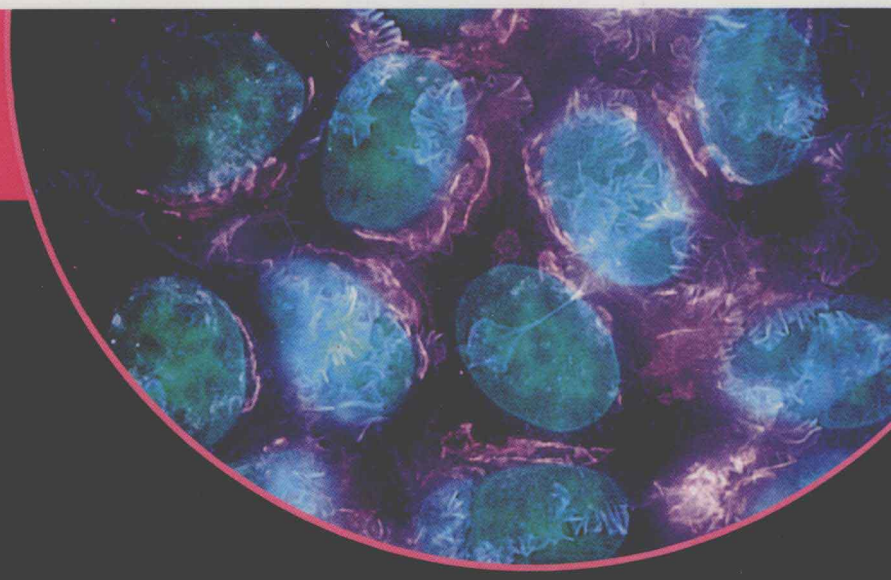

Early Diagnosis and Treatment of Cancer

BREAST

EDITED BY
Lisa Jacobs and Christina A. Finlayson

SERIES EDITOR
Stephen C. Yang

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EARLY DIAGNOSIS AND TREATMENT OF CANCER

Series Editor: Stephen C. Yang, MD

Breast Cancer

Edited by

Lisa Jacobs, MD
Associate Professor
Department of Surgery
Johns Hopkins University School of Medicine
Baltimore, Maryland

Christina A. Finlayson, MD
Professor
Department of Surgery
University of Colorado School of Medicine
Aurora, Colorado

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ELSEVIER

SAUNDERS
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1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

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To all women who have participated in clinical trials. These are the true heroes of breast cancer research; their courage and generosity have paved the way for each improvement in breast cancer therapy.

L.J.
C.A.F.

To my daughters Catherine and Elizabeth in the hopes that the continuing research prevents them from ever facing this disease.

L.J.

Endless thanks to my parents, Richard and Ann Finlayson, without whom I would have never started on this path, and my husband, Emerson Lomaquahu, whose love and support keep me going.

C.A.F.

Series Preface

Seen on a graph, the survival rate for many cancers resembles a precipice. Discovered at an early stage, most cancers are quickly treatable, and the prognosis is excellent. In late stages, however, the typical treatment protocol becomes longer, more intense, and more harrowing for the patient, and the survival rate declines steeply. No wonder, then, that one of the most important means in fighting cancer is to prevent or screen for earlier stage tumors.

Within each oncologic specialty, there is a strong push to identify new, more useful tools for early diagnosis and treatment, with an emphasis on methods amenable to an office-based or clinical setting. These efforts have brought impressive results. Advances in imaging technology, as well as the development of sophisticated molecular and biochemical tools, have led to effective, minimally invasive approaches to cancer in its early stages.

This series, *Early Diagnosis and Treatment of Cancer*, gathers state-of-the-art research and recommendations into compact, easy-to-use volumes. For each particular type of cancer, the books cover the full range of diagnostic and treatment procedures, including pathologic, radiologic, chemotherapeutic, and surgical methods, focusing on questions like these:

- What do practitioners need to know about the epidemiology of the disease and its risk factors?
- How do patients and their families wade through and interpret the myriad of testing?
- What is the safest, quickest, least invasive way to reach an accurate diagnosis?
- How can the stage of the disease be determined?
- What are the best initial treatments for early-stage disease, and how should the practitioner and the patient choose among them?
- What lifestyle factors might affect the outcome of treatment?

Each volume in the series is edited by an authority within the subfield, and the contributors have been chosen for their practical skills as well as their research credentials. Key Points at the beginning of each chapter help the reader grasp the main ideas at once. Frequent illustrations make the techniques vivid and easy to visualize. Boxes and tables summarize recommended strategies, protocols, indications and contraindications, important statistics, and other essential information. Overall, the attempt is to make expert advice as accessible as possible to a wide variety of health care professionals.

For the first time since the inception of the National Cancer Institute's annual status reports, the 2008 "Annual Report to the Nation on the Status of Cancer," published in the December 3 issue of the *Journal of the National Cancer Institute*, noted a statistically significant decline in "both incidence and death rates from all cancers combined." This mark of progress encourages all of us to press forward with our efforts. I hope that the volumes in *Early Diagnosis and Treatment of Cancer* will make health care professionals and patients more familiar with the latest developments in the field, as well as more confident in applying them, so that early detection and swift, effective treatment become a reality for all of our patients.

