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Review Article

Breast Cancer

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ABSTRACT

Breast cancer (BC) is the most frequently diagnosed cancer in women worldwide with more than 2 million new cases in 2020.Its incidence and death rates have increased over the last three decades due to the change in risk factor profiles, better cancer registration, and cancer detection. The number of risk factors of BC is significant and includes both the modifiable factors and non-modifiable factors. Currently, about 80% of patients with BC are individuals aged >50.Survival depends on both stage and molecular subtype. Invasive BCs comprise wide spectrum tumors that show a variation concerning their clinical presentation, behavior, and morphology. Based on mRNA gene expression levels, BC can be divided into molecular subtypes (Luminal A, Luminal B, HER2-enriched, and basal-like).The molecular subtypes provide insights into new treatment strategies and patient stratifications that impact the management of BC patients. The eighth edition of TNM classification outlines a new staging system for BC that, in addition to anatomical features, acknowledges biological factors. Treatment of breast cancer is complex and involves a combination of different modalities including surgery, radiotherapy, chemotherapy, hormonal therapy, or biological therapies delivered in diverse sequences. Body fatness is a dynamic exposure throughout life. To provide more insight into the association between body mass index (BMI) and postmenopausal breast cancer, we aimed to examine the age at onset, duration, intensity, and trajectories of body fatness in adulthood in relation to risk of breast cancer subtypes. Based on self-reported anthropometry in the prospective Norwegian Women and Cancer Study, we calculated the age at onset, duration, and intensity of overweight and obesity using linear mixed-effects models. BMI trajectories in adulthood were modeled using group based trajectory modeling. We used Cox proportional hazards models to calculate hazard ratios (HRs) with 95% confidence intervals (Cis) for the associations between BMI exposures and breast cancer subtypes in 148,866 postmenopausal women. Advanced glycation end products (AGEs) are reactive metabolites intrinsically linked with modern dietary patterns. Processed foods, and those high in sugar, protein and fat, often contain high levels of AGEs.

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Increased AGE levels are associated with increased breast cancer risk, however their significance has been largely overlooked due to a lack of direct cause-and-effect relationship. Immunohistochemistry and immunofluorescence were used to assess cellular proliferation and stromal fibroblast and macrophage recruitment. The Kruskal–Wallis test were used to compare continuous outcomes among groups. Mammary epithelial cell migration and invasion in response to AGE-mediated fibroblast activation was determined in two compartment co-culture models. In vitro experiments were performed in triplicate. The nonparametric Wilcoxon rank sum test was used to compare differences between groups. Deep learning analysis of radiological images has the potential to improve diagnostic accuracy of breast cancer, ultimately leading to better patient outcomes. This paper systematically reviewed the current literature on deep learning detection of breast cancer based on magnetic resonance imaging (MRI). The literature search was performed from 2015 to Dec 31, 2022, using Pubmed. Other database included Semantic Scholar, ACM Digital Library, Google search, Google Scholar, and pre-print depositories (such as Research Square). Articles that were not deep learning (such as texture analysis) were excluded. PRISMA guidelines for reporting were used. We analyzed different deep learning algorithms, methods of analysis, experimental design, MRI image types, types of ground truths, sample sizes, numbers of benign and malignant lesions, and performance in the literature.

INTRODUCTION

Anatomy and Physiology:

The female breasts are modified sweat glands. The breast tissue develops from the milk line.[1]At birth there is no difference between male and female breasts. Pubertal growth is due to glandular and fibrofatty proliferation.[39][1] The amount of fibroglandular tissue decreases with age. Multiple hormonal stimulation significantly increases the volume of the breast tissue during pregnancy. Each breast is comprised of 15-20 lobes interspersed with adipose tissue and connective tissue arranged in radial fashion extending from the nipple.[17][14] The nipple is situated In the center of a darker area of skin called the areola. The areola contains small glands, called Montgomery glands, which lubricate the nipple during breastfeeding. There are no muscles in the breasts, but the pectoral muscles lie under each breast and cover the ribs.

- Female breasts consist of mammary glands, responsible for milk production.
- Hormones like estrogen and progesterone influence breast development.
- During puberty, hormonal changes lead to breast development, including glandular tissue and ducts.
- The menstrual cycle can cause temporary changes in breast size and tenderness.
- Pregnancy triggers further breast development in preparation for lactation.
- Prolactin and oxytocin play key roles in milk production and ejection during breastfeeding.
- Breast milk provides essential nutrients and antibodies to nourish and protect the infant.
- Regular breast self-exams and mammograms are important for breast health and cancer detection.

