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REVIEW ARTICLE

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The pressing need for better histologic-mammographic correlation of the many variations in normal breast anatomy

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Abstract Mammography screening calls for a reevaluation of the working relationship between physicians dealing with the diagnosis and treatment of breast diseases. In this new era, histologic-mammographic correlation needs to be extended to correctly describe the deceptive mammographic findings that correspond to variations in normal breast tissue. Progress in histologic-mammographic correlation can only be made by overcoming the limitations inherent to the traditional histologic technique by examining a histologic specimen of greater length, width, and depth. There are several distinct advantages to using the large-section histology technique in the diagnosis of breast diseases. The subgross (three-dimensional) histology technique serves to bridge the gap that separates the pathologist and radiologist, bringing them to a common ground for a better understanding of breast morphology. These improvements in communication between the members of the diagnostic team will serve to optimize the sensitivity and specificity of breast cancer diagnosis.

Keywords Normal breast · Mammographic patterns · Large sections

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Introduction

The introduction of large-scale, population-based mammography screening of asymptomatic women at regular intervals added a new dimension to the traditional interaction between pathologists and radiologists. Rather than having a predominance of pathologic lesions, the vast majority of screening mammograms show no pathologic abnormality, but encompass a wide spectrum of normal breast appearance.

The histologic diagnosis of the mammographically detected lesions remains of paramount importance, while the emphasis shifts to ever smaller lesions as a result of screening. However, in this new era, histologic-mammographic correlation needs to be extended to correctly describe the deceptive mammographic findings that correspond to variations in normal breast tissue.

Many large mammographic screening centers have each collected hundreds of thousands of mammograms, generating a database for recognizing, describing, and classifying the radiological anatomy of the normal breast. Mammographic examinations at regular intervals have also given us a unique opportunity to follow and describe the dynamic changes of the normal breast tissue as a function of aging. Imaging the ever changing nature of normal breast tissue and the transition between normal and aberrant development and involution brings us closer to an understanding of the natural history of different breast diseases.

Epidemiological studies [4, 10, 12] have shown a correlation between the mammographic parenchymal patterns and the risk of developing breast cancer. These empirical observations, complemented by statistical risk analyses, call for a more systematic histologic description of the mammographic patterns and an explanation of the differences in the risk of developing breast cancer.

Our current knowledge of the microscopic structure of the normal breast is based on traditional anatomic studies and on histologic examination of surgical and autopsy specimens [2, 5, 9, 11,13]. Although the structural and functional elements of the breast are well described and many variations have been recognized, these form a series of static images, each at a given point in time. This information needs to become more applicable to the radiologist, who in contrast follows the dynamism of development and involution of the normal parenchyma and its variations through serial mammograms of many individual women.

Bridging the gap between the macroscopic mammographic and microscopic histologic images of the breast

Several factors have restricted improvements in histologic-mammographic correlation. First of all, the focus at microscopic examination is on the detection and classification of any abnormality. In addition, examination of small, selected, fragmented tissue samples limits the opportunity to appreciate the patterns of normal breast parenchyma, which are evident on the mammogram. Thus the shortcomings of using small tissue blocks become even more restrictive when dealing with histologic-mammographic correlation of the normal breast.

The microscopic examination of breast specimens employs a resolution far superior to that of the mammogram, but includes only the tissue contained within the 4- to 5-μ-thick slices obtained from a small paraffin block. This represents the anatomic structure of an extremely limited sample of the breast. The mammogram provides an excellent overview of the relative proportions of the different tissues within the breast, but it has a resolution on the order of 80–100 μ.

The mammographic image is a summation of all the thousands of terminal ductal lobular units (TDLU) and their supporting connective tissue. Clarification of radiological anatomy can be greatly facilitated by examining a histologic specimen of greater length, width, and depth.

The advantages of using the large-section histology technique in the diagnosis of breast diseases include reliable and reproducible tumor size measurement, better description of the extent of breast diseases, especially certain subtypes of breast cancer, detection of additional invasive foci, better assessment of margins, and undoubtedly a better way to compare with mammography [7]. Although the method is more time consuming than the technique of small-block histology, the advantages far outweigh this inconvenience, especially when the preoperative microscopic diagnosis has already been established using large-core needle biopsy.

Combining the large-section (10×8 cm) histology technique with the subgross, three-dimensional method [1, 3, 8,13] facilitates a better understanding of normal breast morphology and makes a precise correlation with the mammogram possible. The use of the large-section histology technique in combination with the subgross, three-dimensional method therefore provides the best currently available means for understanding the structures seen on the mammogram.

