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Review

Mammography biomarkers of cardiovascular and musculoskeletal health: A review

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ABSTRACT

Breast density (BD) and breast arterial calcifications (BAC) can expand the role of mammography. In premenopause, BD is related to body fat composition: breast adipose tissue and total volume are potential indicators of fat storage in visceral depots, associated with higher risk of cardiovascular disease (CVD). Women with fatty breast have an increased likelihood of hypercholesterolemia. Women without cardiometabolic diseases with higher BD have a lower risk of diabetes mellitus, hypertension, chest pain, and peripheral vascular disease, while those with lower BD are at increased risk of cardiometabolic diseases. BAC, the expression of Monckeberg sclerosis, are associated with CVD risk. Their prevalence, 13 % overall, rises after menopause and is reduced in women aged over 65 receiving hormonal replacement therapy. Due to their distinct pathogenesis, BAC are associated with hypertension but not with other cardiovascular risk factors. Women with BAC have an increased risk of acute myocardial infarction, ischemic stroke, and CVD death; furthermore, moderate to severe BAC load is associated with coronary artery disease. The clinical use of BAC assessment is limited by their time-consuming manual/visual quantification, an issue possibly solved by artificial intelligence-based approaches addressing BAC complex topology as well as their large spectrum of extent and x-ray attenuations. A link between BD, BAC, and osteoporosis has been reported, but data are still inconclusive. Systematic, standardised reporting of BD and BAC should be encouraged.

1. Introduction

Cardiovascular disease (CVD) represents the leading cause of mortality and morbidity in both women and men and constitutes a major health and economic burden for healthcare systems all over the world [1]. In Europe, 47 % of all deaths in females are caused by CVD: ischemic heart disease and stroke account for 38 % and 26 % of all CVD deaths, respectively [1]. Indeed, estrogen has a protective role against CVD during the fertile age [2], this protection however tends to vanish during the menopause transition, thus contributing to increase CVD risk, together with other adverse physiological and metabolic changes occurring in this time of life, such as alterations in body composition, lipid profile, and vascular function [3]. Furthermore, female-specific risk factors strictly related to reproductive life (such as preterm delivery, hypertensive pregnancy disorders, and gestational diabetes mellitus) might contribute to the worsening of CVD risk profiles, especially in young women [4].

Even though the awareness about CVD in women has increased during the past decades with a corresponding decline in female CVD mortality (in Europe, from 374 to 209 deaths per 100.000 in the period between 1985 and 2014) [5], both women and primary care physicians still have a tendency to underestimate this risk of developing CVD, increasing the disparity between men and women in the prevention, diagnosis, and treatment of CVD [6]. Even the most updated prediction models used to estimate the risk of fatal and nonfatal CVD apply age- and sex-specific multipliers without including risk factors specific to the female sex, further limiting the development of sex-specific strategies for the primary prevention of CVD [7,8].

In Europe, breast cancer awareness campaigns have been crucial to highlight the importance and efficacy of early diagnosis through

Abbreviations: CVD, cardiovascular disease; BI-RADS, Breast Imaging-Reporting and Data System; BAC, breast arterial calcifications; CI, confidence interval.

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mammographic screening [9], achieving satisfactory attendance rates in the majority of organized screening programmes [10]. However, alongside the early detection of breast cancer, mammography has been reported to be useful for the identification of ancillary features unrelated to oncological disease, such as mammographic breast density and breast arterial calcifications (BAC), both of which have been recognized as important biomarkers of cardiometabolic risk [11,12]. This progressive awareness is paving the way towards an extension of the preventive role of mammography beyond breast cancer screening, acknowledging its potential to offer an insight into women's cardiometabolic health.

In this narrative review, we therefore aim to present a conceptual framework about the potential of using mammography-derived biomarkers such as breast density and BAC for stratifying female CVD risk, also exploring their relation with indicators of metabolic risk and frailty such as bone mineral density and reduced muscle mass.