Stephen C. Yang, MD
The Arthur B. and Patricia B. Modell
Professor of Thoracic Surgery
Chief of Thoracic Surgery
The Johns Hopkins Medical Institutions
Baltimore, Maryland

Preface

Breast cancer is the most common malignancy to occur in women. It is estimated that in 2009 approximately 192,500 women were diagnosed with invasive breast cancer and 62,300 were diagnosed with in situ disease. Breast cancer is the second most common cause of cancer death in women, with an estimated 40,000 women dying of the disease in 2009. The combination of the high incidence of the disease, strong grassroots advocacy, and consistent, focused research has resulted in numerous advances in the treatment of breast cancer over the past several decades. In this book we provide a comprehensive review of current recommendations for the clinical management of early breast cancer, including prevention, diagnosis, and treatment. We also include some of the new and innovative interventions on the horizon that have not yet become standard.

The battle against breast cancer mortality begins with prevention. The decision to pursue breast cancer prevention must be based on an accurate assessment of risk, and this risk assessment is aided by risk assessment models. For patients at very high risk, genetic assessment with germ-line gene mutation testing such as BRCA becomes important. Even for those patients without a genetic mutation or at low risk for a mutation, interventions for breast cancer prevention may still be desirable. Previously, surgery was the only option for risk reduction, but now hormonal therapies are available. In addition, evidence is building for lifestyle changes that each individual woman can adopt to reduce her personal risk of developing breast cancer. These options provide the patient and the physician with a range of effective risk reduction strategies that can then be selected to meet the patient's desired level of risk reduction while taking into consideration the risks and process involved in the strategy. It is possible that new biomarkers will be developed that will further improve risk assessment for individual patients and further allow us to tailor our recommendations for prevention based on the degree of risk and potentially to select the mechanism of prevention most effective for a given patient.

Diagnostic evaluations of patients at risk for breast cancer are also evolving, and controversial changes in screening recommendations have recently been published. The goal of screening is to diagnose and treat patients with breast cancer before there has been systemic spread. The biggest challenge with our current screening techniques is the high rates of false positives. These result in a large number of women undergoing biopsies for benign disease. Another challenge in our screening process is the diagnosis and management of ductal carcinoma in situ (DCIS). Although we are able to identify DCIS as a very early breast cancer, the natural history of this disease process is not well understood, and the need to pursue aggressive treatment is being questioned. This has prompted some groups to recommend changes in the screening recommendations to reduce the number of patients with DCIS who are diagnosed and treated. Methods of screening and diagnostic imaging are included in this text to further define the current standard of care.

Pathologic assessment of diagnostic tissue and surgical specimens is critical to understanding the prognosis for the patient and for making treatment recommendations to the patient. Stage of diagnosis based on the Tumor, Node, Metastasis (TNM) staging system provides basic prognostic information on which many treatment recommendations are made. We fortunately now have other prognostic markers such as grade and Ki-67 and genetic markers such as oncotype DX that provide further prognostic accuracy and allow more informed treatment recommendations. The importance of pathologic assessment in the treatment recommendations for patients supports the extensive review of pathologic assessment included in this text.

The treatment of breast cancer continues to be based on surgery, chemotherapy, hormonal therapy, and radiation therapy: each approach remains a mainstay in the overall treatment

plan. Modifications in the recommendation for each of these components are based on estimates of local, regional, or systemic recurrence. Each of these therapies has become more targeted. Surgical management now involves improved selection for breast preservation by using improved diagnostic tests and neoadjuvant therapy to encourage patients to seek breast preservation. The broad improvements in screening, diagnosis, and systemic therapies have allowed surgeons to decrease the extent of surgical therapies both in the regional nodal basin and in the breast. The same concepts apply to the use of radiation therapy. The selection of patients for elimination of radiation therapy or reduction in the extent of radiation therapy has become possible through research in patient selection and improvements in radiation therapy techniques that reduce complications, field of exposure, and time commitment required for treatment. Systemic adjuvant therapies have also become more targeted, with far more patients avoiding chemotherapy with the use of hormonal therapy. In addition, newer systemic agents that provide improved systemic control with reduced risk are being utilized. The selection of patients for systemic hormonal therapy now has many additional possibilities, and patients and their physicians are able to select their treatment choices based on therapeutic benefit and side effect profile in a much more informed manner.

Prevention, diagnosis, and management of breast cancer are all continually evolving, and we include each of these subjects in this book. One of the most satisfying aspects of caring for patients with breast disease is that in each step of the process we are able to offer a variety of options with differing levels of risk and benefit. Patients and their health care providers are able to weigh the risks and benefits of their options and then make well-informed decisions. This is the result of an extensive research effort into all aspects of breast cancer prevention, diagnosis, and treatment. Fortunately, even with the array of options currently available, even more are on the horizon that promise further reductions in risk by more targeted therapies, better predictors of risk of disease development or progression through biomarkers, and improved diagnostic accuracy.

Lisa Jacobs, MD
Christina A. Finlayson, MD

Contributors

Benjamin O. Anderson, MD
Professor of Surgery and Global Health-Medicine, University of Washington; Joint Member, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center; Director, Breast Health Clinic, Seattle Cancer Care Alliance, Seattle, Washington

Erica D. Anderson, BS, MD
Assistant Professor, Emory University School of Medicine, Atlanta, Georgia

Jennifer E. Axilbund, MS
Research Associate in Oncology, Johns Hopkins University; Senior Genetic Counselor, Johns Hopkins Hospital, Baltimore, Maryland

Brian Bagrosky, MD
Department of Diagnostic Radiology, University of Colorado School of Medicine, Aurora, Colorado

Virginia F. Borges, MD
Associate Professor, Department of Medicine, University of Colorado School of Medicine; Director, Young Women's Breast Cancer Translational Program, University of Colorado Cancer Center, Aurora, Colorado

James P. Borgstede, MD
Professor and Vice Chairman, Department of Radiology, University of Colorado School of Medicine, Aurora, Colorado