Breasts have evolved as a secondary sexual characteristic in females, potentially signaling fertility and reproductive fitness. They may have attracted mates and played a role in human evolution. Breastfeeding fosters emotional bonds between a mother and her child. It provides comfort and security, promoting psychological well-being for both mother and baby.[39][22][19][12].

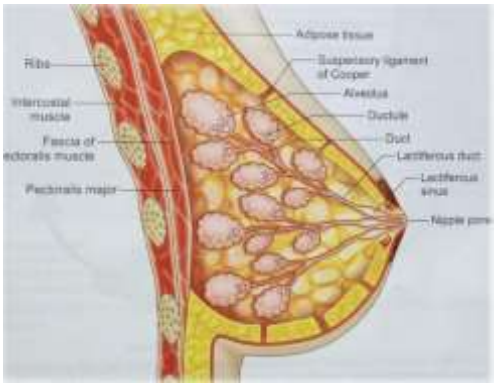


Diagram: A: Structure of the adult female breast.

Terminal Duct Lobular Unit (TDLU):

- The lobules of each breast consist of acini or glands lined by an outer myoepithelial cells

and an inner secretory cells, also known as luminal cells. Each lobe of the breast has one unique terminal duct lobular unit (functional unit), which drains via a branching duct system, ie. Intralobular ducts, interlobular ducts and lactiferous sinuses outside through the nipple. Duct system carries milk to the nipples. Each duct has a lining epithelium surrounded by a thin myoepithelial cell layer responsive to oxytocin, the hormone that stimulates lactation.[35][22][11][4][1]

- During pregnancy (30 weeks), each breast shows controlled proliferation of lobular acini lined by cells containing secretory vacuoles and secretions in their lumina. Breast milk comprises casein, Beta-lactalbumin and milk fat globule derived from the luminal surface of ductal cells. The acinus is lined by epithelial cells surrounded by myoepithelial cells and the basement membrane. On immunohistochemistry, myoepithelial cells show positivity for S-100, a-smooth muscle actin (a-SMA), p63, glial fibrillary acidic protein and GFAP. Myoepithelial cells are most often demonstrated in benign breast tumors. But myoepithelial differentiation is demonstrated in high-grade invasive ductal carcinomas with large central acellular zones.[12][3]
- Benign breast diseases and carcinomas arise in the terminal duct-lobular unit.

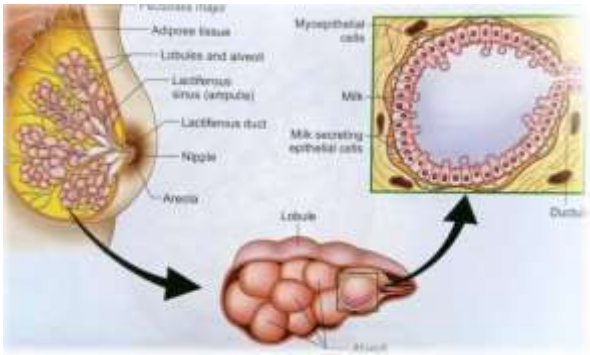


Diagram: B: structure of female breast & Branching system.

BLOOD SUPPLY

The vascular supply of the breast is from internal mammary and lateral thoracic artery. There is communication between lymphatic and venous drainage in subclavicular region.

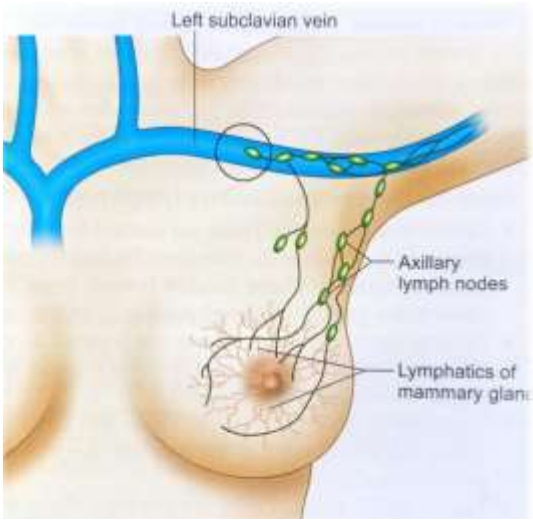


Diagram: C: Indicate a chain of the lymph nodes near the axilla and breast. Another point of contact between the two circulations (lymphatic and venous circulation).