2. Methods

A non-systematic search was performed using MEDLINE (PubMed, www.pubmed.gov) and EMBASE (Elsevier) for major publications (i.e., systematic reviews and meta-analyses, controlled trials, cohort studies) about women-specific CVD risk factors, the relation between breast density and CVD, the relation between BAC and CVD, and any potential exploitation of screening mammography beyond breast cancer screening purposes, including osteopenia/osteoporosis. Establishing a focus on the latest and most relevant publications among the available literature, search terms and keywords were obtained through the SPIDER (Sample, Phenomenon of Interest, Design, Evaluation, Research type) framework [13], as detailed in Table 1. Search terms used to identify literature included: ‘women’, ‘mammography’, ‘mammography features’, ‘breast density’, ‘breast density assessment’, ‘obesity’, ‘menopause’, ‘cardiovascular risk’, ‘cardiovascular risk assessment’, ‘cardiometabolic risk’, ‘cardiometabolic risk assessment’, ‘cardiovascular risk factor’, ‘cardiometabolic risk factor’, ‘breast arterial calcifications’, ‘BAC’, ‘Monckeberg sclerosis’, ‘bone mineral density’, ‘osteopenia’, ‘muscle mass’, and ‘sarcopenia’.

3. Breast density and cardiovascular risk

Mammographic breast density, defined as the proportion of fibroglandular breast tissue relative to breast adipose tissue [14], has been identified as a relevant independent risk factor for breast cancer: indeed, women with dense breasts have a fourfold increase in the risk of developing breast cancer compared to women with fatty breasts [15]. Furthermore, increased breast density has a masking effect on underlying breast lesions, yielding a reduction in the sensitivity of mammography for breast cancer detection [16]. Since high breast density has been reported to account for a substantial proportion of breast cancers in both premenopausal and postmenopausal women [17], it has been integrated into several risk prediction models [18]. Hence, in the actual era of personalized and precision medicine, breast density should be considered in risk-adapted breast cancer screening strategies that can implicate appropriate information of women and supplemental imaging in women with high breast density [19].

Usually, breast density is visually assessed and classified by radiologists from standard two-view mammography according to different scoring systems, such as the most adopted American College of Radiology Breast Imaging-Reporting and Data System (BI-RADS) four-category scale [20], the Boyd six-category scale [21], and the Tabar five-category grading system [22]. Particularly, the latest edition of BI-RADS spotlights the distribution of fibroglandular tissue and the resulting masking effect of focal areas of higher density, regardless of the overall amount of fibroglandular tissue [20,23]. However, all these classification systems are highly subjective and dependent on the experience and habit of radiologists, introducing substantial inter- and intra-observer variability in breast density assessment [24–26]. Therefore, to overcome the subjective nature of visual assessment, several fully automated software have been developed, some of them being already commercially available as adds-on implemented to mammography systems, which can provide a robust and reproducible classification [27–30].

It is well established that breast density represents a dynamic trait that tends to decrease with aging, in a more pronounced way over the menopause transition. However, any simplistic interpretation of this phenomenon as “purely chronological” fails to understand that breast density represents a mirror of the hormonal changes occurring in the mid-life of women: these modifications can have a negative impact influencing both the oncological and the cardiometabolic risk.

The reduction of breast density with age (i.e., breast tissue aging) is highly consistent across different groups of women worldwide and is the result of a common biological process based on the decline of circulating reproductive hormones during the transition towards menopause [31]. In particular, the physiological reduction of hormones with a mitogenic action on breast cells results in a lobular involution and a gradual decrease in the extent of ductal epithelium [32,33]. The decrease of breast density is therefore the observable proxy of this complex interaction between menopause-induced estrogen deficiency and the physiology of breast cells, which also influences breast cancer risk, as already modelled by Pike et al. [34] in 1983. From a cardiometabolic point of view, the menopause-induced decline of reproductive hormones also leads to dysregulation of lipid metabolism and vascular dysfunction, influencing cardiovascular health [3].