Daniel Bowles, MD
Fellow in Hematology and Medical Oncology, University of Colorado School of Medicine, Aurora, Colorado

Susanne Briest, MD
Director, Breast Cancer Program, University of Leipzig, Leipzig, Germany

Kristine E. Calhoun, MD
Assistant Professor, Department of Surgery, Division of General Surgery, Section of Surgical Oncology, University of Washington School of Medicine, Seattle, Washington

Judy L. Chavez, RT(R)(M)(BS), RDMS
Supervisor, Breast Procedure Suite, Centrum Surgical Center, In affiliation with Invision/Sally Jobe Breast Care Network and Radiology Imaging Associates, Greenwood Village, Colorado

Chin-Yau Chen, MD
Department of Surgery, Taipei City Hospital Zhong Xing Branch, Taipei, Taiwan

Alex Colque, MD
Plastic Surgery Fellow, The Methodist Hospital, Houston, Texas

Lisa Ware Corbin, MD
Associate Professor, Department of Medicine, University of Colorado School of Medicine, Aurora; Medical Director, The Center for Integrative Medicine, University of Colorado School of Medicine, Aurora, Colorado

Donald C. Doll, MD
Staff Physician, Division of Hematology, Oncology Section, James A. Haley Veterans Hospital, Tampa, Florida

Anthony D. Elias, MD
Martha Cannon Dear Professor, Department of Medicine, University of Colorado School of Medicine, University of Colorado Cancer Center, Aurora, Colorado

Christina A. Finlayson, MD
Professor, Department of Surgery, University of Colorado School of Medicine, Aurora, Colorado

Michael Ford, MD
Department of Surgery, University of Colorado School of Medicine, Aurora, Colorado

Timothy George, MD
Fellow, Johns Hopkins University School of Medicine; Department of Surgery, Johns Hopkins Hospital, Baltimore, Maryland

Nancy S. Goldstein, DNP, CRNP, RNC
The Johns Hopkins University School of Nursing, Baltimore, Maryland

Amy L. Gross, MHS
Johns Hopkins School of Public Health, Baltimore, Maryland

Lara Hardesty, MD
Associate Professor, Department of Radiology, University of Colorado School of Medicine; Director, Breast Imaging, University of Colorado Hospital, Aurora, Colorado

Lisa Jacobs, MD
Associate Professor, Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland

Peter Kabos, MD
Assistant Professor, Department of Medicine, University of Colorado School of Medicine, Aurora, Colorado

Terese I. Kaske, MD
Radiologist, Breast Imaging Specialist, RIA/Invision Sally Jobe, Englewood, Colorado

M. Catherine Lee, MD
Assistant Professor of Surgery, Division of Oncologic Sciences, University of South Florida School of Medicine, Tampa; Assistant Member, Comprehensive Breast Program, Moffit Cancer Center and Research Institute, Tampa, Florida

John M. Lewin, MD
Section Chief, Breast Imaging, Diversified Radiology of Colorado, PC; Medical Director, Rose Breast Center, Denver, Colorado

Scott W. McGee, MD
Assistant Clinical Professor, Northeastern Ohio Universities, College of Medicine; Akron General Partners Physician Group, Oncology, Akron General Medical Center, Akron, Ohio

Lee Myers, PhD
Senior Clinical Physicist, Johns Hopkins University, Baltimore, Maryland

Samia Nawaz, MD
Associate Professor, Department of Pathology, University of Colorado School of Medicine, Aurora; Staff Pathologist, VA Medical Center, Denver, Colorado

Steve H. Parker, MD
Staff Pathologist, Sally Jobe Breast Center, Greenwood Village, Colorado

Elizabeth Prier, MD
General Surgeon, Private Practice, Boise Surgical Group, Boise, Idaho

Rachel Rabinovitch, MD
Professor, Department of Radiation Oncology, University of Colorado School of Medicine, University of Colorado Cancer Center, Aurora, Colorado

Jon V. Rittenbach, MD
Clinical Laboratory Director and Pathologist (AP/CP), Providence Saint Mary Medical Center; Pathologist, Walla Walla General Hospital; Pathologist, Walla Walla VA Medical Center; Davis-Sameh-Meeker Laboratories, Walla Walla, Washington

Michael S. Sabel, MD
Associate Professor of Surgery, University of Michigan, Ann Arbor, Michigan

Edward R. Sauter, MD, PhD, MHA
Professor of Surgery and Associate Dean for Research, University of North Dakota School of Medicine and Health Sciences, Grand Forks; Surgical Oncologist and General Surgeon, Meritcare Health System, Fargo, North Dakota, and Thief River Falls, Minnesota

Meenakshi Singh, MD
Professor and Vice Chair for Anatomic Pathology, Department of Pathology, Stonybrook University Medical Center, State University of New York at Stonybrook, Stonybrook, New York

Hanjoon Song, MD
Associate, Prima Center for Plastic Surgery, Duluth, Georgia

Michael D. Stamatakos, MD
Assistant Professor, Anatomic Pathology, George Washington University Hospital, Washington, DC

Vered Stearns, MD
Associate Professor of Oncology, Medical Oncology, Johns Hopkins School of Medicine, Johns Hopkins Hospital, Baltimore, Maryland

Kala Visvanathan, MD
Associate Professor of Epidemiology and Oncology, Johns Hopkins Medical Institutions, Baltimore, Maryland

Anna Voltura, MD
Medical Director, Christus St. Vincent Breast Institute; Breast Oncology Surgeon, Christus St. Vincent Hospital, Santa Fe, New Mexico