Lymphatic Drainage:

The breast has extensive lymphatic drainage. Breast has lymphatic node groups: axillary nodes and internal thoracic lymph nodes. Approximately 75% of the lymphatic drainage occurs to the axillary lymph nodes. So there is greater frequency of tumor metastases to these lymph nodes. Approximately 25% of lymphatic drainage from inner quadrants of breast is drained to internal mammary (parasternal) lymph nodes and skin lymphatic channels.[40][17][13] To a lesser extent lymph is also drained to nodes adjacent to the vertebra. There are five groups of axillary lymph nodes:

- Central axiallary nodes: These are located high up in the middle of the axilla, over the ribs and serratus anterior muscle. These receive lymph from the other three groups of lymph nodes.[39][2]
- Pectoral (anterior) nodes: These are located along the lateral edge of the pectoralis major

muscle, just inside the anterior axillary fold.[4][1]

- Subscapular (posterior) nodes: These are situated along the lateral edge of the scapula, deep in the posterior axillary fold.[17][14]
- Lateral lymph nodes: These are situated along the humerus inside upper arm.[13][7]
- Apical lymph nodes: These are situated in the apical region of axilla.

Role of Hormones in Breasts Development

The female breast depends on a variety of hormones for its normal activity. It exhibits structural and functional variation throughout life, especially during puberty, pregnancy, lactation, the normal menstrual cycle, and at the menopause.

Hormones and breast development

Breast development and function depend on the ovarian hormones estrogen and progesterone. Hormones reaching breast via blood stream either interact with membrane receptors (prolactin) or nuclear receptors (estrogen). The hormone receptor interaction activates DNA synthesis of factors responsible for proliferation and differentiation of terminal duct lobular unit. Estrogen elongates the ducts and causes them to create side branches. Progesterone increases the number and size of the lobules in order to prepare the breast for nourishing a baby. Growth hormone, insulin and gluco- corticoids also participate in proliferation of lobules.

Breast changes during pregnancy

After ovulation, progesterone makes the breast cells grow and enlargement of blood vessels filled with blood. At this time, the breasts often become engorged with fluid. These may become tender and swollen. The female breast during pregnancy undergoes lobular hypertrophy; so that lactation can occur by the action of prolactin. Breast histology from a woman 30 weeks pregnant, shows the lobular acini lined by cells containing secretory vacuoles and with pink secretions in their lumens.

Breast lumps and their anatomical correlation:

1. Frequency of Breast Lumps: A breast mass in a woman is likely to be in decreasing frequency due to fibrocystic change (40%), miscellaneous benign lesions (13%), carcinomas (10%) or fibroadenomas (7%) and no disease (30%). The presence of myoepithelial cells in breast epithelial structures typically indicates a benign disease and useful in diagnosis. The p63 is a reliable marker for myoepithelial cells. Other myoepithelial cell markers include S-100, GFAP (glial fibrillary acidic protein) and alpha-smooth muscle actin. Structure of the adult female breast showing major components and location of various lesions.[39][29]

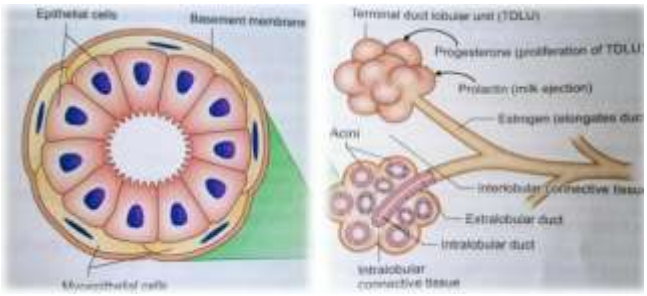


Diagram :D: Two Deep structure of females breast & about membranes.

