Puay Hoon Tan
Aysegul A. Sahin

# Atlas of Differential Diagnosis in Breast Pathology

Springer

# Atlas of Anatomic Pathology

**Series Editor**

Liang Cheng
Indianapolis, Indiana
USA

This Atlas series is intended as a "first knowledge base" in the quest for diagnosis of usual and unusual diseases. Each atlas will offer the reader a quick reference guide for diagnosis and classification of a wide spectrum of benign, congenital, inflammatory, nonneoplastic, and neoplastic lesions in various organ systems. Normal and variations of "normal" histology will also be illustrated. Each atlas will focus on visual diagnostic criteria and differential diagnosis. It will be organized to provide quick access to images of lesions in specific organs or sites. Each atlas will adapt the well-known and widely accepted terminology, nomenclature, classification schemes, and staging algorithms. Each volume in this series will be authored by nationally and internationally recognized pathologists. Each volume will follow the same organizational structure. The first Section will include normal histology and normal variations. The second Section will cover congenital defects and malformations. The third Section will cover benign and inflammatory lesions. The fourth Section will cover benign tumors and benign mimickers of cancer. The last Section will cover malignant neoplasms. Special emphasis will be placed on normal histology, gross anatomy, and gross lesion appearances since these are generally lacking or inadequately illustrated in current textbooks. The detailed figure legends will concisely summarize the critical information and visual diagnostic criteria that the pathologist must recognize, understand, and accurately interpret to arrive at a correct diagnosis. This book series is intended chiefly for use by pathologists in training and practicing surgical pathologists in their daily practice. The atlas series will also be a useful resource for medical students, cytotechnologists, pathologist assistants, and other medical professionals with special interest in anatomic pathology. Trainees, students, and readers at all levels of expertise will learn, understand, and gain insights into the complexities of disease processes through this comprehensive resource. Macroscopic and histological images are aesthetically pleasing in many ways. This new series will serve as a virtual pathology museum for the edification of our readers.

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*To my family – Michael, Rebecca, Deborah, Daniel, and Jessica, with much love.*

Puay Hoon Tan

*To my husband, Toraman, and son, Onur, for their endless love and support, which have shown me what is important in life.*

Aysegul Sahin

# Series Preface

One Picture Is Worth Ten Thousand Words— Frederick Barnard, 1927

Remarkable progress has been made in anatomic and surgical pathology during the last 10 years. The ability of surgical pathologists to reach a definite diagnosis is now enhanced by immunohistochemical and molecular techniques. Many new clinically important histopathologic entities and variants have been described using these techniques. Established diagnostic entities are more fully defined for virtually every organ system. The emergence of personalized medicine has also created a paradigm shift in surgical pathology. Both promptness and precision are required of modern pathologists. Newer diagnostic tests in anatomic pathology, however, cannot benefit the patient unless the pathologist recognizes the lesion and requests the necessary special studies. An up-to-date Atlas encompassing the full spectrum of benign and malignant lesions, their variants, and evidence-based diagnostic criteria for each organ system is needed. This Atlas is not intended as a comprehensive source of detailed clinical information concerning the entities shown. Clinical and therapeutic guidelines are served admirably by a large number of excellent textbooks. This Atlas, however, is intended as a "first knowledge base" in the quest for definitive and efficient diagnosis of both usual and unusual diseases.

The *Atlas of Anatomic Pathology* is presented to the reader as a quick reference guide for diagnosis and classification of benign, congenital, inflammatory, nonneoplastic, and neoplastic lesions organized by organ systems. Normal and variations of "normal" histology are illustrated for each organ. The Atlas focuses on visual diagnostic criteria and differential diagnosis. The organization is intended to provide quick access to images and confirmatory tests for each specific organ or site. The Atlas adopts the well-known and widely accepted terminology, nomenclature, classification schemes, and staging algorithms.

This book Series is intended chiefly for use by pathologists in training and practicing surgical pathologists in their daily practice. It is also a useful resource for medical students, cytotechnologists, pathologist assistants, and other medical professionals with special interest in anatomic pathology. We hope that our trainees, students, and readers at all levels of expertise will learn, understand, and gain insight into the pathophysiology of disease processes through this comprehensive resource. Macroscopic and histological images are aesthetically pleasing in many ways. We hope that the new Series will serve as a virtual pathology museum for the edification of our readers.

Indianapolis, IN, USA — Liang Cheng, MD

# Preface

Breast pathology is key to the diagnosis and management of breast diseases. Interpretation of breast histologic findings constitutes a significant proportion of the daily workload of the surgical pathologist. This task can be challenging and demanding because diagnostic categorization is used to select treatment from a potentially diverse range of options, and the diagnosis of borderline and malignant lesions raises patient anxieties.

In this atlas, we use our collective experience in diagnostic breast pathology to present a pictorial narrative of a wide range of breast conditions that are grouped together along broad themes and histologic patterns, focusing on differential diagnoses and their illustrations. Important morphologic similarities and differences are compared and contrasted through a series of representative photomicrographs, with adjunctive immunohistochemistry used to offer additional support for specific diagnoses. Where relevant, molecular alterations that are characteristic of certain breast lesions are described.

There are many excellent breast pathology textbooks available today that offer encyclopaedic information on a comprehensive list of breast conditions. Our aim in writing this atlas is not to replace or compete with these available textbooks, but to provide a quick visual reference for the practicing surgical pathologist during evaluation of breast lesions. Concise text and explanatory legends accompany the illustrations, many of which are photomicrographs of conditions that could potentially be mistaken for the entity being described; these are arranged together to highlight their differences. Microscopic nuances that help weigh towards certain diagnoses are articulated. Because this is intended to be a working atlas, the list of entities is not exhaustive, including only those that form part of the differential diagnostic spectrum. Some lesions appear in different chapters, illustrating their morphologic heterogeneity.