The ratio of dense breast tissue volume or area over the whole breast, the common way to represent the breast density, also represents a potential proxy of body fat composition. In premenopausal women, adiposity and body fat distribution are inversely and significantly correlated with breast density [35–37]. In addition, Janiszewski et al. [38] reported that breast volume might be an indicator of fat storage in the visceral depots, which are independently associated with higher CVD risk. Indeed, visceral adipose tissue is associated with a chronic low-grade inflammation and dysregulation of the endocrine and immune system, leading to an insulin resistant, prothrombotic, and proinflammatory state resulting in endothelial damage, atherosclerosis, and therefore CVD [39,40]. All these results are also supported by Schautz et al. [41], who described a strong relation between low breast density and a body fat distribution characterized by increased truncal subcutaneous adipose tissue, correlated with an adverse profile of cardiometabolic risk factors. However, no association between breast density and the proportion of visceral adipose tissue was reported in this study.

Sardu et al. [42] found a significant association between reduced breast density in the premenopausal period and an increased risk of cardiovascular adverse events. The authors hypothesised that breast adipose tissue per se could have an excessive inflammatory activity and could directly contribute to subclinical damage of vessels, resulting in a more aggressive and rapid progression of CVD, further accelerated

Table 1
The SPIDER (Sample, Phenomenon of Interest, Design, Evaluation, Research type) tool for qualitative evidence synthesis.

SPIDER item	Descriptors
Sample	Women undergoing mammography
Phenomenon of interest	Women-specific cardiovascular and metabolic risk factors: breast density and cardiovascular disease, breast arterial calcifications and cardiovascular disease, and any further mammographic feature for the assessment of cardiovascular and metabolic risk, including osteopenia and osteoporosis
Design	Published literature of any research design, including guidelines and editorials
Evaluation	Characteristics, association, impact, opinion
Research type	Qualitative, quantitative, and mixed-method peer-reviewed studies

during the menopause transition due to hormonal changes. Indeed, breast adipose tissue is an endocrine organ that can express adipogenic, pro-inflammatory, and estrogen synthetic genes, particularly in obese women [43]. Similarly, in a recent study on 1406 women, Al-Mohaissen et al. [44] observed that the BI-RADS density category *a* was closely related to increased body mass index, potentially representing a readily-available body fat distribution indicator; also, category *a* was independently associated with a 1.6-fold increase in the odds of hypercholesterolemia. Finally, in a recent study including 57,867 women who attended mammographic screening in Sweden, Grassmann et al. [12] showed that a higher breast density in women without cardiometabolic diseases was associated with a lower risk of diabetes mellitus, hypertension, chest pain, and peripheral vascular disease. Conversely, women with a lower breast density were at increased risk for cardiometabolic diseases. Even though those findings could have been due to the effect of body mass index on breast density and cardiometabolic diseases, statistical significance remained unchanged after adjustment for this confounder.

4. Breast arterial calcifications

4.1. Breast calcifications and cardiovascular risk

In the context of breast cancer screening mammography reading, calcifications are classified either as typically benign or of suspicious morphology: the former are discarded, while the latter prompt second-level investigations [20]. However, some calcifications (which are considered as surely benign, as is the case of BAC) carry information about women's cardiovascular health. Indeed, a recent work by Grassmann et al. [12] on 57,867 women and 49,583 of their sisters found that the quantity of calcifications was directly associated with a greater risk of cardiometabolic mortality in women with pre-existing cardiometabolic disease (hazard ratio 1.79, 95 % confidence interval (CI) 1.24–2.58, $p = 0.002$). Nonetheless, the authors did not distinguish among different types of calcifications (as they used an automated tool to quantify calcium) and not all calcifications can be considered equal, at least with regards to the associated cardiovascular risk [45].