2. Nipple: The nipple may be site of Paget's disease (ductal carcinoma involving nipple skin), nipple adenoma and breast abscess.[12]

3. Lactiferous Ducts and Sinuses: The lactiferous ducts are the most common site of intraductal papilloma, galactocele (blocked lactiferous duct in a lactating woman), breast abscess, or plasma cell mastitis.[10]

4. Large Ducts: Large ducts are the most common site for fibrocystic change and most ductal carcinomas.[3]

5.Terminal Duct Lobular Unit (TDLU): The terminal lobules are involved in sclerosing adenosis (a variant of fibrocystic change), lobular and tubular carcinomas.[12]

6. Interlobular or Intralobular Stroma of the Breasts: The breast interlobular stroma is the source of phyllodes tumor. On the other hand,

fibroadenoma is derived from intralobular stroma.[19]

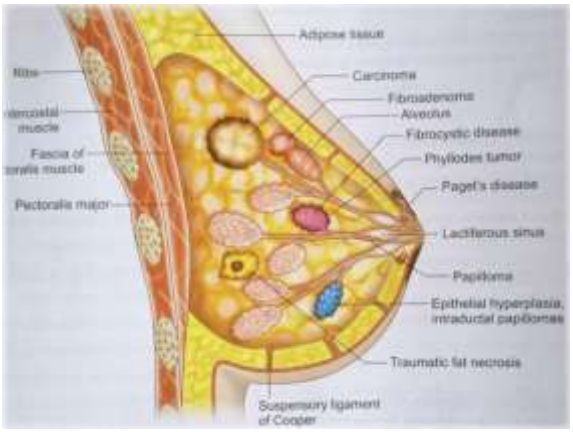


Diagram: E: Structure of the adult female breast showing major components and location of various lesions.

Clinical presentation:

- Woman with breast disease most often complains of pain, a palpable lump without a discrete lump and nipple discharge. It is most important to evaluate these women because of the possibility of breast carcinoma.[11][2]
- Patient with breast carcinoma may present with breast lump, change in the symmetry of the breast, change in the nipple (itching, burning, erosion or retraction), pathological fractures and increased serum calcium levels.[9]
- A spontaneous nipple discharge of any kind in a non- breastfeeding and non-lactating woman warrants investigation.[19]

Breast symptoms in disease conditions:

1. Painful Breasts:

i) Premenopausal women: These present with cyclic pain in bilateral breasts, increasing severity from mid- cycle onwards, and pain improving at menstruation. Women often report fullness, heaviness, areas of tenderness and increased breast size during 3-7 days before each menstruation.[17]

ii) Postmenopausal women: These present with continuous localized breast pain not related to cyclic changes. Approximately 90% of painful breast diseases are benign and 10% of breast carcinoma present with pain.[39]

2. Breast Lumps: The most common palpable lumps are fibrocystic disease, fibroadenoma and invasive breast carcinoma. Premenopausal women most often develop benign palpable masses in 90% and breast carcinoma in 10%. Risk of breast carcinoma increases with advancing age. In clinical practice, Indian women with breast carcinomas report late with evidence of metastases.[24][22][19]

3. Nipple Discharge:

i) Milky nipple discharge: It occurs due to increased prolactin level in pregnant women, oral contraceptive therapy, pituitary adenoma, tricyclic antidepressant and methyldopa.[10][9]

ii) Serous/bloody discharge: It occurs due to intraductal papilloma or breast carcinoma.[3]

iii) Eczema-like lesion with blood stained discharge: A rash, often eczema-like lesion, on the nipple or surrounding area and blood stained discharge from nipple is seen in Paget's disease of nipple (ductal carcinoma involving overlying skin).[41][22]

4. Nipple Retraction: Indrawing (retraction) of the nipple due to desmoplasia in an underlying advanced scirrhous breast carcinoma is a late feature. Nipple retraction also occurs due to fibrosis in chronic inflammation of the breast.[10]

5. Overlying Skin Edema: The "peau d'orange" (skin edema) appearance of the breast skin occurs due to obstruction of the dermal lymphatic by tumor cells.[6]

Clinical examination: Clinician should note these characteristics in women with breast diseases:[16]

Location: Quadrants.

Size: Dimensions.

Shape: Lump oval, lobulated or indistinct.

Consistency: Soft, firm or hard.

Movable: Freely movable or fixed.

Distinction: Solitary or multiple.

Nipple: Displaced or retracted or nipple discharge.