We hope that this atlas will be a useful microscope tableside companion for the busy surgical pathologist, who could pick it up and have a quick and convenient pictorial guide to differential diagnoses of challenging breast lesions. Pathologists are by nature visual beings, and we trust that the illustrations in this atlas will be enjoyed, much as we delighted in putting them together.

Singapore, Singapore — Puay Hoon Tan
Houston, TX, USA — Aysegul A. Sahin

# Acknowledgments

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We are indebted to our colleagues in the breast pathology teams of the Department of Anatomical Pathology, Singapore General Hospital, Singapore, and the MD Anderson Cancer Center, Houston, Texas, for the camaraderie and generous sharing of interesting and challenging breast pathology cases which have contributed to the wealth of material that form, and continue to add to, a great educational resource in breast pathology.

# Contents

# Normal Breast and Physiological Changes

1

The breast is a modified sweat gland located in the superficial fascia of the anterior chest wall. The mature female breast has a distinctive protuberant, mound-shaped, or conical form and covers the area from the second or third rib to the sixth or seventh rib (Fig. 1.1). The nipple projects from the anterior surface and consists mainly of dense fibrous tissue covered by hyperpigmented skin and contains bundles of smooth muscle fibres. The skin immediately surrounding the nipple, called the areola, is also more pigmented than the rest of the breast skin. The areola contains sebaceous glands and numerous sensory nerve endings but lacks pilosebaceous units and hair (Figs. 1.2 and 1.3).

The breast is made up of glandular and ductal elements embedded within fibrofatty tissue with a ratio of glandular to fibrofatty tissue that varies among individuals (Fig. 1.4) [1]. In addition, with the onset of menopause and decreased oestrogen levels, the relative amount of fatty tissue increases as the glandular tissue diminishes. The breast ductal system consists of 15–20 branching ducts, which radiate from the nipple to continue to the functional units of the breast, the terminal ductal lobular units (TDLUs) (Fig. 1.5). The TDLUs consist of the intralobular ducts and round saccules called ductules, which differentiate into the secretory units or acini during pregnancy and lactation. The terms ductules and acini are often used interchangeably. Individual TDLUs vary greatly in size and typically enlarge to become functional during lactation (Fig. 1.6). The TDLUs are embedded in specialised, hormonally responsive connective tissue stroma called intralobular stroma (Fig. 1.7) [2–8]. The largest amount of breast parenchyma is located in the upper outer quadrant, where the majority of cancers develop. An axillary tail of breast tissue often extends into the axilla. Before puberty, female and male breasts have the same appearance. The structure of the breast is under the influence of hormones, growth, and differentiation factors. When puberty begins in females, mammary ducts branch out, terminal duct buds are formed, and the stromal component (mainly adipose tissue) of the breast proliferates. Both stroma and epithelium undergo changes during the menstrual cycle, pregnancy, lactation, and menopause. During male puberty, breast development is limited to rudimentary large duct development without breast enlargement.

The mammary epithelium is ectodermally derived. Small segments of lactiferous duct orifices at the nipple are lined by

