


Association of Mammographic Features and Major Adverse Cardiac Events in Postmenopausal Women: A 10-Year Retrospective Cohort Study

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Objective: Cardiovascular disease is the leading cause of death in postmenopausal women, and certain mammographic features have been linked to cardiovascular risk. This study aimed to investigate the association between mammographic features and the incidence of major adverse cardiac events (MACE) over a 10-year follow-up period in postmenopausal women.

Methods: This retrospective cohort study included postmenopausal women with available mammographic data, including mammographic breast density (MBD), breast arterial calcification (BAC), and microcalcifications at the Central Hospital of Wuhan between January and December 2012. The primary outcome was the incidence of MACE over a 10-year period.

Results: Among the 857 postmenopausal women, the average age was 59.51 ± 7.31 years. Participants were categorized into four MBD types: Type A (n=249), Type B (n=254), Type C (n=228), and Type D (n=126). Participants with Type B MBD exhibited the highest risk of MACE (13.7%), followed by Type A (10.6%), Type C (4.8%), and Type D (4.0%). Kaplan-Meier analysis revealed that MBD classification and BAC were significantly associated with MACE incidence ($P < 0.05$). The Cox proportional hazards regression found that type A (HR = 3.12, 95% CI: 1.21–8.02), Type B (HR = 2.57, 95% CI: 0.98–6.73) and BAC (HR = 2.37, 95% CI: 1.12–5.0) were significantly associated with an increased risk of MACE. No significant correlation was found between microcalcifications and MACE risk ($P > 0.05$).

Conclusion: Mammographic features such as MBD and BAC may be associated with an increased risk of MACE in postmenopausal women. These findings suggest that incorporating cardiovascular risk assessment into routine mammography screening could enhance health management and preventative strategies for postmenopausal women.

Keywords: mammographic breast density, breast arterial calcification, major adverse cardiac events, cardiovascular risk, postmenopausal women, retrospective cohort study

Introduction

Postmenopausal women represent a unique population with distinct physiological changes that elevate their risk of cardiovascular disease (CVD), a leading cause of mortality in this group, accounting for approximately one-third of all deaths.^{1,2} Specific risk factors for cardiovascular disease in women include early menarche, the absence of oral contraceptive use, and reproductive history.³ However, these tools have limitations in sensitivity and specificity and may not fully capture the unique risk profile of postmenopausal women.

Mammography is a widely used and critical tool for routine breast cancer screening.⁴ Recent research suggests that mammographic features such as mammographic breast density (MBD) and breast arterial calcification (BAC) might also serve as indicators for cardiovascular risk.^{5–7} These X-ray features offer several advantages: they are non-invasive, widely accessible, and can be easily integrated into routine screening protocols. Despite these potential benefits, there is limited research on the use of mammographic features to predict MACE in postmenopausal women.

Current research has indicated a possible association between mammographic features, such as BAC and microcalcifications, and the risk of cardiovascular disease.^{8,9} BAC, visible in routine mammograms, are deposits of calcium in the arteries of the breast. These calcifications are not related to breast cancer but are considered a marker of systemic atherosclerosis, which is a well-known risk factor for CVD.⁸ Microcalcifications, although primarily investigated for their association with breast cancer, might also reflect underlying metabolic conditions that contribute to cardiovascular risk.⁹ Despite these findings, there is a notable scarcity of long-term follow-up data and comprehensive studies that directly link specific mammographic traits to the incidence of MACE in postmenopausal women.

Therefore, this study aims to employ a retrospective cohort design to examine the association between mammographic features in postmenopausal women and the incidence of MACE over a decade.

Methods

Study Design and Patients

This retrospective cohort study included postmenopausal women with available mammographic data, including mammographic breast density (MBD), breast arterial calcification (BAC), and microcalcifications at the Central Hospital of Wuhan between January and December 2012. Inclusion criteria included required participants to be postmenopausal women with no history of breast surgery, malignant tumors, or MACE. The inclusion criteria were: 1) postmenopausal women. The exclusion criteria included: 1) History of breast surgery; 2) History of heart failure; 3) History of myocardial ischemia; 4) History of other tumors; 5) Did not die of heart failure or myocardial ischemia during the 10-year follow-up period. This study was approved by the ethics committee of the Central Hospital of Wuhan (Approval No. WHZXKYL2022-037). As this is a retrospective study, informed consent was exempted.