Skin over the lump: Erythematous, dimpled or retracted.
Tenderness: Tender on palpation or not.
Lymphadenopathy: Lymph nodes palpable or not.
Distant metastases: Organs involved.
Clinical examination of the breast is an important aspect of breast health and can be performed by healthcare professionals or individuals for self-examination. Here are the key steps for a clinical breast examination:

1. Palpation: Use the pads of your fingers to gently palpate the entire breast and the area around the nipple. Pay attention to any lumps, thickening, or areas of tenderness. Check the axillary (underarm) area for any enlarged lymph nodes.[33][14]
2. Nipple Examination: Examine the nipples for any discharge, changes in color, or inversion. Gently squeeze the nipple and check for any abnormal discharge.[3][1]
3. Position and Technique: It's important to perform the examination in different positions, such as lying down with one arm behind your head, standing in front of a mirror, and raising your arms. Use various techniques, including circular motions, vertical strip patterns, or radial patterns, to ensure comprehensive coverage of the breast.
4. Regularity: Perform breast examinations regularly, typically once a month for self-exams. Healthcare professionals may perform clinical breast exams during routine check-ups, usually annually for women.[4]
5. Inspection: Begin by visually inspecting the breasts. Look for any changes in size, shape, or symmetry. Check for skin changes such as redness, dimpling, or puckering. Look for any visible lumps or masses.[39][3][1]

Pain and tenderness in breasts	• Mastitis (acute or chronic) • Mammary duct ectasia • Breast abscess • Galactocele • Fibrocystic disease (cyclic pain)
Onset of lump	• Fat necrosis-associated with trauma • Fibrocystic disease-associated with menstrual cycle • Duration and rate of growth of lump (fibroadenoma showing slow growth no apparent change in size in 6+ months and rapid growth in breast carcinoma)
Breast lump frequency	• Fibrocystic change (40%) • No disease (30%) • Miscellaneous benign lesions (13%) • Breast carcinomas (10%) • Fibroadenomas (7%)

Clinical presentation	**Pathological correlation**
Metastases	• Lymph nodes involvement in axillary and supraclavicular regions. • Visceral metastases. • Bone pain and pathological fractures occur due to metastases.
Microcalcifications on mammography	• Dystrophic calcification associated with fibrocystic changes such as cysts and adenosis. • Carcinoma in situ or invasive carcinoma
Skin features	• Peau d'orange Lymphatic blockage by cancer cells and puckering. • Tethering: Due to invasion of Cooper's ligament in breast cancer • Erythema:Acute mastitis and Paget's disease of nipple
Nipple retraction	• Breast carcinoma • Inflammatory breast lesions undergoing fibrosis • Fat necrosis of breast
Manual examination of breasts	• Diffuse: Fibrocystic disease • Discrete: Neoplasm or cyst • Mobile lump: Fibroadenoma • Bulky tumor: Phyllodes tumor and giant fibroadenoma

	• Immobile lump: Invasive breast carcinoma
Nipple discharge	• Milky nipple discharge (galactorrhea) occurs due to increased prolactin level during pregnancy, pituitary adenoma, oral contraceptive therapy, tricyclic antidepressant, methyldopa) • Serous/Bloody (intraductal papilloma/cancer) Nipple shows rash, eczema-like or blood-stained discharge in Paget's disease of nipple (ductal carcinoma involving overlying skin)

If you notice any changes during a self-exam or if a healthcare professional detects something concerning during a clinical breast examination, further evaluation, such as imaging (mammography, ultrasound) and possibly a biopsy, may be recommended to determine the nature of the breast changes. Regular breast examinations are important for the early detection of breast abnormalities or cancer.[23]

INFLAMMATORY DISORDERS

Key Fact

- Inflammatory diseases of the breast are rare Acute infection occurs only in the lactating breast.
- Periductal mastitis is also known as Zuska's disease or squamous metaplasia of lactiferous ducts.
- Fat necrosis occurs due to trauma to breast especially in obese women.
- Duct ectasia shows many thick walled dilated ducts filled with yellow-brown cheesy secretions.
- Granulomatous mastitis occurs in systemic granulomatous disease, eg. Tuberculosis, sarcoidosis. Wegener's granulomatosis, fungal infection, breast implants or unknown etiology. There is involvement of lobular epithellum.
- Lipogranulomas are caused by rupture of a paraffin-filled polythene sac implanted silicone prosthesis previously as a device for breast augmentation.