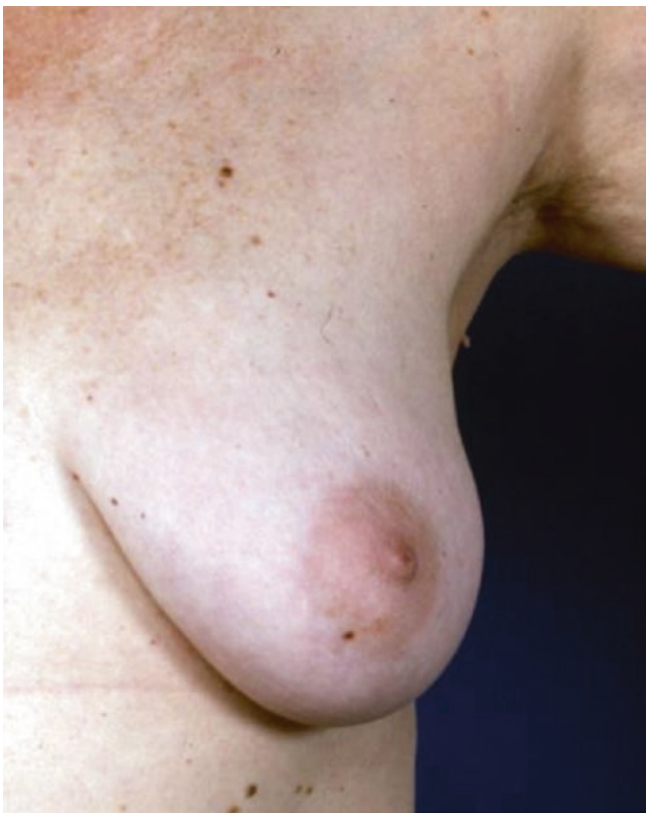

**Fig. 1.1** Normal adult female breast. Photograph of a normal female prior to undergoing prophylactic mastectomy



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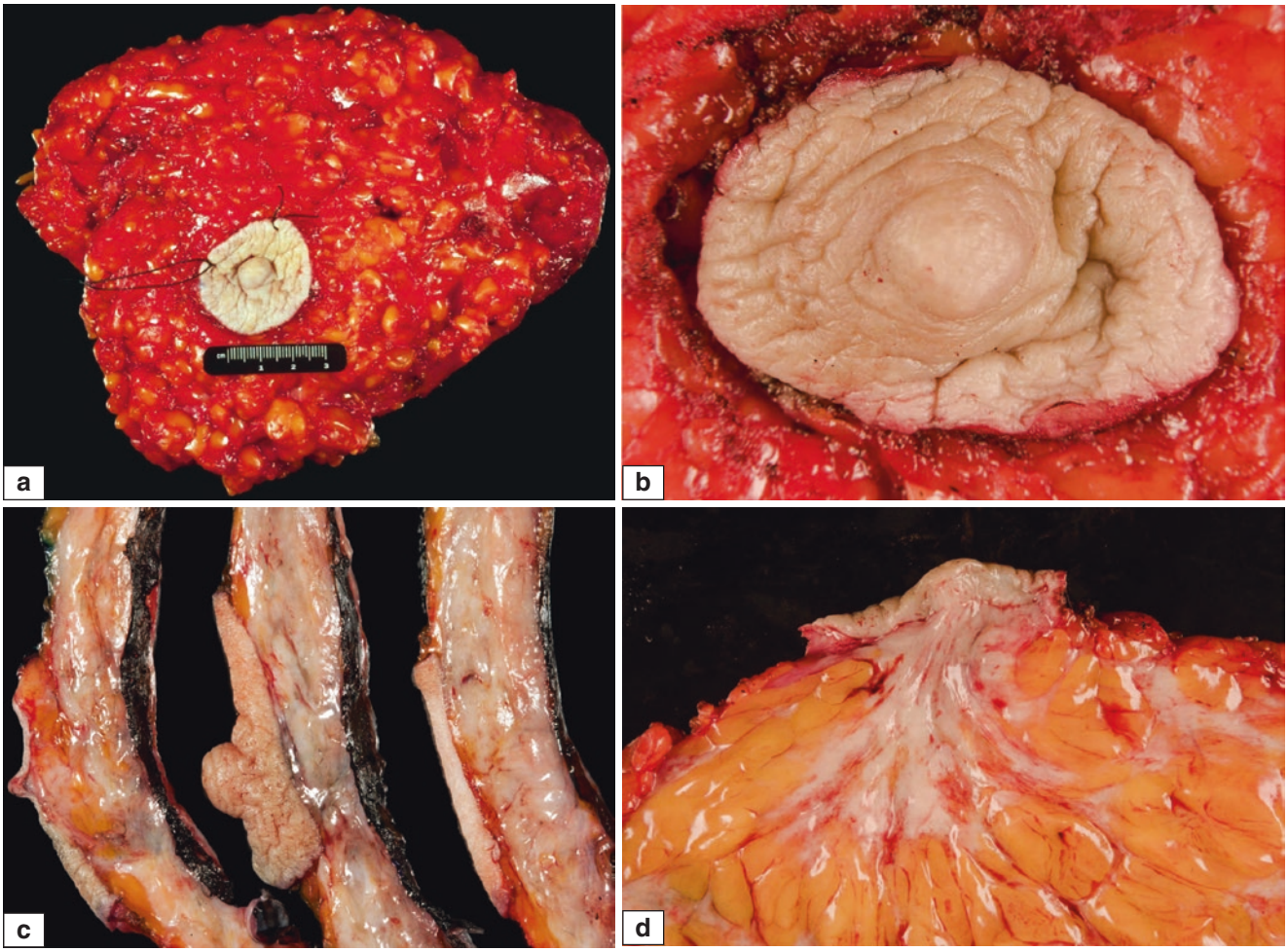


**Fig. 1.2** Normal adult female breast. Gross features. (**a**) Skin-sparing total mastectomy specimen showing full extension of breast tissue with the nipple located in the normal central position. (**b**) Higher magnification of the nipple-areolar complex. (**c**) Cut section through the nipple shows dense subareolar fibrous connective tissue. (**d**) Higher magnification of (**c**) showing subareolar fibrous tissue radiating into the fatty breast parenchyma

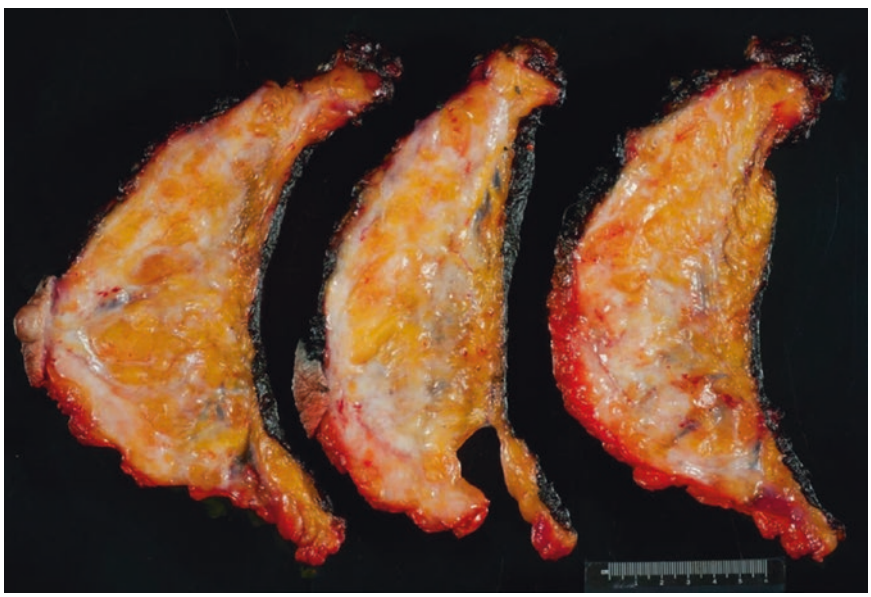

**Fig. 1.3** Normal adult female breast. Gross features. Cut sections of breast mastectomy specimen. The ratio of fat to fibrous tissue is variable and correlates with mammographic density