Richard Zellars, MD
Associate Professor, Department of Radiation Oncology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland

Constance R. Ziegfeld, RN
Clinical Nurse Specialist, Johns Hopkins University, Baltimore, Maryland

Contents

1 The Normal Breast and Benign Diseases of the Breast

Samia Nawaz

KEY POINTS

- The functional unit of the female breast is the terminal duct lobular unit (TDLU).
- The entire ductal system is lined by two cell layers: inner epithelial cells and outer myoepithelial cells.
- Ectopic breast tissue in the axilla may raise clinical concern for metastasis.
- Inverted nipples may be congenital or may be associated with breast carcinoma.
- Acute mastitis and inflammatory carcinoma may look alike clinically.
- Chronic mastitis and fat necrosis can result in a hard irregular mass and mimic malignancy.
- Fibroadenoma is the most common benign neoplasm of the female breast, composed of benign proliferation of stroma and epithelium.
- Sclerosing adenosis is a proliferation of the stroma and the smallest tubules within the TDLU. It may mimic carcinoma clinically, radiologically, and histologically. The presence of myoepithelial cells confirms the benign nature of the lesion.
- Ductal hyperplasia (proliferation of the ductal epithelial lining cells) may be of the usual type (mild, moderate, or florid) or atypical and may have varying degrees of risk for future cancer.
- Atypical lobular hyperplasia (proliferation of the epithelium lining the lobules) is associated with an increased risk of future carcinoma. There is no such entity as lobular hyperplasia of the usual type.

The Normal Breast

The breast is a modified, specialized apocrine gland located in the superficial fascia of the anterior chest wall (Fig. 1-1). The nipple projects from the anterior surface and is hyperpigmented. It is composed of dense fibrous tissue covered by skin and contains bundles of smooth muscle fibers, which assist with milk expression. The skin adjacent to the nipple is also hyperpigmented and is called the areola.

The breast parenchyma consists of 15 to 20 lobules, which drain secretions into a ductal system that converges and opens into the nipple.[1] The functional unit of the breast is the terminal duct lobular unit (TDLU) (Fig. 1-2), which is composed of the terminal (intralobular) duct, and its ductules/acini (also referred to as lobules). The terminal ducts join together to form the larger ducts, which have a dilatation (lactiferous sinus) just before they open into the nipple. The TDLUs are embedded in loose specialized, hormonally responsive connective tissue stroma, the intralobular stroma. The dense fibrous tissue between the breast lobules is called interlobular stroma, which is not responsive to hormones (Fig. 1-3).

Lymphatic drainage of the breast is to the *axillary*, *supraclavicular*, and *mediastinal* lymph nodes.

Histology

The entire ductal system, extralobular large and intermediate ducts, as well as the intralobular (terminal ducts and ductules/lobules), is lined by two cell layers: inner epithelial cells and an outer interrupted layer of myoepithelial cells.[1] The latter cells have contractile properties and assist in expelling milk. Special techniques can be used to highlight the myoepithelial cells. Immunohistochemical stains for muscle-specific actin (MSA), S100, p63, and calponin can be used to detect the myoepithelial cell layer (Fig. 1-4).

The largest ducts change from a columnar epithelial lining to a squamous epithelial lining just distal to the lactiferous sinus, beyond which it becomes stratified squamous epithelium and merges with the surface skin.

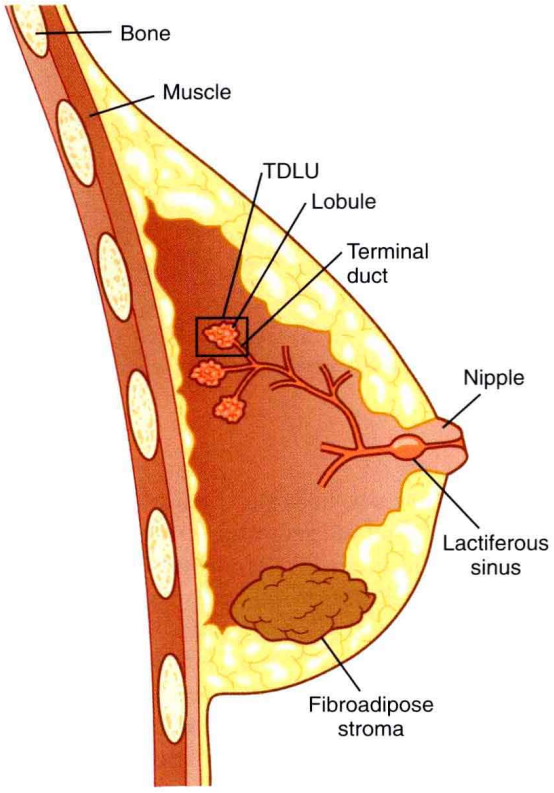

Figure 1-1. Normal breast. Diagram of breast composition and location. TDLU, terminal ductal lobular unit.

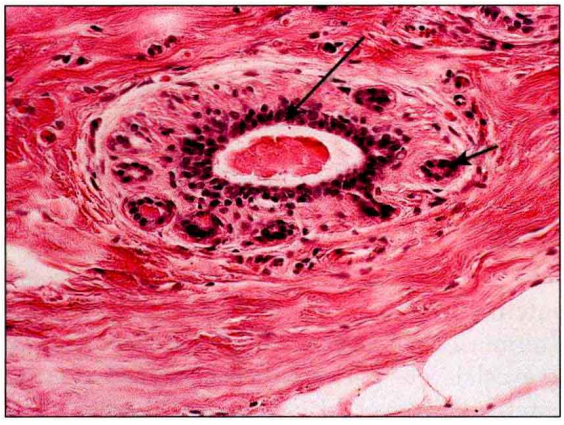

Figure 1-2. The terminal ductal lobular unit (TDLU) is the functional unit of the breast. The large arrow indicates the terminal (intralobular) duct. The short arrow identifies the ductules (lobules) (H&E, ×200).