Data Collection and Definition

Mammography was performed using a Mammomat Inspiration digital mammography machine. The primary mammographic characteristics of interest were MBD, BAC, and microcalcifications. The photographic position included bilateral cranial-caudal (CC) and mediolateral oblique (MLO) views. The exposure conditions were standardized with a fixed 26kV automatic exposure setting, resulting in an average exposure of 28.6 mAs and an average radiation dose of 0.7mGy.

A retrospective analysis of the mammography images of the enrolled subjects was conducted by two experienced radiologists, with 5 and 10 years of experience, respectively, following the Breast Imaging Reporting and Data System (BI-RADS) standard (2013 version).¹⁰ In cases of differing opinions, the radiologists discussed and reached a consensus. The mammographic features analyzed in this study included MBD, BAC, and microcalcifications.

Mammographic density¹⁰ was defined as the ratio of mammary gland epithelial tissue and/or fibrous glandular tissue to fatty tissue on a screening mammogram. According to the BI-RADS classification, mammographic density was categorized into four types: BI-RADS-A: Predominantly fatty breast (glandular density < 24%); BI-RADS-B: Scattered areas of fibro glandular density (glandular density 25% to 49%); BI-RADS-C: Heterogeneously dense breast tissue, with some non-dense areas (glandular density 50% to 74%); BI-RADS-D: Extremely dense breast tissue (glandular density >75%) (Figure 1).

BAC¹¹ was identified by linear or parallel “tram-track” calcifications on mammography. Microcalcifications⁹ were defined as calcifications with a diameter of 1 mm on the mammogram. Postmenopausal status was defined based on self-reported menstruation characteristics, specifically if the last menstruation occurred more than one year ago. BAC appear on mammograms as linear, parallel opacities, typically showing a “tram-track” appearance.¹¹ The incidence rate was calculated as the ratio of the number of patients with the endpoint event in each group to the total number of patients in each group.

Outcomes and Follow-Up

MACE was defined as the composite endpoint of hospitalization for heart failure and ischemic cardiovascular events. Data on MACE and their timing were collected through telephone follow-up, hospitalization records, and third-party sources at the 10-year follow-up visit.

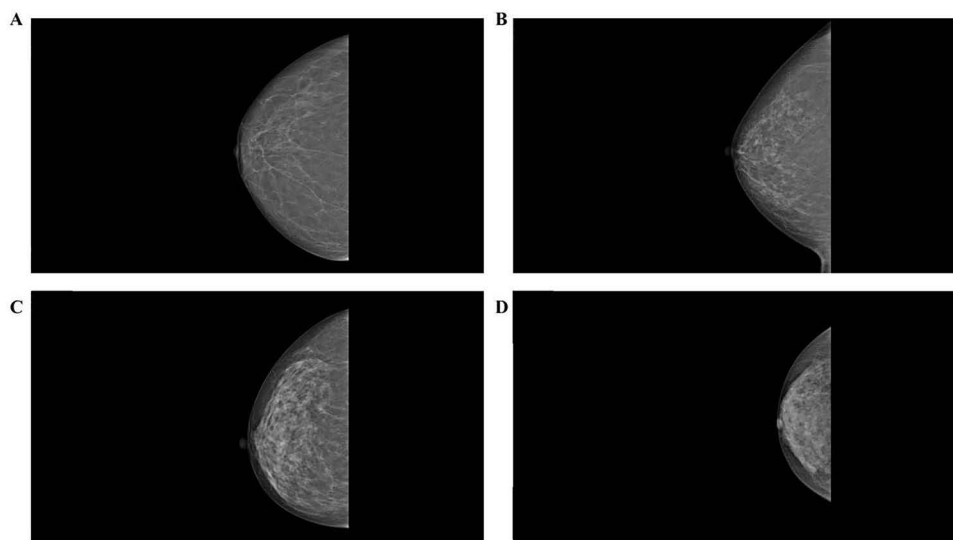


Figure 1 Four types of mammographic density according to the BI-RADS (Breast Imaging Reporting and Data System) classification. (A) represents a fatty breast (type A); (B) represents the fibro glandular breast (type B); (C) represents the non-uniform dense breast (type C); (D) represents extremely dense breasts (type D).

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 and R 4.4.2 software. Continuous variables are presented as means \pm standard deviations or medians with interquartile ranges (IQR). Categorical variables are shown as frequencies and proportions. Student's *t*-test or Mann–Whitney *U*-test was used for continuous variables, and chi-square or Fisher's exact test for categorical variables. First, in order to effectively control the influence of confounding factors on the results of the study, we chose the R package “ipw” to implement the proposed probability-weighted matching method. This method equalizes these potential interfering factors among the matched groups by carefully evaluating and calculating each confounding factor, thus ensuring comparability among the study groups. After completing the proposed probability-weighted matching and obtaining the precise weight values, we further utilize the R packages “survminer” and “survival” to construct the COX regression model and conduct the PH hypothesis testing. The *P* value < 0.05 was considered statistically significant.