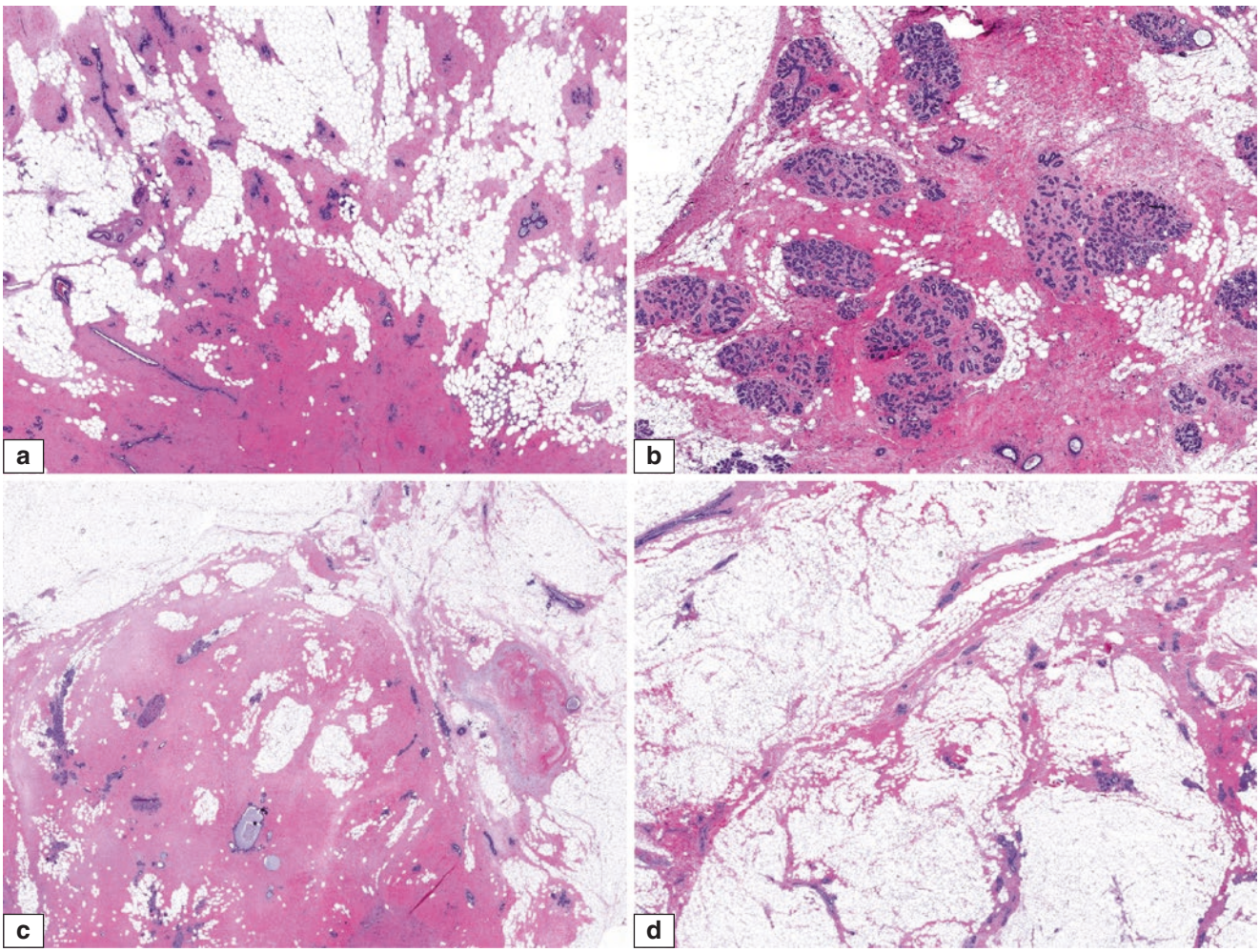


**Fig. 1.4** Normal adult female breast. Histologic features. (**a–d**) H&E sections showing varying ratios of fat to fibrous tissue in stroma and various amounts of glandular elements from different cases

squamous epithelium, while the rest of the breast ductal system is lined by two cell layers, inner luminal cells and outer myoepithelial cells, surrounded by the basement membrane (Fig. 1.8). Extension of squamous epithelium beyond lactiferous duct orifices represents squamous metaplasia. The luminal cells are usually low columnar to cuboidal, and myoepthelial cells are located between luminal cells and the basement membrane. The myoepithelial cells are often ovoid to spindle shaped and have scant cytoplasm. The mammary ducts and lobules are embedded in fibrofatty stroma. Interlobular stroma contains adipose tissue, fibroblasts and elastic fibres. Scant inflammatory cells, including lymphocytes, plasma cells, mast cells, and histiocytes, are commonly seen. Rarely, stromal cells show prominent myoid differentiation (Fig. 1.9). The intralobular stroma is usually loose and more cellular than the interlobular stroma, and unlike the interlobular stroma, it usually does not have adipose tissue. Intralobular stroma is hormone sensitive and shows cyclic histologic changes.