Specifically, BAC, are a local expression of Monckeberg sclerosis, which appear as parallel or tubular opacities associated with blood vessels [20] and evolve within the tunica media and the internal elastic lamina of large and medium-sized arteries [46–48]. They have been associated with cardiovascular risk for more than two decades [49]. Monckeberg sclerosis is a histopathologic entity distinct from atherosclerosis involving coronary arteries, related to a pro-osteogenic environment, with the deposition of hydroxyapatite crystals in conditions of altered mineral metabolism [50] while atheromatic plaques are characterized by macrophagic activation and cholesterol deposition. In fact, no signs of inflammation were found in BAC plaques by histologic studies [48,51]. It is supposed that calcified vessels become stiffer, leading to increased pulse pressure that could lead to CVD [45]. Indeed, postmenopausal women with BAC included in a substudy of the MINERVA (multiethnic study of breast arterial calcium gradation and CVD) cohort [52], had an odds ratio of 1.36 (95 % CI 1.01–1.87, $p = 0.04$) for having an ankle-brachial index <0.90, a marker of peripheral artery disease [53]. The authors however did not observe any significant association between BAC severity and peripheral artery disease, perhaps because of the relatively small size of the BAC positive group. Conversely, such quantitative association was reported in a previous case-cohort study by Hendriks et al. [54], who reported a hazard ratio of 2.93 (95 % CI 1.05–8.16) for peripheral artery disease compared to women without BAC.

BAC are a relatively common incidental finding, observed in around 13 % of mammograms [55], their most important predictors being increasing age, diabetes, and parity [55]. Furthermore, hormonal levels seem to impact on BAC, as BAC prevalence rises after menopause [55], while it is reduced by 50 % in women aged over 65 years under hormonal replacement therapy [56]. BAC are associated with hypertension (pooled odds ratio 1.80, 95 % CI 1.47–2.21), but not with other established cardiovascular risk factors, such as hypercholesterolemia (odds ratio 1.31, 95 % CI 0.97–1.77), and present a negative association with smoking habit (odds ratio 0.54, 95 % CI 0.42–0.70) [57], which again underlines the distinct pathologic pathway that leads to BAC pathogenesis.

Nevertheless, BAC presence is significantly associated with coronary artery disease (odds ratio 2.61, 95 % CI 2.12–3.21), and women with a moderate to severe BAC load have a 2.95 odds ratio (95 % CI 1.49–5.84) for coronary artery disease. A retrospective study published by Margolies et al. [58] in 2016 found a strong, quantitative association between BAC and coronary artery disease, with the incidence of higher BAC scores increasing accordingly to coronary artery calcium score measured at coronary computed tomography. Furthermore, BAC scores from 4 to 12 (representing a marked BAC burden) had an adjusted odds ratio of 3.2 (95 % CI 1.8–5.9) for the presence of coronary artery calcium. Moreover, a BAC score > 0 showed an equivalent area under the receiving operator curve to that of Framingham risk score for the detection of CAC. A subsequent retrospective cohort study by Yoon et al. [59] confirmed the association between BAC presence and BAC score to subclinical coronary artery calcium, with adjusted odds ratios of 2.87 (95 % CI 1.67–4.93) and 1.20 (95 % CI 1.10–1.31) respectively. They also confirmed the prognostic value of BAC assessment, showing net reclassification improvements after adding BAC presence to the 10-years atherosclerotic cardiovascular disease−ASCVD risk score calibrated for the Korean population, with a net reclassification index of 0.052, and significant, albeit small improvement of the AUC from 0.66 to 0.68 ($p = 0.010$) for the presence of coronary arteries plaques. The recently published results from the MINERVA cohort study [60], conducted on women aged between 60 and 79, reported that women with BAC have a 1.51 (95 % CI 1.08–2.11) increased hazard of hard atherosclerotic CVD events (acute myocardial infarction, ischemic stroke, CVD death), and a 1.23 (95 % CI 1.00–1.52) increased hazard of global CVD events. Iribarren and colleagues also evaluated the performances of the American College of Cardiology/American Heart Association Pooled Cohort Equations for atherosclerotic CVD risk assessment combined with the presence of BAC, significantly improving its performances, with a net reclassification index of 0.11. A previous prospective cohort study [61] on 1454 women with a 5-year follow up reached similar conclusions, reporting a significantly higher likelihood of developing coronary artery disease for women with BAC than those without (6.3 % vs 2.3 %, $p = 0.003$).

