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Breast composition: Measurement and clinical use

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ABSTRACT

Breast density is a measure of the extent of radiodense fibroglandular tissue in the breast. The risk of developing breast cancer and the risk of missing cancer at screening rise with higher breast density. In this paper, the historical background to breast density measurement is outlined and current evidence based practice is explained. The relevance of breast density knowledge to mammographic practice and image interpretation is considered in the light of clinical assessment and notification of mammographic breast density (MBD). The current work also discusses risk stratification for decision-making regarding screening frequency and better modalities for earlier detection of breast cancer in the dense breast. Automated volumetric approaches are explained while ultrasound, digital breast tomosynthesis, molecular breast imaging, and magnetic resonance imaging are introduced as valuable adjuncts to digital mammography for imaging the dense breast. The work concludes on the important note that screened women should be notified of their breast density, and such notification should be accompanied with clear and adequate information about breast density and cancer risk, strategies associated with lower MBD, as well as best screening intervals and pathways for women with dense breasts. Adoption of these strategies may be crucial to early detection and treatment of cancer and improving survival from the disease.

Introduction

Breast density is a measure of the extent of radiodense fibroglandular tissue in the breast.[1] A meta-analysis of breast cancer risk factors indicates that the risk of breast cancer from high breast density is twice higher than other risk factors except family history of the disease in women 40–49 years.[1] However, it is still contentious whether density is an independent risk factor or merely stimulates other risk factors to cause cancer. Regardless of these contentions, studies have shown that high breast density is associated with a 4–6 fold increased risk of breast cancer,[2–5] and that a 1% increase in breast density is associated with 2% increase in breast cancer risk.[4]

Dense breast tissue has been shown to offer more opportunities for breast cancer to develop, especially in younger women.[3,6–8] Additionally, there is a genetic predisposition to breast density,[9,10] and other established risk factors for breast cancer such as hormonal agents,[11,12] lifestyle, and reproductive characteristics are associated with high breast density.[13–16] Importantly, breast density is a potentially modifiable risk factor for breast cancer,[17,18] and lower density has been shown to be a prognostic factor for the effect of interventions on breast cancer risk.[19] Some lifestyle parameters responsible for high breast density and breast cancer are controllable,[20] and consumption of food species such as vegetables, vitamin D, and calcium may have an ameliorative impact on the breast density and breast cancer risk.[21,22]

Breast density is also a significant factor in interval breast cancer (cancer detected within 12 months after a normal screening mammogram), accounting for about 50%.[3,5] Women with dense breasts are 4.7–17.8 times at risk of interval breast cancer relative to those with non-dense breasts.[3,23–25] Mammographic breast density also reduces mammographic sensitivity and limits earlier detection of breast cancer with 2-dimensional mammography

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through masking effects.[23,26] Therefore, it is increasingly important to assess breast density of women undergoing screening mammography and inform women of their density. Such breast density data can improve women's awareness of their risks of breast cancer and interval cancer, and the potential of cancer being missed in their mammograms. This will allow for shared decision-making between screened women and their physicians concerning strategies to reduce the associated risks and facilitate better decisions regarding screening.[17,19,27]

National level breast density information will enable breast cancer risk stratification,[27,28] leading to selection of appropriate imaging pathways such as ultrasound,[29,30] digital breast tomosynthesis (DBT),[31] and magnetic resonance imaging (MRI)[30] to improve cancer detection in the dense breast. Breast density data can also be used to select personalised and appropriate screening intervals for screened women, such as screening less often and with digital mammography only for lower risk, fatty breasts and more frequently with DBT and whole breast Ultrasound for the denser breast. Data on breast density will enable use of breast density as a marker for monitoring the effect of breast cancer prevention and control interventions.[17,19]

The relevance of breast density information in clinical decision-making for screened women underscores the need for methods of breast density assessment to be standardized, reliable, and reproducible, as this will support clinical decisions made from breast density assessment. In this paper we revisit breast morphological and radiographic anatomy. We also examine the link between breast density and breast cancer, and approaches that have been employed to categorize mammographic breast density before tackling clinical uses.