## Physiological Changes

### Menstrual Cyclic Changes

Both stromal and glandular components of the breast undergo histologic changes during the menstrual cycle. However, these changes are not distinct and specific, unlike changes observed in endometrial epithelium during the menstrual cycle [6–8]. In general, during the proliferative phase (days 3–7), the stroma is dense and hypovascular. Crowded and poorly oriented ductal epithelial cells line the acini, and mitoses are easily found, while myoepithelial cells are inconspicuous. Acinar lumens are closed and no secretion is found. In the follicular phase (days 8–14), epithelial cells become columnar, mitotic activity decreases, acinar lumens form but no secretion is evident, and myoepithelial cells become easily identifiable at the periphery of acini. During the secretory phase (days 15–27), myoepithelial cells become

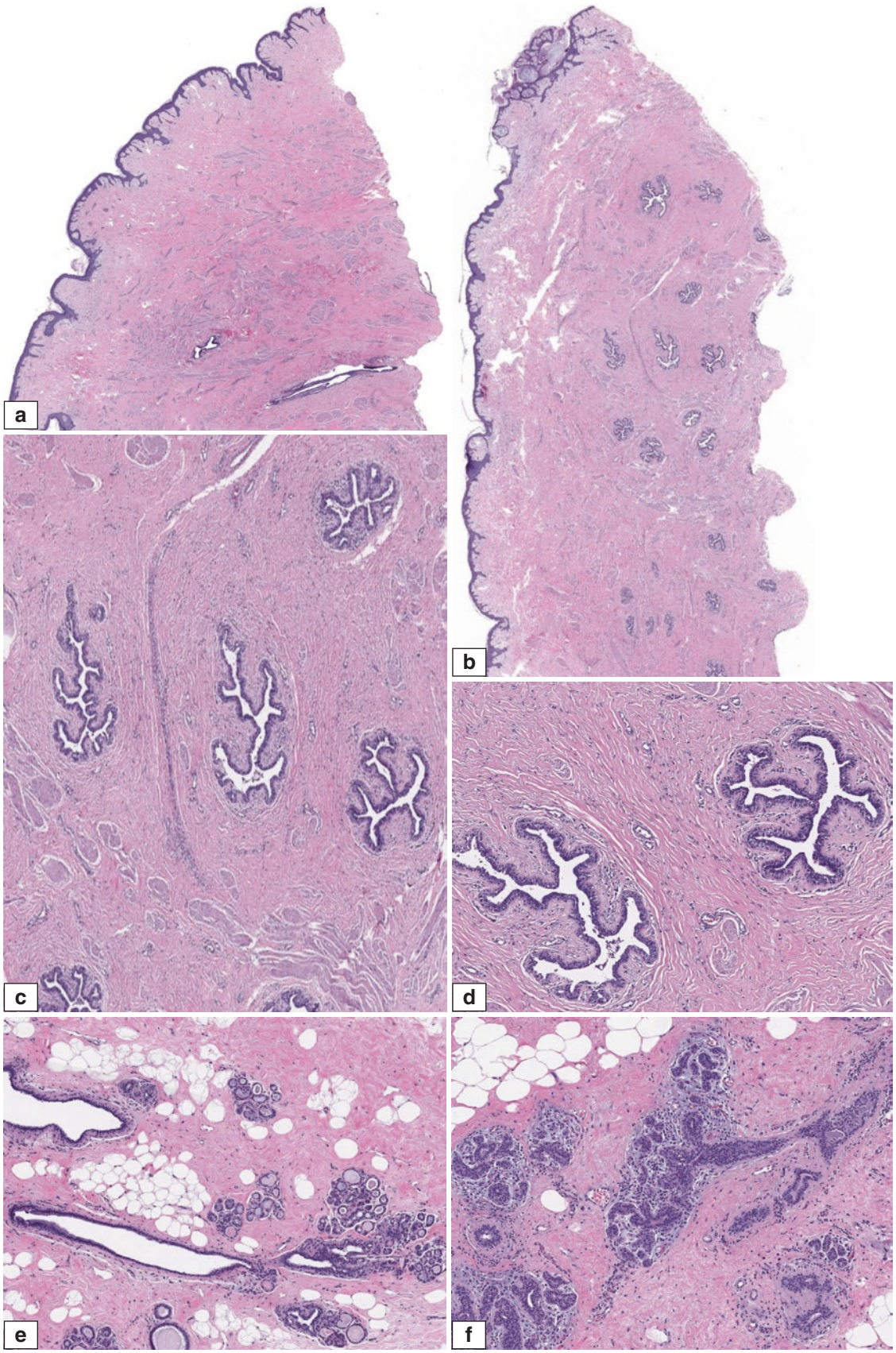


**Fig. 1.5** Normal adult female breast. Histologic features. (**a–d**) H&E sections of the nipple-areolar complex showing nipple or lactiferous ducts extending from the skin surface into the breast parenchyma. The lactiferous ducts show a branching shape and are lined by bilayered epithelium (luminal epithelial and outer myoepithelial cells). There may be stromal folds protruding into the ductal lumens which should not be mistaken for a papillary lesion. Smooth muscle bundles are seen among the lactiferous ducts. (**e**, **f**) Terminal ductal lobular unit, which is the functional unit of breast parenchyma, consists of a feeding duct with branching acini embedded in connective tissue