ACUTE MASTITIS: Milk stasis is the main predisposing factor of lactation mastitis. If not treated appropriately, lactation breast abscesses can recur, which may be complicated by a fistulous tract. It is caused by Staphylococcus aureus that can enter the breast tissue through cracks and fissures in the nipple. This disorder is usually secondary to obstruction of the duct system by inspissated secretions. Complications of duct ectasia include abscess formation, fistulous tract and nipple retraction. Associated fibrosis and calcification in duct ectasia can simulate breast carcinoma.[39][29]

1. Age Group: Breast infection of overlying skin commonly affects women aged between 18 and 45 years, which may be primary or secondary due to infected sebaceous cyst in overlying skin. Females with pituitary prolactinomas occasionally are associated with galactorrhea.[23][21]

2. Clinical Features: The breast becomes tense, hot, and very painful. Axillary lymph nodes may become enlarged and tender.[22]

3. Therapeutic Correlation: It may be treated by mechanical suction, frequent emptying of the breasts, and administration of antibiotics.[39]

PERIDUCTAL MASTITIS: Periductal mastitis is also known as Zuska's disease or squamous metaplasia of lactiferous ducts.

1. Age Group: Periductal mastitis occurs especially in smokers.

2. Pathogenesis: Tobacco use alters the epithelium of lactiferous sinuses Keratin is trapped into ducts. Nipple inversion occurs due to fibrosis. Recurrences are common.

Light Microscopy

Histological examination reveals chronic and granulo matous inflammation.

MAMMARY DUCT ECTASIA: Duct ectasia of major subareolar ducts is characterized by inflammation and dilation of the major ducts. The ducts are filled with debris, resulting in dilatation, g rupture and inflammation. Possible etiological factors of duct ectasia are infections and cigarette smoking.[38][33]

1. Clinical Features: Some women present with greenish brown cheesy nipple discharge, slit-like nipple retraction, or palpable lump simulating cancer that may be hard or doughy there is no increased risk for breast carcinoma.[23][14][9][3]

Light Microscopy

It shows dilated ducts with fibrosis of wall, inflammatory cell infiltrate with plasma cells, and inspissation of lipid rich material within duct lumen.

Gross Morphology

- When cut across it shows many thick walled dilated ducts filled with yellow brown cheesy secretions.
- In women above 50 years of age, frequent incidental pathological finding is fibrocystic change in 30-40% of cases in surgically excised breast tissue and in autopsy specimens.

2. Management: Antibiotics and surgical removal of dilated duct cures these patients.

FAT NECROSIS: Fat necrosis of breast most often occurs in women >55 years. It is most common chronic inflammatory lesion which follows foreign body giant cell reaction and fibrosis due to lipid released from traumatized during lactation resulting in hypersensitivity reaction in multiparous women adipocytes.[5][2]

1. Pathogenesis: Trauma to the breast is most common cause of fat necrosis, followed by prior surgical intervention and radiation therapy. It occurs when lipase enzyme breaks down intracellular triglycerides into free fatty acids. These free fatty acids combine with sodium, magnesium or calcium ions to form soaps. The tissue becomes opaque and chalky white.[4]

2. Clinical Features: Patient develops unilateral localized breast mass, which may be painful in acute stage. Clinical examination of affected breast reveals a firm, superficial irregular mass, erythema of the overlying skin, dimpling and nipple retraction mimics carcinoma.[5]

3. Radiological Findings: Breast shows calcified lesion.

Gross Morphology

It shows chalky white areas of fat saponification. Variegated color and areas of hemorrhage are demonstrated on the cut surface of this lump. It is gritty to cut because of the presence of spotty calcification.

Light Microscopy

- In the response to fat necrosis there is an initial acute inflammatory reaction consisting of necrosis of adipocytes and hemorrhage. It is followed by chronic inflammatory response in which numerous plasma cells are seen.
- Macrophages phagocytose lipid released from adipocytes, forming multinucleate giant cells, as well as foam cells, also termed lipophages. There is presence of foreign body giant cells and dystrophic calcification demonstrated by imaging techniques.
- Fibroblastic proliferation leads to fibrosis resulting in extension to the surrounding tissue. As a result, an irregular, fixed, hard mass may ensue and clinically resemble breast carcinoma. Thus, the lesions often require biopsy to establish their benign character.