Results

Demographic Characteristics

A total of 857 cases were included in the study. The average age of participants was 59.51 ± 7.31 years, ranging from 50 to 86 years, with a median age of 58 years. The women were divided into four groups according to their MBD: Type A ($n=249$), Type B ($n=254$), Type C ($n=228$), and Type D ($n=126$) (Figure 2). Type A participants had an average age of 59.39 ± 7.34 years, with 17 cases of breast artery calcification (BAC), 88 cases of microcalcifications, and 34 cases of MACE, accounting for 13.7%. Type B participants were older, with an average age of 63.93 ± 7.53 years, and had 10 cases of breast artery calcification, 109 cases of microcalcifications, and 27 cases of MACE (10.6%). Type C participants had an average age of 59.79 ± 7.65 years, with 2 cases of breast artery calcification, 25 cases of microcalcifications, and 11 cases of MACE (4.8%). Finally, Type D participants had the youngest average age of 55.45 ± 3.65 years, with 2 cases of breast artery calcification, 50 cases of microcalcifications, and 5 cases of MACE (4.0%). The follow-up time was similar across all groups, averaging from 9.43 to 9.86 months ($P = 0.437$). There were significant differences in the presence of BAC ($P = 0.001$) and microcalcifications ($P < 0.001$) among the different types of MBD (Table 1). Additionally, the incidence of MACE varied significantly across the MBD groups ($P < 0.001$) and BAC groups ($P=0.01$) (Table 2).

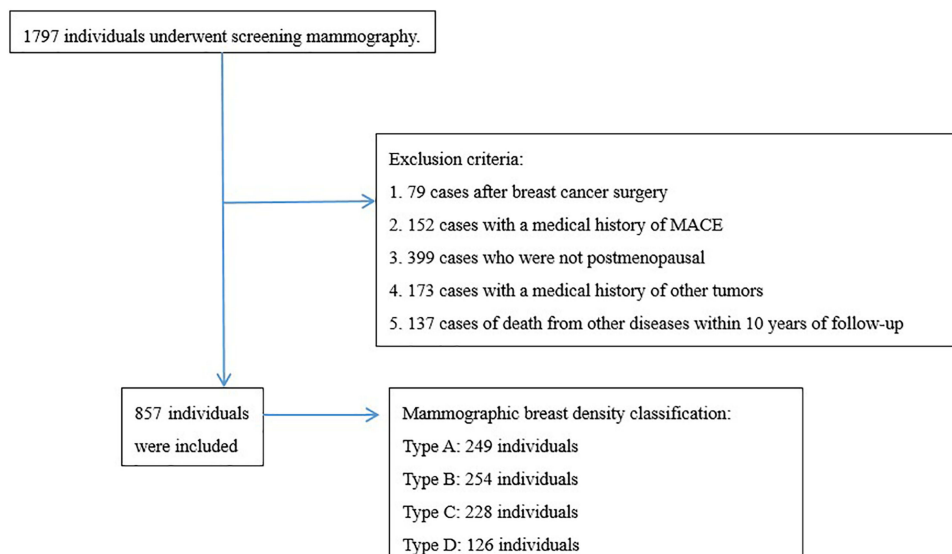


Figure 2 Study flowchart.
Abbreviation: MACE, major adverse cardiac events.

Kaplan-Meier Analysis

Kaplan-Meier curve found that MBD classification and BAC were significantly associated with the incidence of MACE (both $P < 0.05$), however, there was no statistical significance of microcalcifications and the incidence of MACE within 10 years ($P > 0.05$) (Figure 3).

The Cox Proportional Hazards Regression Model

The Cox proportional hazards regression model found that type A (HR = 3.12, 95% CI: 1.21–8.02), Type B (HR = 2.57, 95% CI: 0.98–6.73). BAC (HR = 2.37, 95% CI: 1.12–5.0) were significantly associated with an increased risk of MACE,

Table 1 Basic Demographic Characteristics

Variables	Type A (n=249)	Type B (n=254)	Type C (n=228)	Type D (n=126)	P
Age	55.45±3.65	59.39±7.34	63.93±7.53	59.79±7.65	<0.001
Follow-up time, month	9.43±1.69	9.61±1.46	9.80±1.00	9.86±0.74	0.437
Breast artery calcification	17 (6.8%)	10 (3.9%)	2 (0.9%)	2 (1.6%)	0.001
Microcalcifications	88 (35.3%)	109 (42.9%)	25 (11.0%)	50 (39.7%)	<0.001
MACE	34 (13.7%)	27 (10.6%)	11 (4.8%)	5 (4.0%)	<0.001