Breast composition and radiographic appearances

Breast consists of fibroglandular tissue and fat, and their relative concentration determines the radiographic appearance of the breast.[3] X-ray attenuation is higher in fibroglandular tissue than fat; as a result, fibroglandular tissue appears radiopaque (white) and constitutes a dense area of the breast and fat appears radiolucent (black).[3] The dense portion of the breast contains high concentration of epithelial and stromal cells and collagen.[3,32,33]

Dense breasts are highly radiosensitive due to the high proliferation of epithelial and stromal cells in such breasts.[34] To reduce the potential effect of radiation on the breast, there is a need to optimise the imaging procedure. Optimisation is aimed at producing good quality images at acceptable radiation dose.[35] The key radiographic determinant of image quality and dose is the detective quantum efficiency of the detector and composition of the X-ray spectrum, which in turn depends on the target material, tube voltage (kVp), and filtration.[35] These technical parameters impact not only on the diagnostic value of the image, but also the appearance of breast density to the human visual system.[36,37] This is worrisome in film-screen mammography where radiographers have to manually select these factors.[37] With automatic exposure control (AEC), exposure parameters are selected according to the physical characteristics of the breast or compressed breast thickness.[38] Therefore, the same target/filter/kVp is chosen for a given breast density. Spectral and breast thickness information also influence the accuracy of volumetric breast density assessment.[39,40] Studies have shown that higher atomic number target/filter combinations such as Tungsten/Rhodium (W/Rh) and Tungsten/Silver (W/Ag) produce the optimum spectrum for imaging the dense breast, and improve visualization of the dense breasts and features of cancer at lower doses.[41,42] Therefore, for systems that do not have functional AEC, manual selection of the filter that produces the optimum spectrum for a given breast density is encouraged. Alternatively, dense breasts could be imaged with digital breast tomosynthesis (DBT). The high detector quantum efficiency (DQE), fast read-out ability, and low noise levels of digital detectors used in DBT have enabled acquisition of good quality images at low doses in dense breasts.[43] DBT produces pseudo-cross-sectional images that reduce tissue superimposition and synthetic (reconstructed) 2-dimensional (2D) images which can be used as substitute for standard 2D images of digital mammography. The combined use of 3D images of DBT and standard 2D images of digital mammography (DM) has been shown to improve diagnostic accuracy,[44,45] but is associated with increased radiation dose.[43] However, use of reconstructed 2D images as substitute for standard 2D images has been found to be associated with a 45% reduction in mean glandular dose.[43,46]

Mechanisms linking breast density to breast cancer

Two theories have been postulated to explain the mechanisms linking breast density and breast cancer. The first mechanism involves mitogen (a chemical substance that encourages a cell to commence cell division, triggering mitosis),[47] and mutagen effects (a physical or chemical agent that changes the genetic material of an organism and thus increases the frequency of mutations above the natural background level).[48] The second mechanism involves biological interaction among epithelial and stromal cells, collagen and the breast microenvironment.[32,33]

It has been shown that mitogenic followed by mutagenic activity are at least in part, responsible for high breast density and breast cancer, where individuals with both high breast density and breast cancer demonstrate similar mitogen[47] and mutagen characteristics.[48] It is well known that mitogens induce cell proliferation, primarily affecting epithelial and stromal cells leading to increased fibroglandular tissue and higher levels of breast density mostly in premenopausal women.[47,49] Concomitantly, this increased presence of proliferating cells is very sensitive to mutagens resulting in changes and potential errors in DNA replication and strand recombination.[50] Examples of specific mitogens that are responsible for both high breast density and breast cancer are insulin-like growth factor 1 and prolactin.[47,49] A mutagen of oxidative stress that has been shown to be associated with breast density and cancer is cytochrome P450 1A2 (CYP1A2).[48]

It has also been shown that breasts with high density and those with cancer exhibit similar biological characteristics such as increased concentration of epithelial and stromal cells and collagen.[32,33,51] Epithelial cell proliferation is necessary for breast density increases, however since breast cancer primarily evolve from epithelial cells, increased numbers of epithelial cells in the dense breast increase the possibility of cancer.[33] Stromal cells induce cancer by modulating epithelial cells through epidermal growth factor receptor, IGF-1, and TGF-β.[52] Stromal cells are also progenitors, of collagen and stromal matrix which promote mammary gland development and tumour invasion[52–54] and since collagen is linked to IGF-1 quantities and tumour reorganization,[53] there are increased opportunities for cell proliferation and transformation to cancer. Also, the extracellular matrix expresses increased concentration of proteoglycans (lumican and decorin) in stroma associated with high breast density and cancer. These proteoglycans bind growth factors and increase breast tissue stiffness implicated in breast cancer.[51] Together these intercellular interactions in the breast microenvironment result in each cell type becoming more tensile and more rigid, generating mechanical forces that can increase breast density and cancer risk.[51,55]

Breast density is associated with established risk factors for breast cancer except age and body mass index.[11,12] Genome-wide studies have shown that breast cancer susceptibility genetic