4.2. Barriers to the use of BAC in clinical practice

The aforementioned results advocate for the inclusion of BAC in cardiovascular risk scores [62], particularly for postmenopausal women. Nonetheless, despite the fact that an overwhelming majority of women would prefer to be informed about their BAC status [63], BAC are currently not integrated in CVD risk prevention strategies and even BAC reporting in mammography interpretation is still scarce [64]: although over 80 % of European breast radiologists declared they are aware of the association between BAC and CV risk, less than 65 % of them report on BAC. Moreover, most of the radiologists who report BAC merely describe them as present, while just over 25 % of radiologists use an ordinal visual scale for BAC evaluation and only one radiologist uses a quantitative assessment. Indeed, there are a few issues hindering a more widespread adoption of BAC detection and reporting in routine clinical practice.

First, until recently, data concerning the impact of BAC presence and quantity on prospective cardiovascular outcomes was scarce. Moreover, the data reported in the context of the MINERVA study [52] have to be considered carefully. For instance, the authors did not observe any quantitative association between BAC burden and hard atherosclerotic CVD events, but only a threshold effect for global CVD in women over

the 95th percentile of BAC. Furthermore, around 75 % of women included in the MINERVA cohort were under lipid-lowering medication, which may yield an unknown impact on BAC, suggesting an overall already well treated group of women [65]. Besides, evidence from the SCOT HEART study suggests that BAC, albeit being associated with higher cardiovascular risk scores, have a poor diagnostic accuracy for coronary arteries calcium [66]. Therefore, further studies are needed to assess the role of BAC presence and extent in different populations of women.

Second, one pivotal obstacle in BAC assessment lies in the time needed to evaluate them. Indeed, if spotting BAC presence may be considered relatively immediate (excepting the case of small, tiny calcifications not definable as surely being BAC), measuring their extension may be a painstaking process. In fact, quantification methods based on manual measurements may take up to 3 minutes per mammogram [67], which would put further strain on radiologists, especially in the case of screening reading. In addition, methods based on subjective visual assessment may not ensure optimal reproducibility [67].

Several quantification methods have been proposed over the years, from 4-points Likert scales [68] and 12-points semiquantitative scales [58,67] to quantitative scores that evaluate the calcium mass performing a densitometry using carefully calibrated mammography systems, as in the MINERVA study [69]. However, the necessity of calibrating mammography systems clashes with the potential immediate application of BAC evaluation in the context of the available mammography systems already employed for routine breast cancer screening and clinical assessment.

4.3. Artificial intelligence for BAC assessment

It is worth noting that artificial intelligence could be useful to address the limitations intrinsic to BAC assessment, ensuring a processing time compatible with everyday practice, helping reduce the ever-increasing radiologic workload, and minimising operator-dependency. Although different approaches have been proposed, fully automated BAC quantification remains an open challenge, as BAC present with a complex topology, strongly influencing their appearance on different mammographic views, with a large spectrum of extent and x-ray attenuations. Furthermore, most available approaches still rely on manual BAC segmentation to train the models, thus being vulnerable to inter-reader variability, as highlighted in a paper by Trimboli et al. [70] in which the authors developed a semi-automatic tool for BAC quantification.

In 2017, Wang et al. [71] developed a model for BAC quantification based on a deep convolutional neural network that achieved comparable performance to a human expert at free-response receiver operating characteristic analysis and good results in calcium mass quantification (coefficient of determination of 96.2 %). More recently, Guo et al. [72] introduced the Simple Context U-Net to extract multilevel contextual details using two different dilated convolutional layers and yielded an F1 score value of 0.73 for BAC vessel segmentation and a correlation value of 0.87 with ground truth calcification volume. In the future, weakly supervised approaches may overcome the need of images annotated on a pixel basis as ground truth, further reducing operator-dependency.