The subgross, three-dimensional histology technique serves to bridge the gap which separates the pathologist and radiologist, bringing them to a common ground for a better understanding of breast morphology.

Subgross morphological description of the mammographic image

The TDLU are seen on the mammogram as 1- to 2-mm *nodular densities*, provided that the individual units are outlined by adipose tissue. This silhouette of the TDLU may represent a wide variety of functioning or involuting TDLU, as well as “aberrations of the normal development and involution” (ANDI) [6]. The latter includes, among other things, several types of adenosis, apocrine metaplasia, microcystic involution, minor cysts, and fibroadenomatoid change.

The ducts, vessels, and fibrous strands may all be seen as *linear densities* of varying thickness on the mammogram.

The connective tissue, which surrounds and supports these structures, has two distinct radiologic appearances. The adipose tissue is *radiolucent*, clearly outlining the individual linear and nodular structures. In contrast, the fibrous tissue is *radiopaque* and obscures the fine details of the glandular elements.

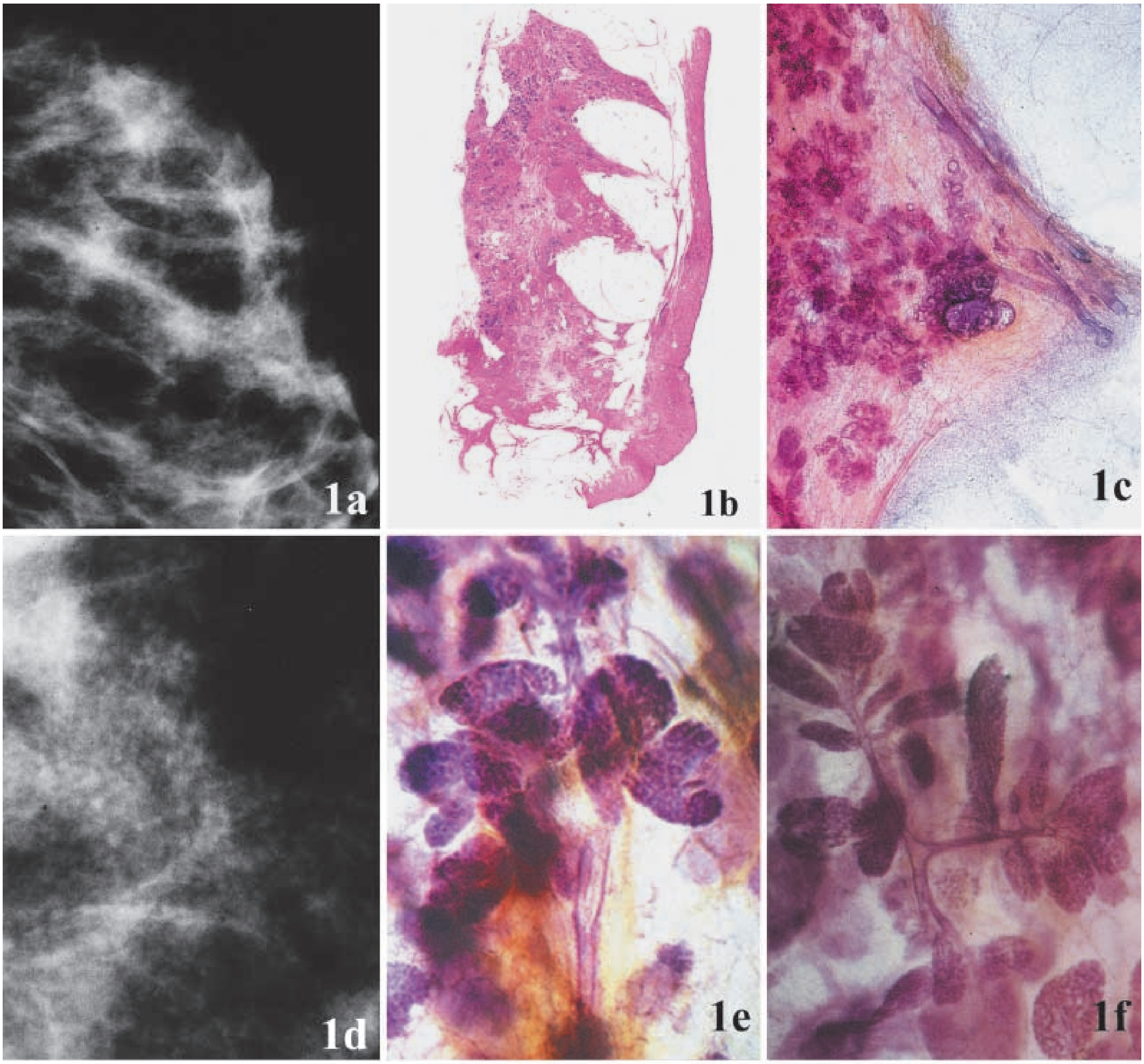
While the histologic image can demonstrate structural elements down to the cellular details with ease, the mammographic image is a composite of the four basic building blocks described above: nodular and linear densities, radiolucent adipose tissue, and homogeneous, radiopaque fibrous tissue. These four building blocks in specific combinations form the five basic mammographic parenchymal patterns.