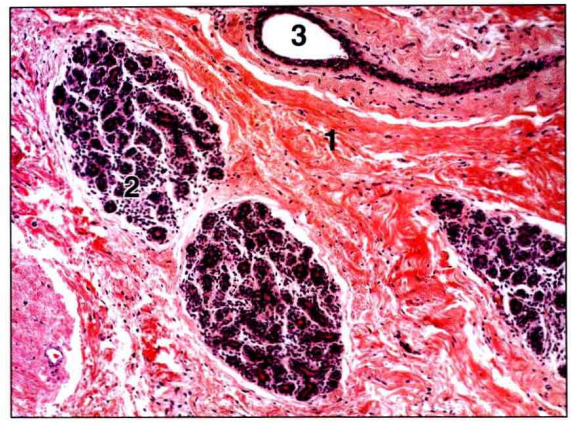

Figure 1-3. Normal female breast. Lobules (2) scattered within interlobular stroma (1). A larger duct is also seen (3) (H&E, ×100).

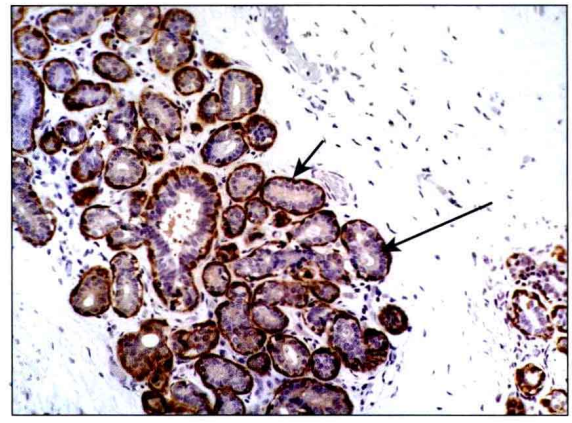

Figure 1-4. Two-cell lining of the ductal system. The inner layer consists of epithelial cells (*long arrow*), and the calponin stain highlights the outer myoepithelial cells (*short arrow*) (Calponin stain, ×200).

Physiologic Changes in Female Breast Histology

During childhood and before puberty, the female breast is composed of a branching ductal system that lacks lobular units. At puberty, female glandular tissue proliferates under stimulation of estrogen and progesterone. Once formed, the lactiferous ducts and interlobular duct system are stable and unaffected by fluctuating hormone levels during the menstrual cycle, pregnancy, and lactation. The TDLUs, however, are dynamic and undergo changes with alterations in hormone levels. These changes involve both the epithelium and the intralobular stroma.

Menstrual Cycle

The following are pre- and postmenstrual phases of the menstrual cycle:

Follicular phase: During the follicular phase of the menstrual cycle, the TDLUs are at rest and do not show any growth. The intralobular

stroma is dense and indistinct from the dense interlobular stroma.

Luteal phase: After ovulation, the terminal duct epithelium proliferates, and the number of terminal ducts within a lobule increases and the basal epithelial cells become vacuolated. The intralobular stroma is edematous and loose and becomes distinct from the interlobular stroma. These changes manifest as progressive fullness, heaviness, and tenderness of the breast.

Menses: As the levels of estrogen and progesterone fall with the onset of menstruation, there is an increase in apoptosis in the TDLU. Lymphocytes infiltrate the intralobular stroma, which becomes dense. The TDLU finally regresses to its resting appearance.

Pregnancy: During pregnancy, there is a striking increase in the number of terminal ducts, and the TDLUs are enlarged in response to the rising sex hormone levels.

Lactation: In the lactating breast, the individual terminal ducts form acini, which show epithelial vacuolization as a result of the presence of secretions that also fill their lumina (Fig. 1-5). After lactation, the units involute and return to their old structure.

Postmenopause: After menopause, the TDLUs atrophy owing to the low hormone levels so that only small residual foci remain. The lactiferous ducts and interlobular duct system remain, but the interlobular stroma is reduced in amount accompanied by a relative increase in fatty tissue.

The normal male breast differs in structure from the female breast in that there are no lobules. The male breast consists of ductal structures surrounded by fibroadipose tissue (Fig. 1-6).

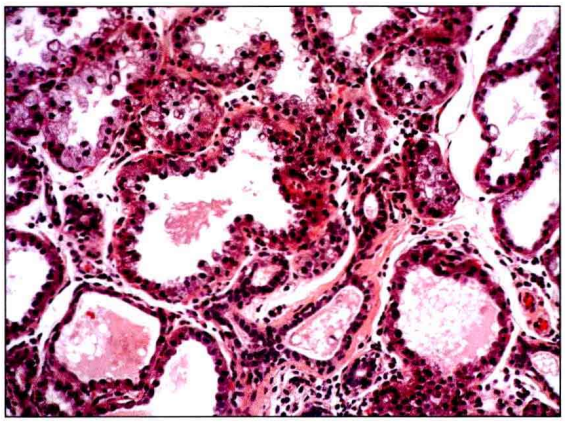

Figure 1-5. Lactating breast. Increased number of lobules with cytoplasmic vacuoles and intraluminal secretion (H&E, ×200).