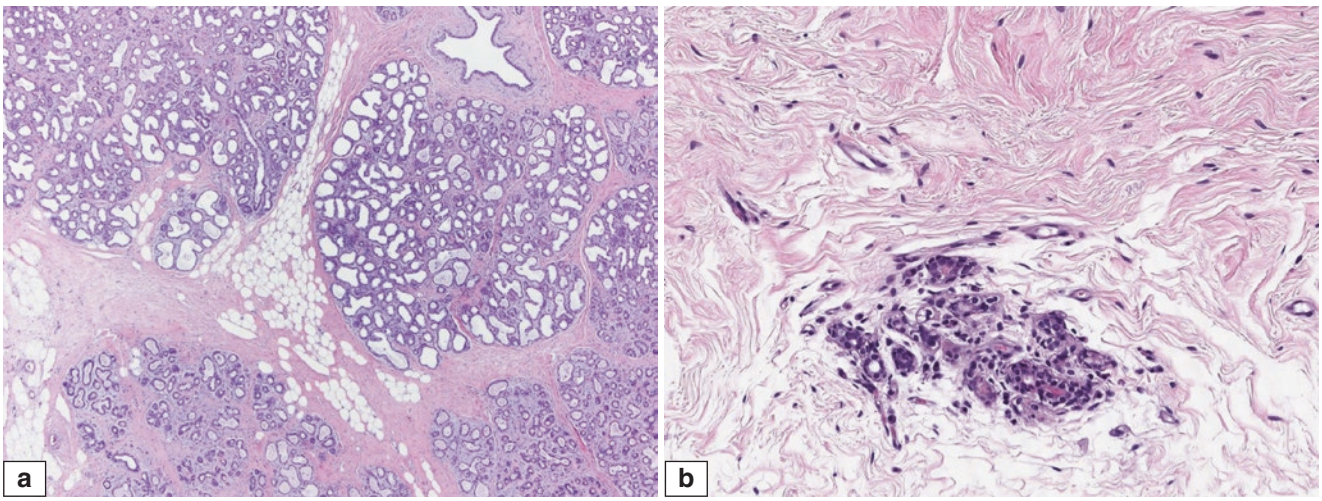


**Fig. 1.6** Normal adult female breast with physiological changes. Histologic features. (**a**) Expanded terminal ductal lobular unit of a lactating breast comprises an increased number of acini with luminal secretions. (**b**) Atrophic terminal ductal lobular unit of a postmenopausal female

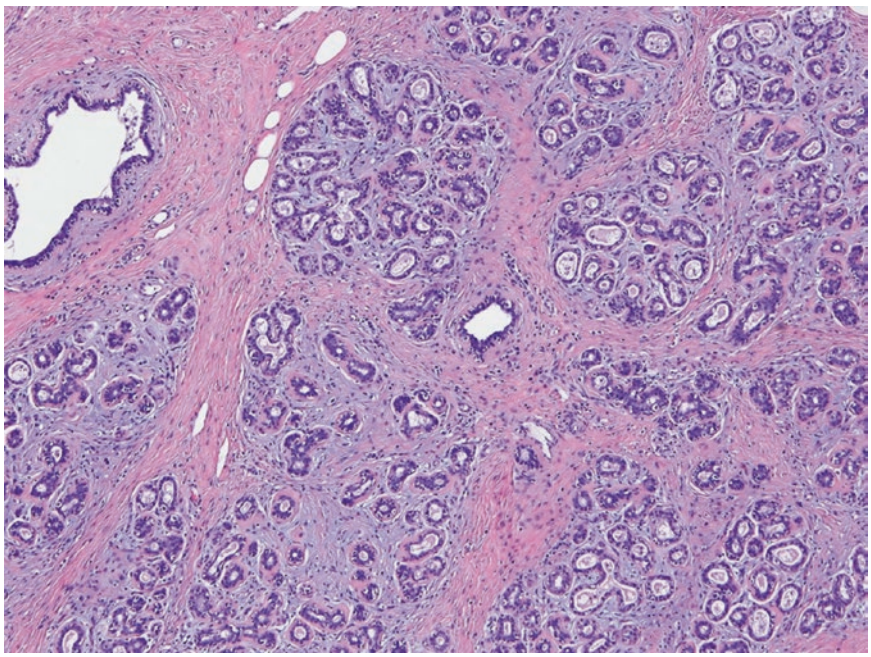

**Fig. 1.7** Normal adult female breast. Histologic features. Intralobular stroma shows a loose myxoid appearance, with less collagenisation compared to interlobular fibrous tissue

more prominent with their clear cytoplasm, lumens are open and contain variable amounts of secretions, and the stroma becomes loose and oedematous. The late secretory and early menstrual phase (days 28–2) is characterised by regression of lobules with the stroma becoming compact and may contain inflammatory cells (Fig. 1.10) [9–11].

## Pregnancy- and Lactation-Related Changes

As a consequence of hormonal changes, the breast tissue becomes fully mature and functional during pregnancy and lactation. During pregnancy, terminal ducts and lobular acini grow progressively, resulting in lobular enlargement, whereas stromal components decrease (Figs. 1.11 and 1.12). The cytoplasm of acinar cells becomes vacuolated and secretions accumulate in the lumens. During lactation, lobular acinar lumens become distended with abundant secretions. The lobular acinar epithelium contains numerous lipid vacuoles and has a characteristic "hobnail" appearance (Fig. 1.13). The myoepithelial cells become inconspicuous.

Lobular regression happens when lactation ceases. The lobular epithelium becomes flat, interlobular stroma increases and may contain lymphocytes and plasma cells.

The process takes several months to complete and occurs in a heterogeneous fashion. While some lobules show complete involution, others may still show lactational changes for several months and even a year after cessation of lactation.

## Menopause-Related Changes

With the onset of menopause, the number and cellularity of lobules decrease (Fig. 1.14). In older women, only ducts may remain. Atrophic acini may become cystic and calcifications are commonly found in these cystic acini. Intralobular stroma becomes fibrocollagenous and generalised fatty replacement of stroma occurs progressively. Postmenopausal hormone replacement therapy stimulates breast epithelium and may increase breast density.