The five mammographic parenchymal patterns

Screening of an asymptomatic population for any disease will give a normal examination result for the vast majority. Screening for breast cancer is no exception. The anatomic structure of the breast shows great diversity, since the relative proportion of the basic structural elements of the breast can vary enormously in different regions of the same breast, within the same individual over time, and among different individuals. This often makes it very difficult to describe a “normal” mammogram. Classification of normal breast anatomy into structural groups based on histologic-mammographic correlation will simplify the decision process required to differentiate normal from abnormal [4, 10,12].

Mammographic pattern I

Mammographic pattern I (Fig. 1) is characteristic of younger women. Normal TDLU are distributed throughout most of the breast, supported by both adipose and fi-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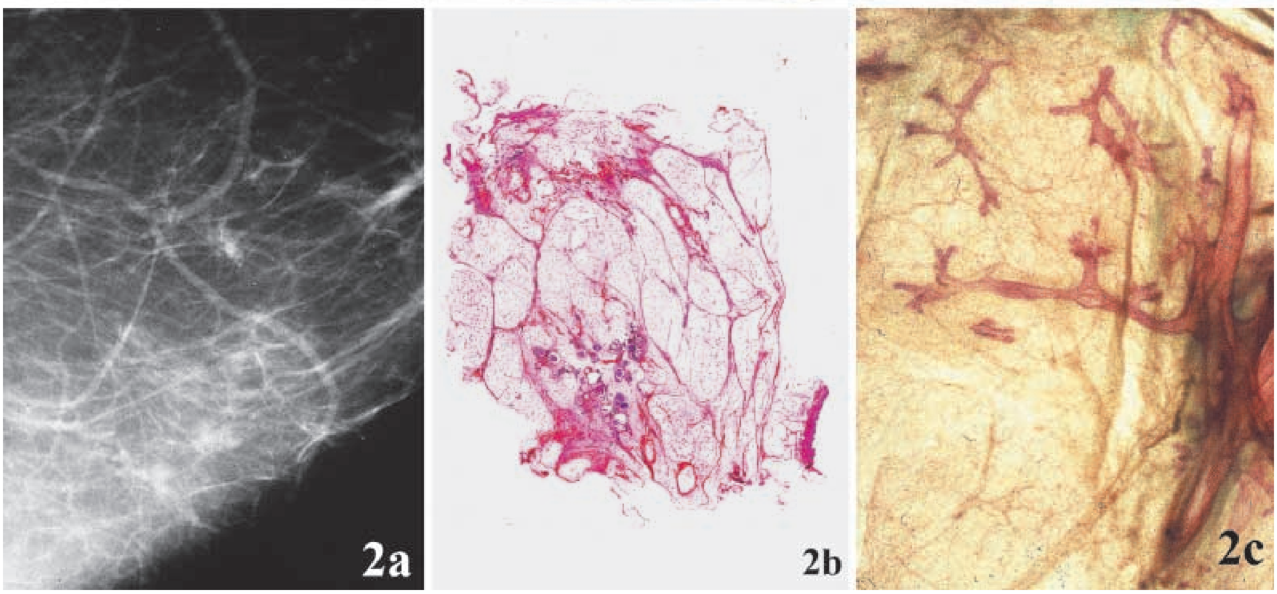
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brous tissue. The anterior contour of the parenchyma is scalloped, and Cooper's ligaments are readily apparent. These so-called ligaments actually are composed of normal TDLU, small ducts, and interlobular fibrous tissue. With involution, pattern I regresses gradually to either mammographic pattern II or III.