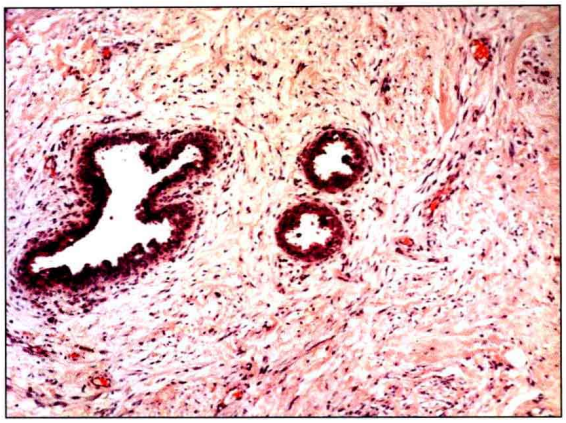

Figure 1-6. Normal male breast consists of a few ductal structures and stroma. There are no lobules (H&E, ×100).

Abnormalities of Breast Development

The following are abnormalities that can occur in breast development:

Mammary heterotopia (accessory breasts or nipples) may occur anywhere along embryonic mammary ridges, the most common sites being the chest wall, axilla, and vulva. It may manifest as polythelia (supernumerary nipples) or polymastia (aberrant breast tissue).[2] The accessory breast tissue responds to hormonal changes and, if located in the axilla, it may enlarge and raise concern for metastases.

Congenital inverted nipples are clinically significant, since a similar change may be produced by underlying cancer.

Juvenile hypertrophy (virginal hypertrophy) is a rare condition in adolescent girls in which the breasts (usually both; rarely only one) markedly enlarge owing to hormonal stimulation. No endocrine abnormality is detected. Patients present with embarrassment, pain, and discomfort. Reduction mammoplasty improves the quality of life.

Hamartoma is a well–circumscribed, often encapsulated mass composed of varying combinations of benign epithelial and stromal elements including fat.[3] Hamartoma is usually asymptomatic. It may manifest as a palpable mass, or it may be detected by mammography. Hamartoma may cause breast deformity if it is very large.

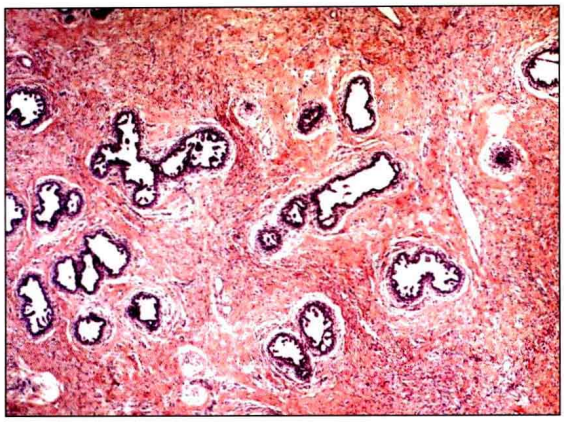

Figure 1-7. Gynecomastia. Stromal and ductal proliferation in the male breast (H&E, ×100).

Gynecomastia

Gynecomastia is defined as enlargement of one or both breasts in a male.[4] Many cases are idiopathic. In some cases, gynecomastia may be caused by excessive estrogen stimulation. Predisposing factors include the following:

- Hormonal imbalance, as may occur in puberty or old age
- Exogenous hormones
- Drugs, including dilantin, digitalis, and marijuana
- Klinefelter syndrome (testicular feminization)
- Testicular tumors
- Liver disease

On palpation, a firm disc-shaped subareolar mass is noted. Microscopic features of gynecomastia include ductal epithelial hyperplasia, stromal edema, and fibrosis around ducts (Fig. 1-7).

Inflammatory and Reactive Breast Lesions

The following are inflammatory and reactive breast conditions of various causes:

Acute inflammation of the breast (acute mastitis) is associated with redness, swelling, pain, and tenderness and may occur during the early postpartum months as a result of lactation (puerperal mastitis).[5] *Staphylococcus aureus* is the most common infecting agent. There are two general categories of predisposing factors:

- Cracks in the nipple and stasis of milk due to improper nursing technique
- Stress and sleep deprivation, which may lower the immune status and cause engorgement by inhibiting milk flow

At the microscopic level, cellulitis of the interlobular connective tissue is seen. Diagnosis is made on clinical grounds, and antibiotics lead to complete resolution. Delay in treatment may lead to abscess formation and requires drainage of pus.

Inflammatory breast carcinoma should be ruled out when there is no response to antibiotic therapy.

Chronic mastitis may be idiopathic[6–8] or in response to infection (tuberculosis), foreign material (silicone), or systemic disease (sarcoidosis). Diagnosis requires microbiologic, immunologic, and histologic evaluation. Idiopathic granulomatous mastitis[7] is diagnosed after exclusion of specific etiologic agents. Microscopically, chronic mastitis shows granulomas with or without caseation. Surgical excision may be followed by recurrence, abscess formation, or fistula formation.

Mammary duct ectasia is a distinct entity that usually occurs in perimenopausal women as a result of obstruction of the lactiferous ducts by inspissated luminal secretions. Obstruction leads to dilatation of the ducts and periductal chronic inflammation (Fig. 1-8). Grossly, chronic mastitis may produce irregular masses with induration that closely mimic breast carcinoma, and biopsy may be required to exclude carcinoma.

