

Commentary

Can the stroma provide the clue to the cellular basis for mammographic density?

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Abstract

Mammographic density is recognised as a useful phenotypic biomarker of breast cancer risk. Deeper understanding is needed of the cellular basis, but evidence is limited because of difficulty in designing studies to validate hypotheses. The ductal epithelial components do not adequately explain the physical and dynamic features observed. The stroma is thought to interact with ductal structures in cancer initiation. Stromal tissues might account for the mammographic features, and this interplay can be hypothesised to relate risk to density. In a paper in this issue of *Breast Cancer Research*, Alowami has shown a relationship between density and stromal proteins, which might provide useful insight into mammographic density.

Keywords: breast cancer risk, mammographic density, stromal proteins

Introduction

For many years it has been recognised that radiographic density of the breast tissues on the mammogram is associated with the risk of developing cancer, and that women with the densest pattern have a 4–6 times relative risk of breast cancer compared with women with the most lucent pattern. Recently the huge potential of this observation for detecting and monitoring risk has been recognised, and is enabled by the implementation of routine mammographic screening of the normal population and those at increased risk in whom screening can start from as young as 30 years. The cellular basis for the differences between individuals has never been fully explained. There has been no firm evidence for the quasi-pathological descriptions used. The paper by Alowami and colleagues in this issue provides an interesting clue, supported by data, for the stroma and its proteins as determinant factors in this radiographic density on the mammogram [1].

Breast density as a biomarker of risk

Wolfe first described a means of categorising the appearances of breast tissue on the mammogram and showed

that the densest patterns were associated with an increased risk of developing breast cancer when compared with mammograms showing chiefly fatty appearances [2]. For years this was debated and doubted in the literature, but in the late 1990s many observers confirmed this relationship conclusively, and the risk–density relationships were explored in high-quality epidemiological studies. This literature has recently been comprehensively reviewed by Heine [3,4] and appraised by Byrne [5] for the way in which it reveals an understanding of breast cancer.

One of the commonest reasons for having an increased risk of breast cancer is family history, and a recent study of twins has demonstrated that about 60% of the density can be accounted for by heritable factors, the remaining proportion lying in lifestyle and mutable factors [6]. Density has been shown to be associated with the lifestyle risk factors known for breast cancer such as late age at first birth, and nulliparity [7]. It is also increased in women on hormone replacement therapy (HRT) [7] and decreased in women on tamoxifen [8]. It has been associated with dietary constituents believed to be associated

with breast cancer causation [9]. The two major risk factors for breast cancer that are inversely related to breast density are raised body mass index [10] and age [11], both of which give rise to more fatty breasts.

When the nature of the tumours associated with higher risk patterns on mammography is examined, they are more likely to be grade 3 tumours, with nodes positive, of large size and with ductal carcinoma *in situ*; this is independent of the masking effect of dense glandular tissue on mammographic diagnosis [12,13]. Change in density occurs with time, diminishing with advancing age, but increasing on HRT. This change can be measured, and might be a method of monitoring the effects of intervention on individual risk [14] – as for example with chemoprevention. Does change in density actually denote change in risk? This link has not yet been made in the published evidence available.

Knowledge of the cellular basis for mammographic density

What, then, is known of the cellular basis for these observations? The literature on this is much smaller, and the question is curiously difficult to answer. There are limitations on all available methods, which introduce different biases. Some workers have looked at autopsy material and have been able to examine the relationship between dense patterns and evidence of, for example, proliferative fibrocystic change [15]. In this situation, although detailed and accurate pathological examination can be performed, the mammography is suboptimal because it is on a post-mortem mastectomy specimen. When the problem is tackled with a case-control study, the controls do not have their tissue examined, whereas examination of the cases might be biased owing to the reason for obtaining biopsy tissue. In contrast, the mammography is from live women with standard techniques [16]. The tissues are rarely 'normal' because the two main types of specimens examined are benign tissues from patients with cancer or prophylactic mastectomies in high-risk women. This shortfall might be resolved by using biopsy material from the control population, but this raises both ethical difficulties and technical problems in relating the biopsy site to the mammographic feature.

