BBA - Reviews on Cancer 1869 (2018) 310–320

Contents lists available at ScienceDirect

BBA - Reviews on Cancer

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

Review

Microcalcifications in breast cancer: From pathophysiology to diagnosis and prognosis

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ARTICLE INFO

Keywords:
Breast cancer
Microcalcifications
Mammography
Mineralisation
Tumour microenvironment

ABSTRACT

The implementation of mammographic screening programmes in many countries has been linked to a marked increase in early detection and improved prognosis for breast cancer patients. Breast tumours can be detected by assessing several features in mammographic images but one of the most common are the presence of small deposits of calcium known as microcalcifications, which in many cases may be the only detectable sign of a breast tumour. In addition to their efficacy in the detection of breast cancer, the presence of microcalcifications within a breast tumour may also convey useful prognostic information. Breast tumours with associated calcifications display an increased rate of HER2 overexpression as well as decreased survival, increased risk of recurrence, high tumour grade and increased likelihood of spread to the lymph nodes. Clearly, the presence of microcalcifications in a tumour is a clinically significant finding, suggesting that a detailed understanding of their formation may improve our knowledge of the early stages of breast tumourigenesis, yet there are no reports which attempt to bring together recent basic science research findings and current knowledge of the clinical significance of microcalcifications. This review will summarise the most current understanding of the formation of calcifications within breast tissue and explore their associated clinical features and prognostic value.

1. Introduction

Breast cancer survival rates have increased significantly in recent years [1], due to a combination of improved treatment options and increased detection of early-stage tumours. As with other forms of cancer, patients whose breast tumours are detected at an early stage will typically respond much better to treatment: 5-year survival rates for stage-I breast cancer are close to 100%, compared to approximately 20% for patients with a stage-IV diagnosis [2].

To aid in this crucial endeavour of early detection, many countries now offer X-ray based mammography screening programmes to women in high-risk age brackets, typically beginning between 40 and 50 years and continuing until 65–75 years, varying from country to country [3]. Many studies have demonstrated a significant improvement in breast cancer survival following introduction of mammography screening. A meta-analysis of 11 large-scale studies (all with a cohort size of at least 50,000) by the Independent UK Panel on Breast Cancer Screening demonstrated a reduction in relative risk of breast cancer mortality of 20% in patients who had undergone screening versus those who had not [4]. Other studies have reached similar conclusions [5–11].

However, the adoption of mammography screening is not without controversy. Many of the lesions detected through mammography are small, benign growths unlikely to progress to malignant breast cancer and pose little threat. A meta-analysis by the Cochrane collaboration also found a 20% decrease in mortality but reached very different conclusions. Pointing out issues with inadequate randomisation and bias associated with reporting cause of death, they concluded that several studies should be excluded from consideration. When these studies, deemed inadequate, were removed from the analysis, the benefit of screening declined from an initial relative risk value of 0.81 to 1.02 [12]. These findings have been challenged by several groups [13,14], although other studies have been more supportive. For instance, a recent study argued that in many countries, breast cancer mortality had already started to decline before the implementation of

Abbreviations: ALP, alkaline phosphatase; BI-RADS, Breast Imaging Reporting and Data System; BMP2, bone morphogenetic protein 2; BSP, bone sialoprotein; CA1, carbonic anhydrase I; COX2, cyclooxygenase-2; DCIS, ductal carcinoma in situ; EMT, epithelial-mesenchymal transition; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HA, hydroxyapatite; IL-1β, interleukin 1 beta; MGP, matrix gla protein; MMP, matrix metalloproteinase; NLRP3, NLR family pyrin domain containing 3; OSN, osteonectin; OPN, osteopontin; Pi, phosphate; Pit-1, sodium-dependent phosphate transporter 1; PPi, pyrophosphate; PFS, progression-free survival; PGE2, prostaglandin E2; RUNX2, runt-related transcription factor 2; SPCA, secretory pathway Ca^{2+}-ATPase; TGF-β, transforming growth factor beta; TRPC1, transient receptor potential channel 1; TRPM7, transient receptor potential cation channel, subfamily M, member 7; VSMC, vascular smooth muscle cells

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https://doi.org/10.1016/j.bbcan.2018.04.006
Received 23 March 2018; Received in revised form 18 April 2018; Accepted 18 April 2018
Available online 21 April 2018

Table 1
Breast imaging and reporting data system (BI-RADS) categories for mammography and its association with microcalcification appearance.