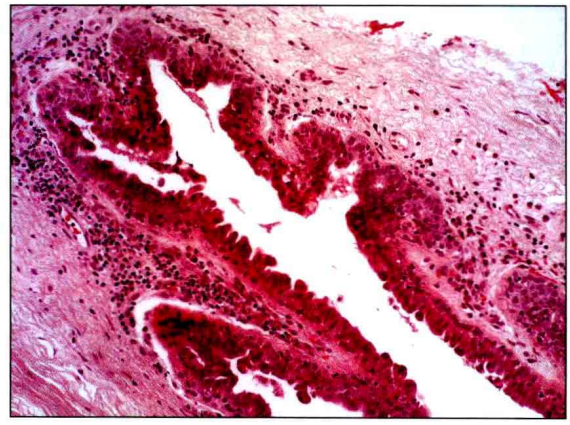

Figure 1-8. Mammary duct ectasia. A dilated duct and periductal chronic inflammation (H&E, ×200).

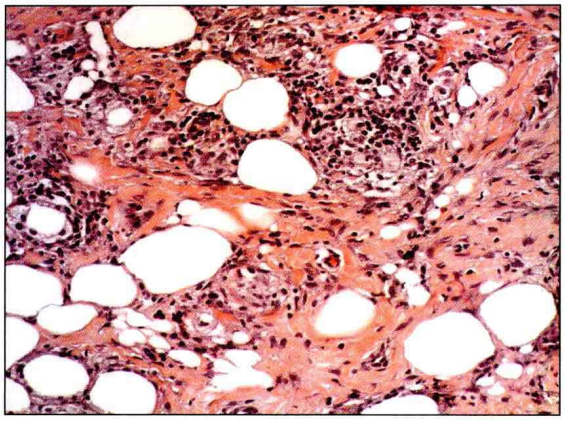

Figure 1-9. Fat necrosis. Necrotic fat cells with inflammatory cells (H&E, ×200).

Fat necrosis is a benign disease involving adipose tissue in the supporting stroma of the breast.[9] The cause may be related to ischemia and trauma (accidental or surgical). In the early phase, it is characterized by collection of neutrophils and histiocytes around the necrotic fat cells (Fig. 1-9). Later, histiocytes join to form giant cells, and fibrosis and calcification occur. The clinical importance of fat necrosis is that this may present as a hard mass that can be suggestive of carcinoma on physical examination as well as radiologic studies. Microscopic examination confirms the benign nature of the lesion.

Silicone granuloma is formed as a result of leakage of silicone gel from breast augmentation prosthesis.[10] The lesion is composed of numerous microcysts, some of which coalesce to form larger spaces that may be empty or contain refractile material. Foamy histiocytes and foreign body giant cells are also present (Fig. 1-10A and B).

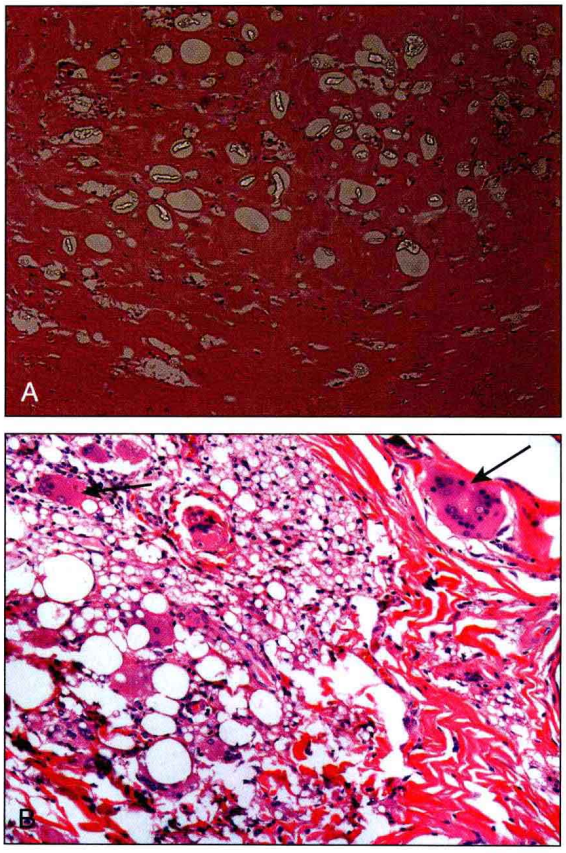

Figure 1-10. Silicone granuloma. A, Microcysts, some of which have coalesced around refractile foreign material. **B,** Foamy histiocytes and foreign body giant cells (*arrows*). (H&E, ×200.)

Diabetic mastopathy is an uncommon condition seen in patients with type 1 diabetes.[11] Patients present with solitary or multiple ill-defined, painless nodules. Diabetic mastopathy mimics carcinoma on clinical examination and radiologic studies. Histologic examination shows dense fibrosis and lymphocytic mastitis. The latter includes B-lymphocyte infiltration surrounding the ducts, lobules, and blood vessels (Fig. 1-11). This is considered an immune response to the abnormal deposits of extracellular matrix due to hyperglycemia.

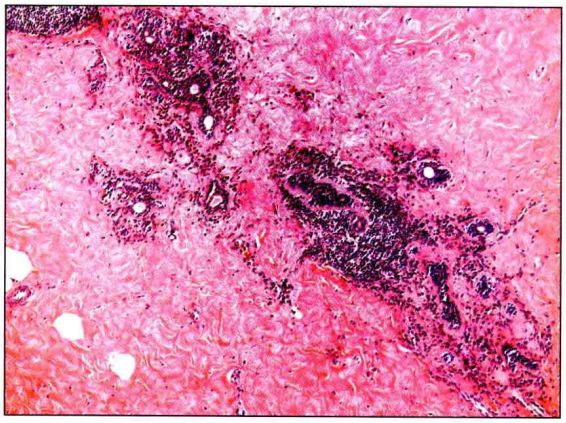

Figure 1-11. Diabetic mastopathy. Dense fibrosis with lobulitis (lobules surrounded by chronic inflammatory cells) (H&E, ×100).

