis addressing this puzzling topic. Only the studies evaluating the sex hormone binding globulin (SHBG) show a consistent inverse relationship with atherosclerosis. Lower SHBG was associated with longitudinal increases in blood pressure in postmenopausal women. El Khoudari et al., followed 249 pre- and perimenopausal women for 9 years and reported that a decrease in SHBG was associated with an increase in carotid intima-media thickness (IMT) progression.[19] In the CARDIA-study (Coronary Artery Risk Development in Young Adults) with 20 years follow-up, SHBG levels were inversely associated with CIMT in young to middle-aged women.[20]

The data about the prophylactic effect of postmenopausal treatment with estrogen with or without progesterone on atherosclerosis are also contradictory. The previously believed benefit of hormone replacement therapy in decreasing cardiac events could never be verified in randomized trials. After 18 years follow-up, the large Women's Health Initiative trial showed no difference in all-case and specific-cause mortality in menopausal women with 6 years estrogen and progesterone treatment.[21] Recently it is hypothesized that the beneficial effect of postmenopausal hormone therapy is limited to young women, in whom hormone therapy is started early; before estrogen receptors on the endothelium disappear.[22-24]

The mechanisms by which sex-hormones might influence atherosclerosis are also not clearly defined. Effect on lipid metabolism is a possible parameter; estrogens alter fatty acid, triglyceride and cholesterol metabolism in the liver.[25] Tamoxifen and Tibolol, two selective estrogen receptor modulators, decrease serum lipoprotein (a) in postmenopausal women.[26,27]

As mentioned previously, the presence of breast arterial calcifications on mammography shows a positive correlation with increased risk for cardiovascular events.[28] To our knowledge, there is only one published study addressing the correlation between mammographic breast density and atherosclerosis. Grassmann et al., reported higher cardiometabolic risk in women with lower breast density. Their study included more than fifty-thousand women in all age groups. The results were adjusted for age and BMI, but not for menopausal status.[6] In our study, only premenopausal women between 40 and 50 years were included. Confirming the results of the previous study, we observed that women with a low-density mammogram (ACR 1) had an increased CIMT in comparison to those with a very dense breast (ACR 4). We assume that this finding is attributable to differences in the serum hormones levels, but as hormones were not evaluated in this study this remains a hypothesis. According to the results of our study, mammographic parenchymal density can be used to screen women for atherosclerosis and women with low breast density should be considered at higher risk for this disease.

## Conclusions

Low-density mammogram (ACR density 1) in premenopausal women is associated with a higher CIMT, therefore mammographic parenchymal density can be used as a screening tool for the presence of atherosclerosis. Whether this observed correlation is actually the consequence of hormonal differences or not remains open to discussion. Further studies evaluating all four classes of breast density and CIMT in pre- and postmenopausal women and assessing simultaneously the serum hormone level could give more information about the cause and effect of this correlation.

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### Competing interests

The authors declare that they have no competing interests.

### Abbreviations

Carotid intima-media thickness: CIMT;
Breast arterial calcification: BAC;
Sex hormone binding globulin: SHBG;
Intima-media thickness: IMT;
Body Mass Index: BMI;
Coronary Heart Disease: CHD;
Coronary Artery Risk Development in Young Adults: CARDIA-study.

### Authors' contributions

HT, PF and NM contributed to the conception and design of the work. AP, HT, SM and GAM contributed to the acquisition, analysis, and interpretation of data for the work. AP and GAM drafted the manuscript. HT, PF and NM critically revised the manuscript. All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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## Role of the funding source

None.

## Availability of data and materials

The data used in this study are available from the corresponding author on request.

## Ethics approval and consent to participate

The study protocol was designed according to the revised guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of our institution (approval number: 5755). All participants signed an informed consent form.

## Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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