5. Breast density and BAC: relations with bone mineral density and muscle mass

Features derived from mammography have also been investigated with regards to overall patient frailty and metabolic risk, such as that linked to osteopenia and osteoporosis, which have also been correlated to cardiovascular health [73]. For instance, likewise breast density, a higher bone density after menopause has long been regarded as a risk factor for breast cancer, whereas a lower breast density has been associated to a higher cardiovascular risk, the presence of BAC, and osteoporosis [74].

Indeed, a previous work by Gupta et al. [75] observed how breast density categories according to the current BI-RADS classification did not show any correlation to bone mineral density calculated at the hip and spine. Conversely, Cho et al. [76] observed a direct link between higher breast density and an increased T-score at dual-energy x-ray absorptiometry in postmenopausal women, with the addition of an underlying higher risk for breast cancer, which could be possibly explained by metabolic processes such as those related to higher levels of growth factors, interleukin, and estrogens.

Bone mineral density has also been studied with regards to BAC by Atci et al. [77], who observed a higher prevalence of osteoporosis in women presenting with BAC, both factors being related to a worse overall cardiovascular status. Moreover, Yoon et al. [59] studied a cohort of asymptomatic women for correlations between bone, breast, and coronary artery disease data, observing a relation between low bone mass assessed via dual-energy X-ray absorptiometry, the presence and severity of BAC, and subclinical coronary artery disease, once again indicating a higher cardiovascular risk. Conversely, a further work by Iribarren et al. [78] did not observe any association between bone mineral density and the presence and severity of BAC in a cohort of postmenopausal women. A further, subsequent analysis by Kim et al. [79] on a cohort pertaining to the same prospective study observed further correlations according to plaque composition. In particular, the extent of calcified or mixed plaques increased as bone mineral density decreased ($p \leq 0.004$).

Concerning another frailty biomarker, skeletal muscle mass, a 2021 study by Lee et al. [80] observed that premenopausal women with a higher skeletal muscle index were more likely to present with denser breasts, hinting a better overall metabolic status, albeit linked to a higher breast cancer risk.

6. Conclusions

As summarised in Fig. 1, mammographic images, routinely acquired as part of breast cancer screening or clinical assessment, present ancillary features. Among them, breast density is usually considered only for breast cancer risk stratification and for suggesting supplemental screening examinations, while BAC are discarded as meaningless and seldom reported only in the assessment setting. These two mammography-derived image biomarkers could instead be highly valuable to improve cardiometabolic risk assessment in women, with no supplementary healthcare costs and radiation exposure.

Efforts should be made for the development and application of female-specific algorithms including these mammographic findings – breast density and BAC – with a known effect on cardiometabolic risk. Artificial intelligence-based tools can play a relevant role in the detection and, in particular, in the reproducible quantification of breast density and BAC. Finally, systematic and standardised reporting of all these ancillary information as part of routine mammography interpretation should be encouraged.

Breast density and BAC are women-specific biomarkers to be included in CVD risk modelling, allowing an effective stratification and supporting the decision-making towards appropriate lifestyle changes and other personalized preventive strategies. This is the potential clinical impact of the use of these image-derived female biomarkers, opening to a scenario where breast radiology and preventive cardiology should operate in a multidisciplinary team.

Contributors

Veronica Magni participated in conceptualization, design, drafting and editing of the paper.

Davide Capra participated in conceptualization, drafting and editing of the paper.