Category	Description	Management	Likelihood of malignancy
0	Incomplete	Additional imaging required	Not applicable
1	Negative	Continue routine screening	0%
2	Benign	Continue routine screening	0%
3	Probably benign	Short interval follow up	0–2%
4		May require biopsy	
A	Low suspicion		2–10%
B	Intermediate suspicion		10–50%
C	High suspicion		50–95%
5	Highly suggestive of malignancy	Biopsy required	> 95%
6	Biopsy proven malignancy	Begin treatment	100%

Mammography Calcification	Description	BI-RADS category
Typically benign	Skin	2 or 3
	Vascular	
	Dystrophic	
	Eggshell	
	Large rod-like	
	Popcorn-like	
Suspicious	Amorphous	4B
	Coarse heterogeneous	4B
	Fine pleomorphic	4B
	Fine linear (casting)	4C
	Fine linear (casting),segmental distribution	5

screening, likely due to improved treatment regimens [15]. The clinical efficacy of screening mammography is also hampered by a low positive-predictive value [16], leading to a significant drive in efforts to further improve the diagnostic power of breast imaging techniques [17]. It is worth noting, that although some disagreement may exist over the efficacy of mammography in population screening, its effectiveness in a diagnostic capacity, where it is usually combined with a clinical exam and biopsy analysis is widely accepted, with sensitivity and specificity of this "triple-assessment" approaching 100% [18–20].

Despite the controversy, mammographic imaging remains a vital tool in early detection of breast cancer in many countries, with most utilizing the Breast Imaging Reporting and Data System (BI-RADS), a standardized system for classifying and reporting clinical findings from mammography. Mammograms are scored on a number of features including density, architectural distortions and calcifications, and placed into one of 7 BI-RADS categories (Table 1), ranging from "Incomplete Assessment" (Category 0) up to "Known Biopsy-Proven Malignancy" (Category 6), each with a recommended course of action [21,22]. One of the most commonly detected mammographic abnormalities are microcalcifications. First identified in 1951 [23], they have long been a highly useful marker of breast cancer, with between 30 and 50% of non-palpable tumours found in screening identified solely due to the presence of microcalcifications [16,24]. They are also present in the majority of ductal carcinoma in situ (DCIS) cases [25]. This review will summarise the most current understanding of the formation of calcifications within breast tissue and explore their associated clinical features and prognostic value.

2. Mammographic characterisation of microcalcifications

Calcifications, when detected by mammography, can be characterised based on a number of attributes, including morphology, size and distribution. Based on these features, radiographers will then assign calcifications to a BI-RADS category indicative of their likelihood of malignancy. Calcification morphologies typically considered low-risk include "popcorn-like", eggshell or dystrophic, whilst calcifications of a coarse heterogeneous or fine linear morphology convey a significantly

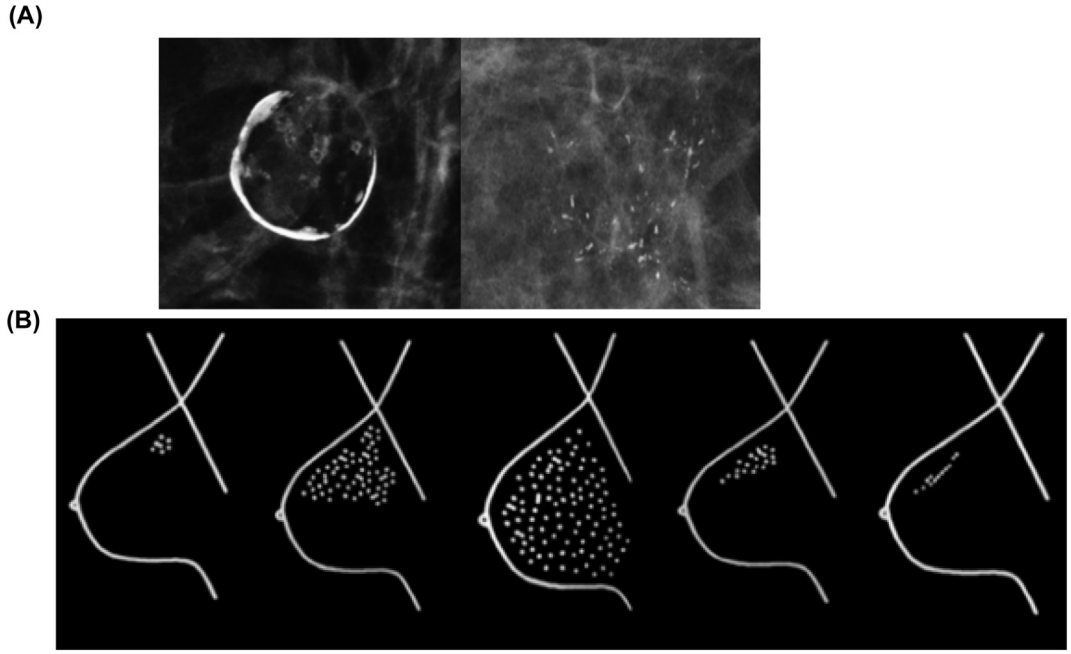

Fig. 1. Morphology and distribution patterns of breast microcalcifications. Representative mammogram images (A) of a benign eggshell calcification (left) and suspicious fine-linear/casting calcifications (right). Adapted and reproduced and from [26]. Commonly observed distribution patterns (B) of mammographically detected breast calcifications, in order of increasing likelihood of malignancy. Order is as follows: diffuse, regional, clustered, segmental, and linear. Adapted and reproduced from [31].