Table 2 Incidence Rate of MACE in Different Types of Mammographic Breast Density

Category	Total Number of Cases (N)	Number of Events (N)	Incidence of MACE (%)	P-value
Type A	249	34	13.7%	<0.001
Type B	254	27	10.6%	
Type C	228	11	4.8%	
Type D	126	5	4.0%	
Breast artery calcification				0.01
Yes	13	6	46.1%	
No	844	39	4.6%	
Microcalcifications				0.482
Yes	445	16	3.6%	
No	412	23	5.6%	

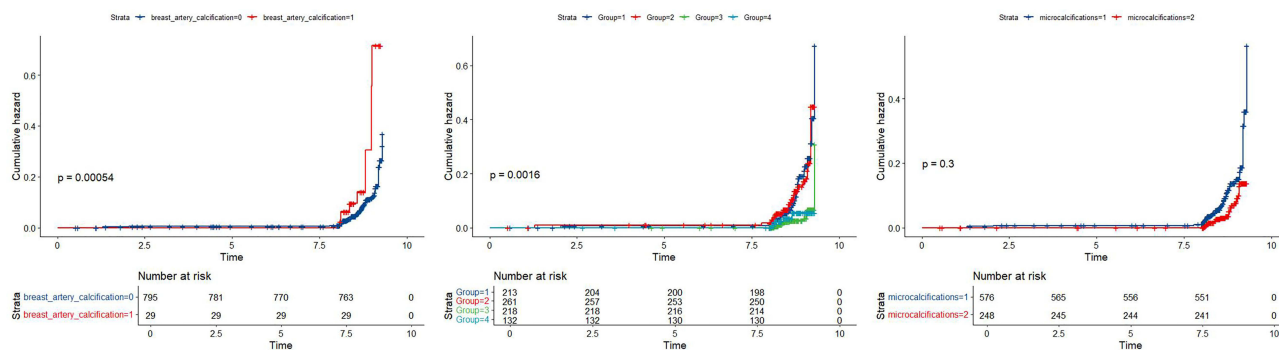


Figure 3 K-M curve. Group1: fatty breast (type A); Group2: the fibro glandular breast (type B); Group3: the non-uniform dense breast (type C); Group4: extremely dense breasts (type D).

type C (HR = 1.10, 95% CI: 0.38–3.12) and microcalcifications (HR = 0.69, 95% CI: 0.41–1.15) shows no significant difference (Table 3).

Discussion

This study of 857 postmenopausal women found that MBD and BAC were significantly associated with increased MACE risk, while microcalcifications were not. These findings suggest incorporating MBD and BAC into cardiovascular risk assessments to improve early identification and intervention for high-risk women.

Excess visceral and subcutaneous adipose tissue may lead to the overexpression of inflammatory and oxidative stress molecules,¹² which are associated with vascular damage, atherosclerosis, and cardiovascular disease. The mammary gland is a specific target organ for fat deposition in women.¹³ After menopause, the decrease in endogenous hormone levels causes an increase in the fat content of the glandular tissue in the mammary glands.¹⁴ This leads to the overexpression of cardiovascular disease risk factors in women with specific physical characteristics and visceral fat accumulation, thereby affecting the incidence of cardiovascular disease. Additionally, the decrease in endogenous estrogen levels post-menopause reduces the protective function of coronary artery and cardiac functions,¹⁵ further impacting cardiovascular disease incidence. Sardu^{13,15} found that breast fat deposition in premenopausal women is an independent predictor of cardiovascular disease, independent of menopausal status, BMI, and other traditional cardiovascular disease risk factors. The excessive activity of the adipose tissue of the mammary gland could play a crucial role in a more aggressive and rapid progression of atherosclerotic plaque, up to the development of the clinical evidence of MACEs in pre-menopausal women, as is observed for other forms of adipose tissue deposition that alter body composition in men and women. This suggests that fat deposition in the breast may increase susceptibility to cardiovascular disease in women, exacerbating the burden of cardiovascular disease beyond traditional risk factors.