Pseudoangiomatous stromal hyperplasia (PASH) is a benign condition characterized by proliferation of interlobular stroma, which may

manifest as a discrete palpable mass (nodular PASH) or by multifocal PASH, which may be found incidentally in benign or malignant breast biopsies.[12] Histologically, the lesion consists of complex slitlike pseudovascular spaces within a dense collagenous stroma. These spaces do not have an endothelial lining compared with true endothelial spaces. Thus, immunohistochemical stains for endothelial markers are negative, which is helpful in differentiating PASH from angiosarcoma.

Radial scar or complex sclerosing lesion is a localized nonencapsulated stellate lesion, which can mimic a carcinoma in a mammogram and a tubular carcinoma in histologic sections. Microscopic sections show a core of fibroelastic tissue with radiating bands of collagen, and within this connective tissue are foci of sclerosing adenosis, ductal hyperplasia, cysts, and apocrine metaplasia[13] (Fig. 1-12A and B).

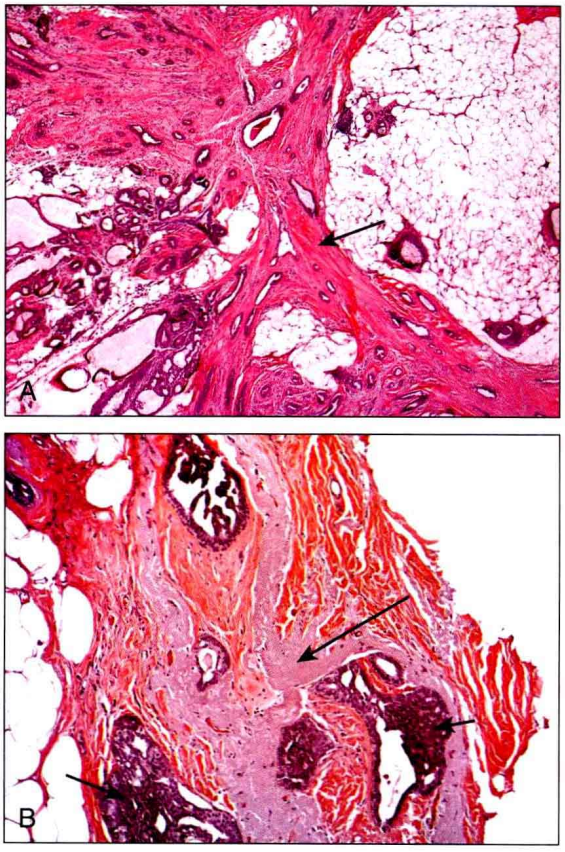

Figure 1-12. Radial scar. **A,** Core of fibroelastic tissue (*arrow*) and ducts with varying degrees of usual hyperplasia. **B,** Radiating bands of dense fibroelastic tissue (*long arrow*) and ductal hyperplasia (*medium* and *short arrows*). (H&E, ×100.)

Fibroepithelial Lesions

A **fibroadenoma** is a benign neoplasm often found in young women between the ages of 15 and 35, but it may occur at any age.[14] Clinically, it is seen as a single, discrete, mobile nontender mass composed of proliferating ducts (*adenoma*) and proliferating specialized intralobular fibroblastic stroma (*fibro*) (Fig. 1-13). Fibroadenoma is not associated with an increased risk of the development of breast cancer. It is cured by excision.

A **lactating adenoma** is a benign lesion in which lactational changes have supervened.[15] It may be associated with rapid increase in size during pregnancy, raising a suspicion of carcinoma.

Phyllodes tumors are rare tumors composed of intralobular stroma and ductal epithelium.[16] There is a spectrum of aggressiveness from benign to malignant (low grade and high grade). Most are benign, remain localized, and are cured by excision. Low-grade malignant phyllodes tumors may recur after excision. High-grade malignant phyllodes tumors can metastasize to distant sites (e.g., lungs).

Most phyllodes tumors grow to a massive size of up to 16 cm. A cut section shows leaflike architecture and clefts (*phyllodes* comes from the Greek word for leaves). Microscopically, the leaflike structures are lined by benign epithelium overlying a stromal overgrowth (Fig. 1-14). Many criteria are used to differentiate benign from malignant phyllodes tumors. Benign phyllodes tumors have no cytologic atypia and less than 5 mitoses/10 HPF. Low-grade malignant

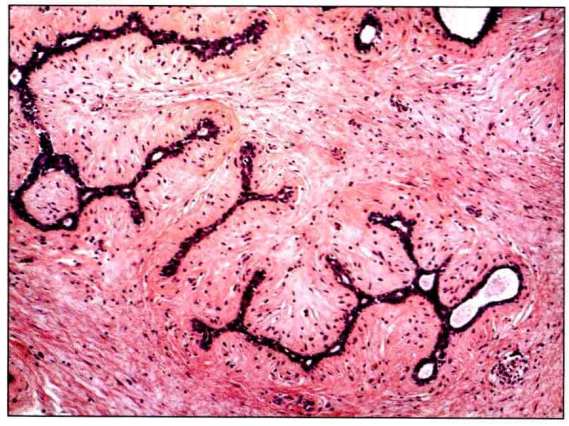

Figure 1-13. Fibroadenoma composed of benign proliferation of ducts and fibroblastic stroma (H&E, ×100).