## Calcifications

Deposition of calcium salts in breast tissue is called calcifications in the breast. Based on the mammographic appearance of calcifications, they can be categorised into three groups: (1) those typically associated with benign lesions, (2) those that are most likely associated with malignant lesions, and (3) indeterminate ones (Fig. 1.15) [12, 13]. Calcifications associated with benign lesions include eggshell, large, coarse, and rod-like calcifications. In addition, skin and vascular calcifications can be identified as benign on mammograms. There is a high probability that pleomorphic, heterogeneous, linear, or branching (casting) calcifications will be associated with malignant lesions. Amorphous and indistinct calcifications are classified as indeterminate. Calcifications in the breast are also categorised based on their distribution. Grouped or clustered calcifications are small areas of calcifications which are common in many benign proliferations, but are also associated with a moderately increased likelihood of malignancy [14–16]. Diffuse scattered calcifications are randomly distributed in breast parenchyma and are almost always associated with benign lesions or normal breast parenchyma. Segmental calcifications are distributed in a duct and their branches and are frequently associated with intraductal epithelial proliferations. In situ carcinomas associated with comedonecrosis are frequently associated with "castlike" microcalcifications [17–20]. If there is a mass associated with microcalcifications, the imaging appearance of the mass is very important

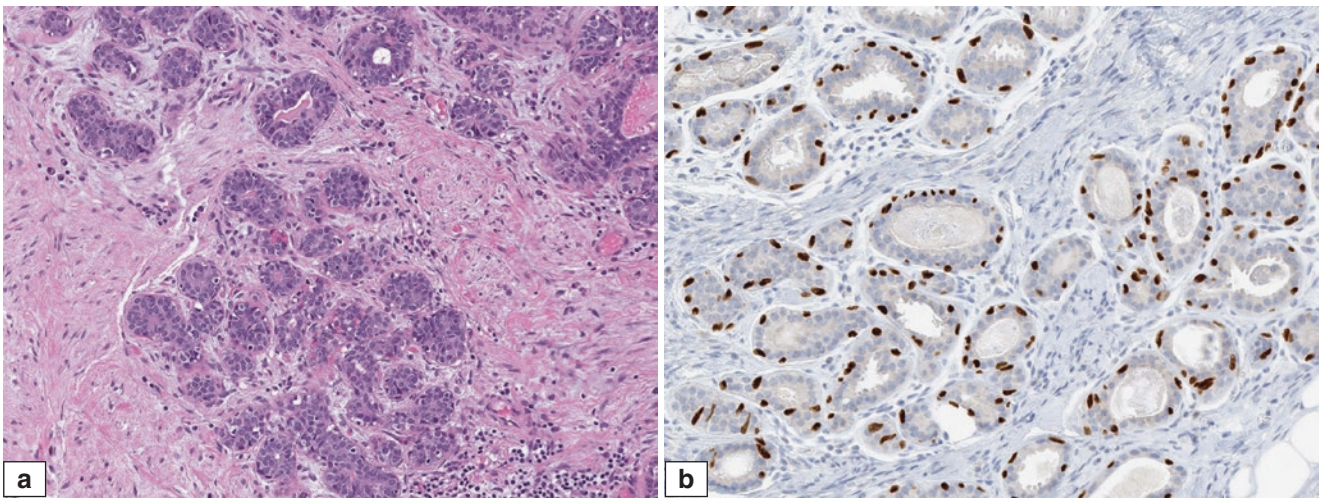


**Fig. 1.8** Normal adult female breast. Histologic and immunohistochemical features. (**a**) A lobule composed of multiple acini. The luminal epithelial cells are surrounded by myoepithelial cells, some of which have clear cytoplasm. (**b**) Immunohistochemical staining for p63 highlights myoepithelial cell nuclei