Currently, the incidence of cardiovascular disease in women is increasing year by year, and it may even surpass that of men after the age of 75.¹⁶ Traditional cardiovascular disease risk factors such as hypertension, smoking, dyslipidemia,

Table 3 Multivariate Cox Regression

Mammographic Features	p	HR	95.0% CI	
			Lower	Upper
Breast density				
Type D	0.006	Ref.	Ref.	Ref.
Type A	0.018	3.117	1.211	8.025
Type B	0.050	2.570	0.982	6.726
Type C	0.870	1.093	0.378	3.161
Breast artery calcification	0.025	2.372	1.116	5.041
Microcalcification	0.158	0.692	0.415	1.154

diabetes, overweight, and obesity may affect women differently than men.¹⁷ Despite efforts to manage these traditional risk factors, they do not appear to significantly reduce cardiovascular mortality in women.¹⁸

MBD reflects the amount of interstitial and/or epithelial tissue in the breast, indicating the proportion of non-radiopaque components to fatty tissue.¹⁰ This study found a significant correlation between MBD characteristics and the incidence of MACE within a 10-year period. As the MBD decreases, meaning the proportion of fatty tissue in the breast increases, the incidence of MACE within 10 years rises. Specifically, the risk of MACE in women with Type B MBD is 6.57 times that of Type A MBD, and the risk in women with Type C MBD is 2.91 times that of Type A MBD, after adjusting for age, microcalcifications, and BAC. There is no statistically significant difference in MACE incidence between Type D and Type A MBD.

This study also found a correlation between the presence of BAC on screening mammography and the incidence of MACE within 10 years in postmenopausal women. The risk of MACE in women with BAC was 2.65 times higher than in those without BAC. BAC is a non-atherosclerotic vascular lesion occurring in the internal elastic lamina or medial layer of the muscle arteries, different from atherosclerotic calcification that involves the intima of large and medium-sized elastic arteries.¹⁹ Research suggests that BAC is associated with an increased risk of cardiovascular events and that the breast may contribute to cardiovascular disease through a different pathway than the atherosclerotic process in arterial intima.²⁰ On the other hand, digital mammography has previously been used to evaluate the strong quantitative association of mammary arterial calcification with coronary artery calcification and for the identification of women at high risk²¹.

This study found no correlation between the presence or absence of microcalcifications on screening mammography and the incidence of MACE within 10 years in postmenopausal women. Microcalcifications are defined as calcifications with a diameter of 1 mm on mammograms. They may result from the epithelial-mesenchymal transition of breast epithelial cells, leading to the formation of a hard extracellular matrix.²² Felix Grassmann⁹ found that an increase in the number of microcalcifications in mammography images was associated with an increased risk of various cardiometabolic diseases, and that the incidence of these diseases was lower in dense breasts. Additionally, a higher number of microcalcifications was frequently observed in the mammograms of women with chronic kidney failure, strongly implying an association with various cardiometabolic diseases.²³ The lack of statistical significance between microcalcification and the incidence of MACE within 10 years in this study may be due to the small sample size and the fact that the study population was from Asia. Therefore, mammography can not only assist in breast cancer screening but also provide a preventive basis for the occurrence of MACE. MBD characteristics and BAC are risk factors for MACE.

However, this study has several limitations. First, the conventional method (BIRADS) used to assess MBD is relatively subjective. Current advancements in quantitative measurements, which utilize computer threshold methods, offer a more accurate assessment of mammographic density than qualitative methods. Second, because the medical records were collected 10 years ago, the electronic medical records were incomplete, particularly regarding clinical data relevant to cardiovascular disease, such as blood glucose and lipid levels. Third, to translate this study's findings into clinical practice, further large-scale randomized clinical trials with a multi-center design are necessary. The use of artificial intelligence for evaluating MBD is gradually increasing in clinical trials, and improvements in electronic medical record systems are providing more complete clinical data. In the next phase of our research, we plan to employ quantitative assessments of MBD, comprehensive clinical data, and data from multiple centers to further elucidate the correlation between mammographic characteristics and the incidence of MACE.

In conclusion, MBD and BAC are linked to higher MACE risk in postmenopausal women, while microcalcifications are not. In the postmenopausal female population, the higher the breast glandular fat content, the higher the 10-year risk of developing MACE may be. Incorporating MBD and BAC assessments into routine mammography could improve cardiovascular risk detection and prevention. Further research is needed to explore these mechanisms.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Ethics Approval and Consent to Participate

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This work was approved by the Ethics Committee of Wuhan Central Hospital (Approval No. WHZXKYL2022-037). As this is a retrospective study, informed consent was exempted by the Ethics Committee of Wuhan Central Hospital. All patient data is confidential.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; All authors gave final approval of the version to be published; All authors have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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