Atherosclerosis 239 (2015) 11–20

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review

Breast arterial calcifications: A systematic review and meta-analysis of their determinants and their association with cardiovascular events

Eva J.E. Hendriks [a, *], Pim A. de Jong [b], Yolanda van der Graaf [a], Willem P.Th.M. Mali [b], Yvonne T. van der Schouw [a], Joline W.J. Beulens [a]

[a] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands
[b] Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands

ARTICLE INFO

Article history:
Received 10 September 2014
Received in revised form
8 November 2014
Accepted 16 December 2014
Available online 24 December 2014

Keywords:
Vascular calcification
Medial arterial calcification
Arteriosclerosis
Epidemiology
Risk factors
Cardiovascular events

ABSTRACT

Objective: Breast arterial calcifications (BAC), regularly observed at mammography, are medial calcifications and as such an expression of arteriosclerosis. Our objective was to evaluate and summarize the available evidence on the associations of BAC with cardiovascular risk factors and cardiovascular risk.
Methods: A systematic literature review and meta-analysis were conducted. Embase and PubMed databases were searched. After critical appraisal, odds ratios were extracted from studies of moderate or good quality that examined risk factors for BAC or associations of BAC with cardiovascular disease. Random effects model meta-analyses were used to calculate pooled odds ratios and 95% confidence intervals (95%CIs).
Results: BAC prevalence is around 12.7% among women in breast cancer screening programs. Increasing age (pooled OR 2.98 [95%CI 2.31–3.85] for every 10 years), diabetes (pooled OR: 1.88 [95%CI 1.36–2.59]) and parity as opposed to nulliparity (pooled OR 3.43 [95%CI 2.23–5.27]) are associated with higher BAC prevalence. Smoking is associated with lower BAC prevalence (pooled OR 0.48 [95%CI 0.39–0.60]). No associations were found with hypertension, obesity or dyslipidemia. Although longitudinal studies (n = 3) were scarce, BAC appear to be associated with an increased risk of cardiovascular disease events (adjusted hazard ratios for coronary heart disease ranging from 1.32 [95%CI 1.08–1.60] to 1.44 [95%CI1.02–2.05]).
Conclusion: BAC appear to be associated with an increased risk of cardiovascular disease events, while only being associated with some of the known cardiovascular risk factors, illustrating that medial arterial calcification might contribute to cardiovascular disease through a pathway distinct from the intimal atherosclerotic process.

Contents

* Corresponding author. Julius Center, University Medical Center Utrecht, Huispostnummer Str. 6.131, P.O. Box 85500, 3508 GA Utrecht, The Netherlands.
E-mail address: E.j.e.hendriks-4@umcutrecht.nl (E.J.E. Hendriks).

http://dx.doi.org/10.1016/j.atherosclerosis.2014.12.035
0021-9150/

1. Introduction

Arterial pathology can occur in all three layers of the arterial wall. In the intima, calcification occurs within plaques and is associated with the well-known atherosclerotic process [1]. In the deeper layers, especially in the media, circular calcifications are fairly common, generally considered innocent, though a scarcely studied phenomenon [2]. The formation of bone tissue in the media is part of a process called arteriosclerosis. Media calcifications could contribute to cardiovascular disease through a different mechanism than atherosclerosis, supposedly by increasing arterial stiffness [3]. If so, this could have important therapeutic and prognostic consequences.

A limited number of articles have been published on the topic of medial calcification. Pathologic studies convincingly demonstrated the presence of medial calcification in the aorta, and in the arteries of the lower extremity, with prevalence increasing with age [4,5]. Furthermore, some studies investigated associations of radiographical medial arterial calcification in the lower extremity with cardiovascular disease outcomes. These studies were mostly performed in highly selected subgroups, such as diabetes patients and renal disease patients [6,7]. Large prospective studies in the general population are lacking, in part because intimal and medial calcification cannot be easily distinguished with non-invasive methods.

An exception is breast arterial calcification (BAC), which is a type of medial calcification that is regularly observed on screening mammography [8]. BAC is a potential women-specific risk factor for cardiovascular disease risk [9–13]. Several studies have suggested that BAC is associated with traditional cardiovascular risk factors, such as hypertension, diabetes and chronic kidney disease [8,14–17]. In 2013, two reviews addressing the relation between cardiovascular risk factors and BAC as well as its association with cardiovascular disease outcomes were published. However, a quantitative pooling of the results was lacking, nor was the potential for confounding systematically addressed [18,19].

Therefore, our objective was to systematically review and critically appraise the literature on the determinants of BAC and its associations with cardiovascular events and to summarize these findings in a meta-analysis, taking into account the potential for confounding and other types of bias.

2. Methods

This review was conducted in concordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [20]. A review protocol outlining the methods was agreed upon before the start of the study and provided in the Supplementary Materials.

2.1. Eligibility criteria

Inclusion criteria were: original research reported in English, German, Dutch or Spanish on women who had undergone mammography that addressed BAC in association with cardiovascular disease, cardiovascular risk factors or reproductive factors; or that reported BAC prevalence in the general population, diabetes patients or renal disease patients. For risk factors or reproductive factors, articles had to present odds ratios (ORs) or data from which these could be calculated for one of the following determinants: age, diabetes, hypertension, dyslipidemia, obesity, renal disease, menopausal status and use of hormone replacement therapy, smoking, parity, and lactation history. Conference abstracts were excluded, as they do not provide sufficient information to make an informed decision on risk of bias.

2.2. Information sources and search strategies

PubMed and EMBASE were searched using a predefined search string provided in the supplement including “breast artery calcification” and its synonyms (Table S1). Our search was updated until the 24th of June 2014. References of all relevant articles were screened to identify potential missing articles.

2.3. Study selection and assessing risk of bias in individual studies

Titles and abstracts were screened by one reviewer (EJEH) to determine whether they reported on the topic of BAC. Two authors assessed all possibly relevant articles independently (EJEH and JWJB), and applied the eligibility criteria to the full text article. Non-concordant judgments were discussed with a third author (PAdJ) and resolved by consensus.

As no universally recommended tool for assessing the quality of observational epidemiological studies exists [21], we used predefined criteria. We assessed articles on the following items: selecting representative study population, selecting appropriate controls (when applicable), methods for measuring BAC, methods for measuring (other) outcomes, dealing with missing data/non-response, statistical methods and controlling for confounding. Every item was rated “unknown/unreported”, “poor”, “moderate” or “adequate” and assigned 0, 0, 1 or 2 points, respectively. Overall quality was calculated by summing all scores and dividing by the number of applicable items (6 or 7). Studies scoring below 1.0 were rated “poor quality”, studies scoring $\geq$1.0 but <1.5 were rated “moderate quality” and studies scoring $\geq$1.5 were rated “good quality”.