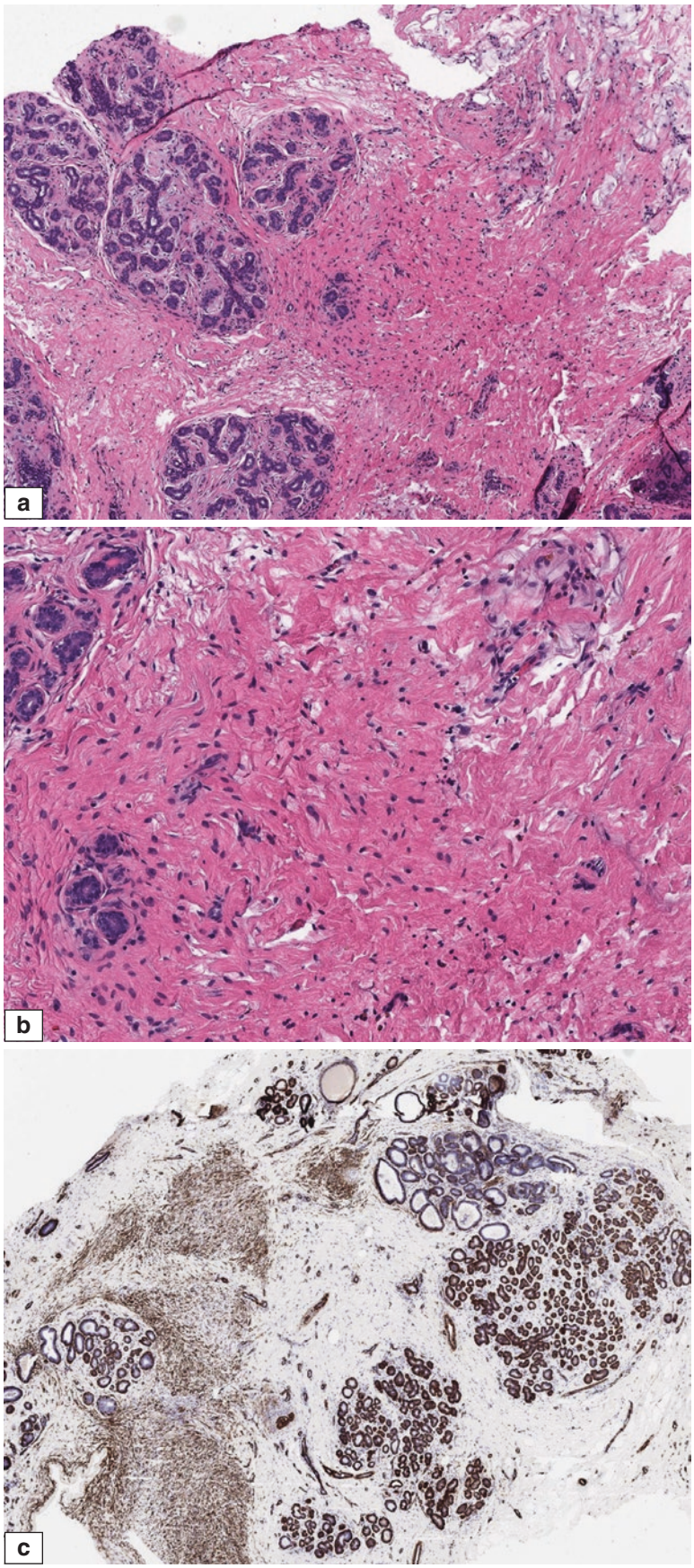


**Fig. 1.9** Normal adult female. (**a**, **b**) Stroma shows myoid cells in addition to fibroblasts. (**c**) Spindle cells with myoid differentiation show immunoreactivity for smooth muscle myosin

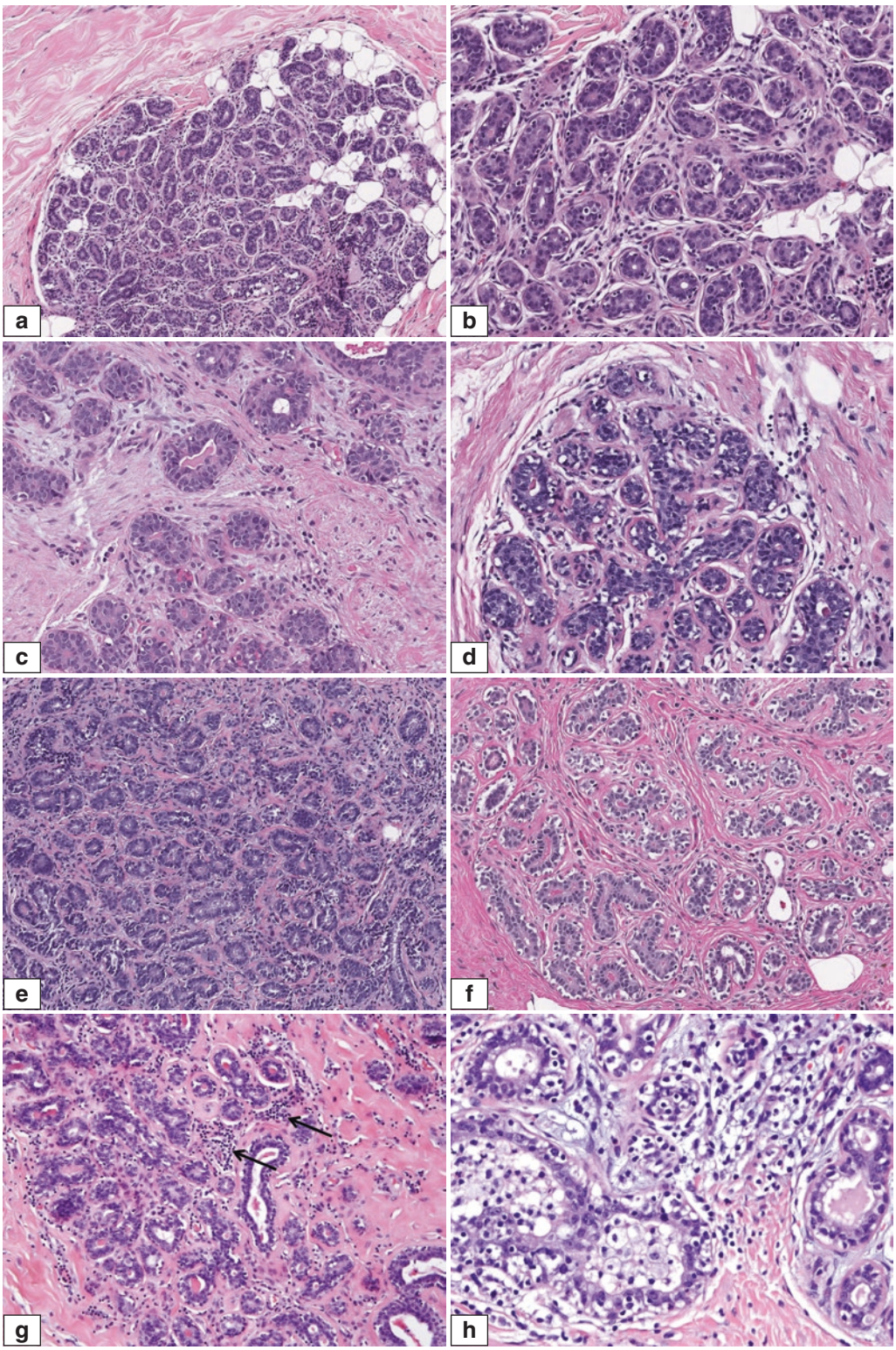


**Fig. 1.10** Normal adult female breast. Histologic features of menstrual cycle phases. (**a**) Proliferative phase: H&E section shows lobular unit composed of tightly packed acini. (**b**) Acini are lined by crowded, poorly oriented cells with little or no lumen formation. No secretion is evident. The intralobular stroma is dense and cellular. (**c**) Follicular phase: H&E shows cells lining the acini becoming columnar with central lumens that are apparent. (**d**) Lumens have minimal secretions. (**e**) Secretory phase: Acini have open lumens which contain secretions. (**f**) The lobular stroma is loose. Both epithelial and myoepithelial cells are distinct. (**g**) Closing of the cycle: Small acini associated with dense stroma which contains inflammatory cells (*arrows*). (**h**) Higher magnification shows distinct clear-cell appearances of peripheral myoepithelial cells