The physical basis for tissue appearances on mammography

Most studies recognise that the radiographically lucent tissue is fat, and that the water-dense material is due to epithelial and stromal elements. The physical methods of measurement essentially divide the tissues into fat and 'glandular elements', namely tissues with the same density as water [17]. Information gained from ultrasound and magnetic resonance imaging [18] might be looking at the same features, but using different physical principles. Their relevance is therefore limited. Mammographers know well

that cancers 'arise' commonly in fatty tissue, and so there is epithelial tissue present that is not seen on the mammogram, but from which the cancer arises. An early (1990) publication from Nottingham describing a case-control study concluded that the density was related to fibrous and adipose tissues in the interlobular stroma and bore no relationship to the epithelial parenchymal content [19].

Relationship of density to epithelial pathologies

Nevertheless, many of the papers since then that explore the issue have concentrated on the relationship to epithelial proliferations – hyperplasia, atypical hyperplasia, carcinoma *in situ* and fibrocystic change, echoing the original name given by Wolfe to the densest pattern, 'DY', hinting at 'dysplasia' as the origin [2]. Several authors [16,20,21] have explored these relationships and have shown a weak link between these epithelial abnormalities and dense patterns. Despite this, it has been increasingly accepted that epithelial proliferation is unlikely to account for the increased mammographic density.

The stroma as a dynamic component in breast carcinogenesis

There is recent evidence that the stroma is not inert but that there might be an interplay between the breast epithelial and stromal compartments, which have an effect on the growth and progression of a breast tumour. Evidence of loss of heterozygosity (LOH) has been demonstrated in both epithelial and stromal compartments by Kurose and colleagues [22] and others, suggesting that stromal changes might have a crucial role in breast carcinogenesis. Finding of LOH in the two compartments does not prove a causality of effect of one component over the other; nonetheless, the data are intriguing. They fit with the non-reductionist view that breast cancer is more than just an abnormality of epithelial cells and that the stroma, inflammatory cells and endothelial proliferation are an integral part of the tumour. Guo and colleagues [23] found that increased tissue cellularity, greater amounts of collagen, increased insulin-like growth factor-1 and tissue metalloproteinase-3 were found in tissue from dense breasts in women under 50 years of age, and proposed a relationship by which increased risk might be mediated.

Density changes with time

A feature of the density problem that must be taken into account in any hypothesis of the underlying cellular process is the relatively rapid changes that can occur in breast density – for example, there is evidence of change within the menstrual cycle [24]. Relatively rapid changes due to hormones have also been shown [25]. Is this to be accounted for by water retention within existing cells, or changes in the number of cells? Further, the relationship holds good at all ages, so findings must apply before and after the menopause.

Evidence from stromal proteins

Watson's group have previously examined the stromal proteins lumican and decorin in breast tumours and normal tissues and have shown that they are inversely regulated in association with breast carcinogenesis [26]. This present contribution explores these proteins and shows them to be related to dense patterns. The authors showed higher collagen density and extent of fibrosis but found no significant difference in the density of ductal and lobular units (epithelial component). This small project starts to elucidate a hypothesis by which density might relate to risk through an interplay between the stromal and epithelial structures. This could provide a means by which change in density might influence factors that have an effect on the initiation and progression of a breast tumour.

Conclusion

Further work in this area might be productive in giving a better understanding of this relationship between density and risk. More understanding is needed if density measures are to be used to estimate individual risk and to monitor change in a meaningful way. The expression of significant cellular markers, stromal proteins, genetic changes (LOH and comparative genomic hybridisation) or expression profiles could be assessed on biopsy specimens in association with the mammograms so that the risk-density relationship can be more fully understood. This might be an ethically justifiable tool for research or in the risk assessment of high-risk women.

Competing interests

None declared.

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