Mammographic pattern II

Mammographic pattern II (Fig. 2) is characteristic of older women, although the rate of regression from pattern I to patterns II and III varies individually. When this pattern is fully developed, both the TDLU and the ducts have become atrophic. Most of the TDLU will be replaced by adipose tissue, which will eventually dominate both the histologic and mammographic image. The adipose background will make the detection of small pathologic abnormalities much easier.

Mammographic pattern III

Mammographic pattern III (Fig. 3), also characteristic of older women, is similar to pattern II with the exception of the prominent retroareolar duct pattern. This may be caused by dilated major ducts and/or periductal fibrosis. Hormone replacement therapy often causes partial reversion of patterns II and III to pattern I.

Mammographic pattern IV

Mammographic pattern IV (Fig. 4) has been found in 12% of women in an asymptomatic population aged 40–74 years [10]. It is noteworthy that this pattern does not change with time. It is characterized by 3- to 6-mm nodular densities, which correspond to enlarged TDLU. At histologic examination, these may correspond to adenosis, microcysts, fibroadenomatoid change, or other ANDI. Sometimes only large fibrous nodules are seen at histology, containing remnants of the terminal duct.

Mammographic pattern V

Mammographic pattern V (Fig. 5) occurs in about 6% of asymptomatic women. The overwhelming predominance of dense fibrous tissue results in a homogeneous ground glass-like radiopacity on the mammogram that obscures practically all soft tissue details. Thus the mammographic image cannot distinguish between pattern V breasts containing active TDLU and pattern V breasts in involution. The atrophic ducts are replaced in this case by fibrous tissue rather than fat. The detection of pathologic lesions may therefore be difficult, except for those containing mammographically detectable calcifications or those causing parenchymal contour changes.

Practical implications

The reliability of mammography to detect breast abnormality, to correctly diagnose it, and to recognize multifocality will be strongly influenced by the nature of the surrounding tissue. The mammographic parenchymal patterns serve as a means of communication between the specialists dealing with the diagnosis of breast diseases. At the one extreme, in a pattern II and III breast, identification and interpretation of the abnormalities will be relatively straightforward for all diagnostic modalities, including palpation, mammography, and histology. At the other extreme, in breasts with mammographic patterns IV, V, and often pattern I, the efficacy of palpation and mammography may be compromised, and the use of additional examination methods (breast ultrasound or magnetic resonance image) may therefore increase sensitivity.In addition, more frequent screening may be justified, especially in cases of strong family history.

The prevalence of breast cancer also varies according to the mammographic parenchymal pattern, being lower in patterns I–III and higher in patterns IV and V [12]. The risk of developing breast cancer increases with age in both the lower- and higher-risk groups and is more than twice as high in women with patterns IV and V than in those with patterns I–III [10], with an approximately 15-year delay in development of breast cancer risk in

◀ **Fig. 1 a** Normal mammogram, pattern I. **b**. The corresponding large section demonstrating Cooper's ligaments. Hematoxylin and eosin, ×0.5. **c** Three-dimensional preparation of the same section showing ducts and lobules within a Cooper's ligament. **d** Radiological details in a pattern I mammogram: small nodular and linear densities. **e,f** The corresponding three-dimensional section with normal terminal ductal lobular units (TDLU)

Fig. 2 a Normal mammogram, patterns II. **b** The corresponding large histologic section demonstrating fatty involution of the breast tissue. Hematoxylin and eosin, ×0.5. **c** Atrophic lobules and ducts in the corresponding three-dimensional section

Fig. 3 a Normal mammogram, pattern III. **b** The corresponding large histologic section in this case demonstrates retromammillary ductectasia. Hematoxylin and eosin, ×0.5. **c** A histological detail. Hematoxylin and eosin, ×20 ▶

Fig. 4 a Normal mammogram, pattern IV. **b** The corresponding large histologic section showing enlarged lobules. Hematoxylin and eosin, ×0.5. **c** Three-dimensional image of adenosis

Fig. 5 a Normal mammogram, pattern V. **b** The corresponding large histologic section demonstrating fibrosis in the interlobular stroma. Hematoxylin and eosin, ×0.5. **c** Higher magnification of Fig. 5b showing many terminal ductal lobular units (TDLU) and interlobular fibrosis. Sirius red, ×40