Andrea Cozzi participated in design, drafting and editing of the

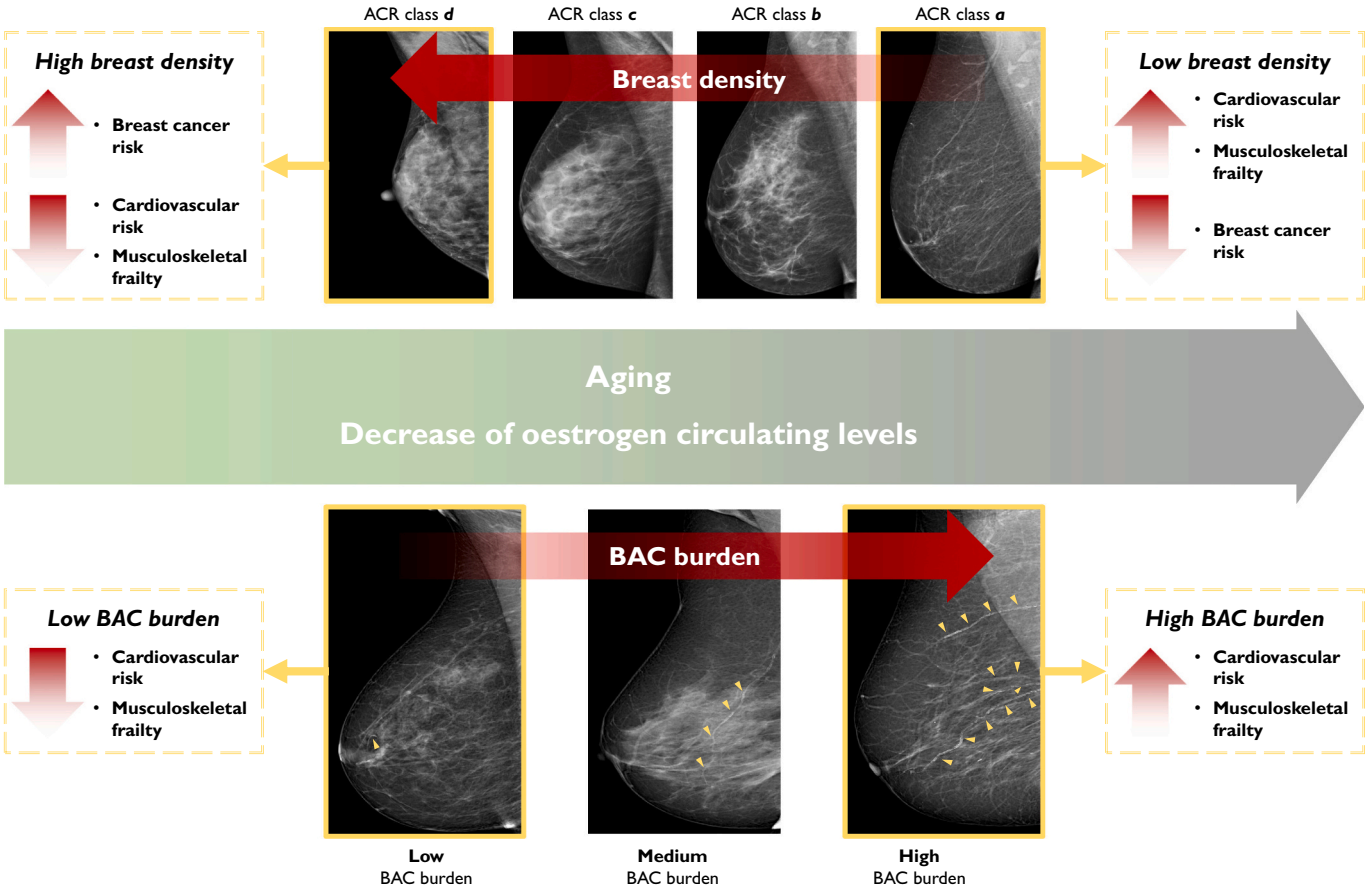

Fig. 1. An overview of how modifications in breast density and breast arterial calcifications burden influence breast cancer risk, cardiovascular risk, and musculoskeletal frailty. Yellow arrowheads in mammographic images indicate breast arterial calcifications. ACR, American College of Radiology; BAC, breast arterial calcifications. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

paper.

Caterina B. Monti participated in drafting and editing of the paper.

Nazanin Mobini participated in drafting and editing of the paper.

Anna Colarieti participated in drafting and editing of the paper.

Francesco Sardanelli oversaw and participated in conceptualization, design, drafting and editing of the paper.

All authors read and approved the final version, and no other person made a substantial contribution to the paper.

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Declaration of competing interest

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