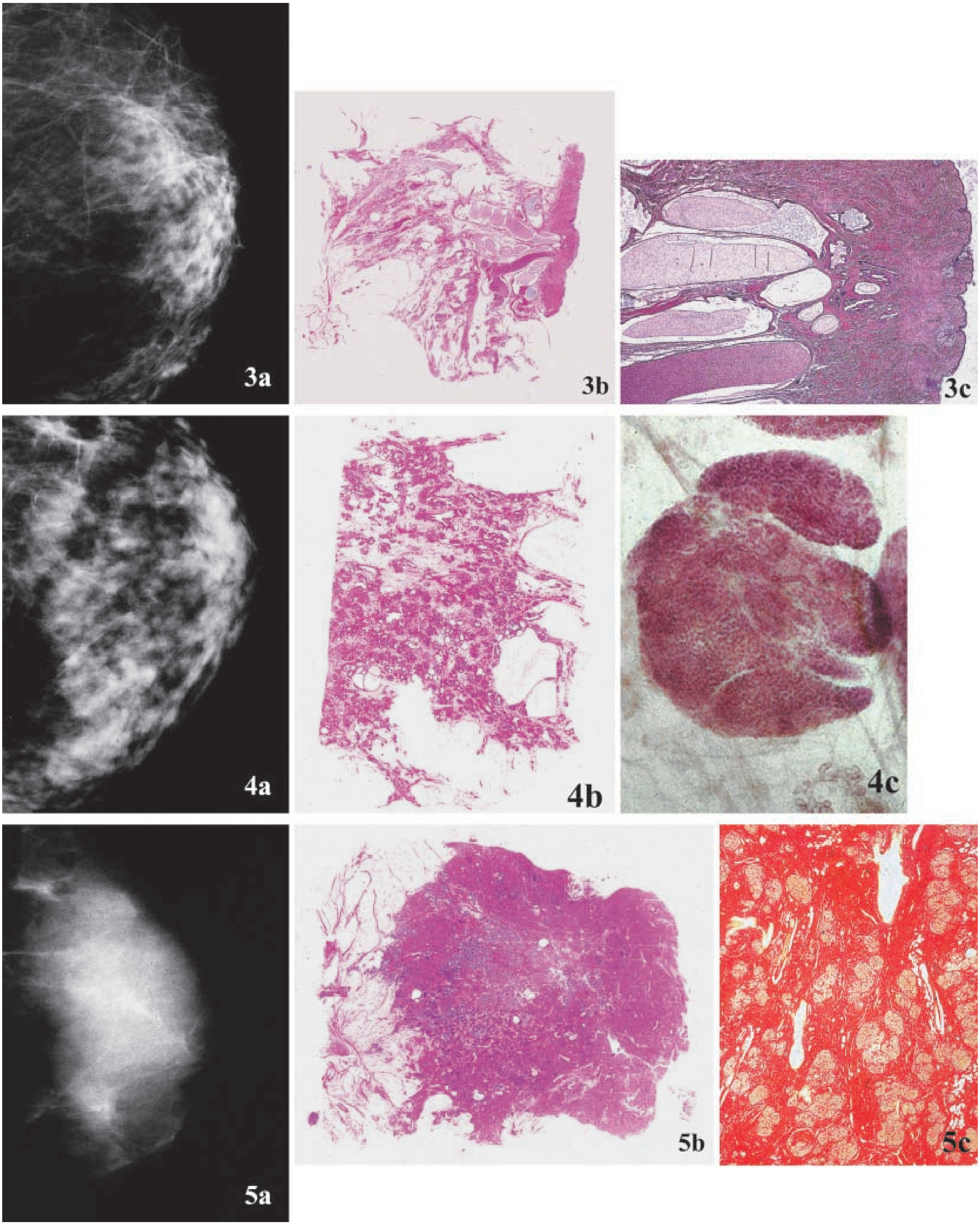

Fig. 3–5

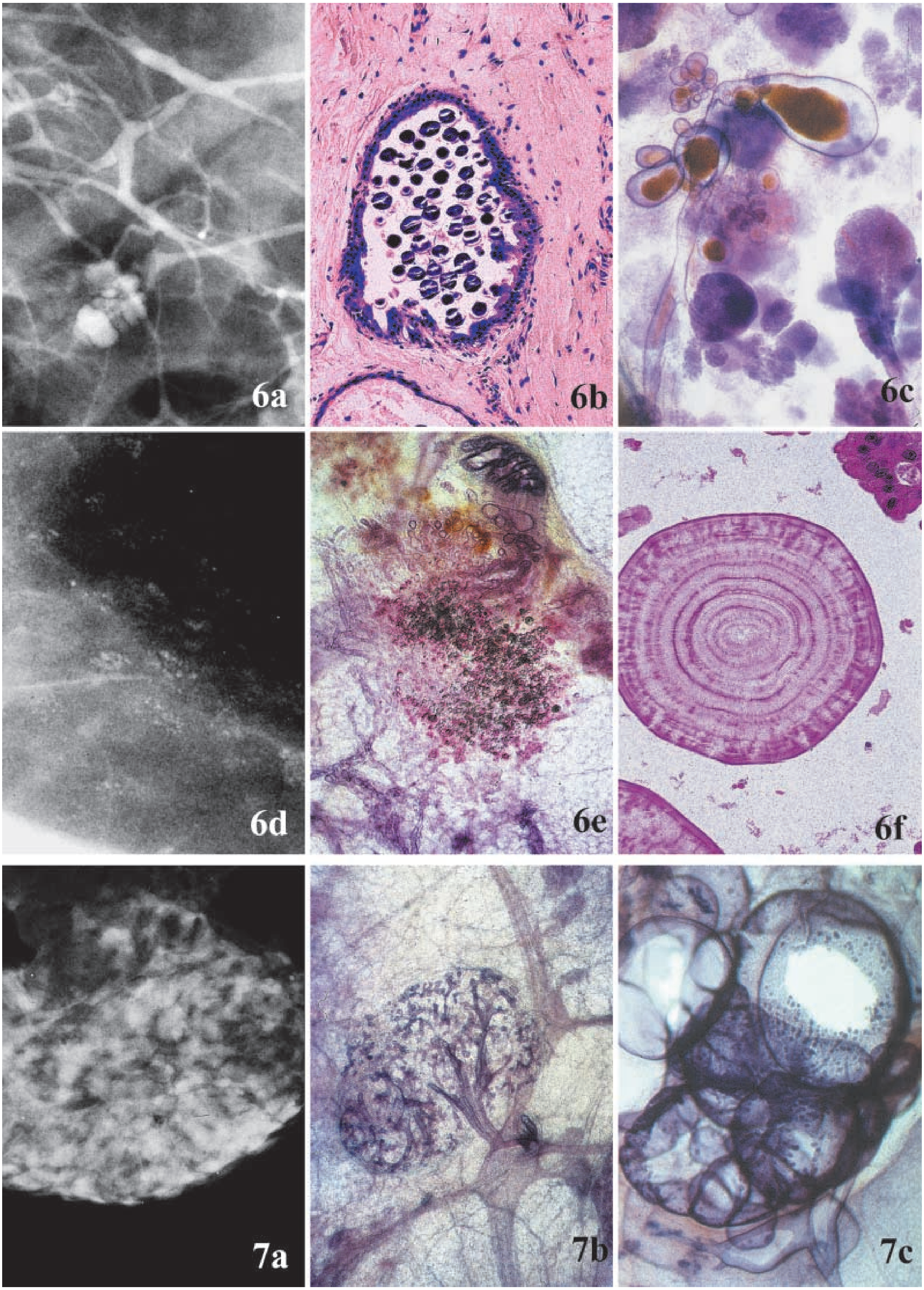

Fig. 6, 7

◀ **Fig. 6 a** Detail of a galactogram with ducts and a group of dilated acini filled with contrast medium. **b** A dilated acinus containing microcalcifications. Hematoxylin and eosin, ×100. **c** Corresponding three-dimensional image of microcystic involution. **d** Multiple clusters of powderish microcalcifications on the mammogram. **e** Three-dimensional image of sclerosing adenosis with microcalcifications. **f** A psammoma body from a case with apocrine metaplasia. Hematoxylin and eosin, ×200

Fig. 7 a Enlarged nodular densities on the mammogram with pattern IV. **b** Three-dimensional image of a lobule showing fibroadenomatoid change. **c** Three-dimensional image of microcysts with apocrine metaplasia

these two risk groups. Due to the considerably higher proportion of women in the lower-risk groups, the majority of breast cancers will be diagnosed in these so-called lower-risk groups.

The correlative approach (mammogram, three-dimensional large histological section) helps the screening radiologist learn how to better select cases for further workup. Certain types of microcalcifications (Fig. 6) and some minor changes representing enlarged nodular densities on the mammogram (Fig. 7) are illustrated to draw attention to the importance of proper histological feedback, which is also relevant for minor variations in the morphology of the normal breast.

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