GRANULOMATOUS MASTITIS: It's a group of immunologic mediated disorder of breast bules. It leads to alteration in the lobular epithelium during lactation resulting in hypersensitivity reaction in multiparous women.[41]

1. Etiology: It occurs in systemic granulomatous disease, e.g. tuberculosis, sarcoidosis. Wegener's granulomatosis, fungal infection, breast implants and unknown etiology. There is involvement of lobular epithelium.[34]

Light Microscopy

- Breast lobules show granulomas, histiocytes, lymphocytes, plasma cells and giant cells by sparing interlobular stromal region.
- Breast tuberculosis: Breast tuberculosis usually occurs due to extension from rib in females. Patient presents with breast abscess and fever. On cut section, breast abscess contains caseous material. Light microscopy reveals epithelioid granulomas, caseous necrosis and Langhans's type of giant cells.
- Sarcoidosis: Breast sarcoidosis is an idiopathic disorder in which abnormal immune system leads to formation of noncaseating granulomas and collection of macrophages. These trigger an inflammatory response that causes extensive tissue damage and scarring. It shows noncaseating granuloma and collection of macrophages. Kveim test is performed by intracutaneous injection of saline suspension of human sarcoidal spleen or lymph nodes which cause appearance of erythematous nodules.
- Wegener's granulomatosis: It is a systemic necrotizing granulomatous vasculitis of unknown etiology or due to inhalation of some infectious agents.

SILICONE BREAST IMPLANTS: Silicone implants in breast are used for cosmetic augmentation. Silicone is a polymer of silica, O, and, H, Due to leakage of silicone implants, chronic inflammation takes place. lipogranulomas are caused by rupture of a paraffin filled polythene sac implanted prosthesis previously as a device for breast augmentation. This is a very old-fashioned type of breast implantation.[27][22]

SCLEROSING LYMPHOCYTIC LOBULITIS: Sclerosing lymphocytic lobulitis is also known as lymphocytic mastopathy. It most often occurs in women with type I diabetes mellitus or autoimmune thyroid diseases. It is considered to be an autoimmune disorder. Patient presents with hard palpable lumps. It is difficult to obtain tissue with needle biopsy due to presence of dense collagenous stroma. It should be differentiated from breast carcinoma.[17][13][1]

FIBROCYSTIC DISEASE

Fibrocystic breast disease is the most common benign disorder of the female breasts. It is caused by abnormal response of breast to ovarian hormones. Patient develops painful multifocal lumps in both breasts. The frequency of fibrocystic change decreases progressively after menopause.[39][33][4]

Although it is a benign condition, the gross and mammographic appearance may mimic carcinoma. And is often difficult to distinguish from carcinoma on frozen section.[37]

Key Facts of Fibrocystic Disease

- It is caused by abnormal response of breast to ovarian hormones.
- Fibrocystic changes occur in glands and stroma. These include fibrosis, duct ectasia, apocrine metaplasia, duct hyperplasia and sclerosing adenosis.
- There is increased risk of development of breast carcinoma plated to the presence of atypical hyperplasia of the glands.
- Sclerosing adenosis can be clinically and radiologically confused with breast carcinoma.

1] Age Group: It affects women in 20 to 50 years of age. About 10% of women have clinically evident disease. It is uncommon before adolescence or after menopause. Approximately 60-90% of breasts show fibrocystic change at autopsy.

2] Etiology: It is postulated that it results due to hormonal imbalance, Le increased uncontrolled response of estrogens on terminal duct lobular unit or to decreased progesterone activity. This hormonal imbalance occurs in functional ovarian granulosa cell tumors and anovulatory cycles. Environmental toxins inhibiting cyclic guanosine monophosphate enzymes by methylxanthines (e.g. caffeine, tea, chocolate), tyramine (e.g. cheese, wine, nuts) and tobacco may also cause fibrocystic change.

3] Clinical Features: Patient presents with bilateral breast palpable lumps (irregular nodularity) with mid-cyclic tenderness varying during the menstrual cycle. Pain is present in the upper outer quadrant of bilateral breasts. Occasionally, there is history of greenish brown to black nipple discharge containing fat, proteins, ductal cells and erythrocytes.

Light Microscopy

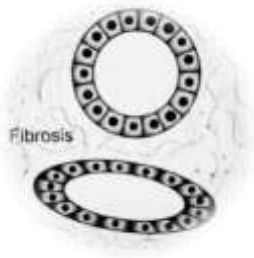
- Fibrocystic changes occur in glands and stroma, Which include fibrosis, duct ectasia, apocrine metaplasia, duct hyperplasia and sclerosing adenosis.
- Histology of fibrocystic disease shows cystic dilatation of the terminal ducts with increased surrounding collagen fibers.
- Fibrocystic changes may be no proliferative or proliferative.

Gross Morphology

- Cut surface is firm grey, white fibrous tissue.
- Some cysts may be quite large, which undergo hemorrhage into the cyst fluid called aloe domed cysts.
- These cysts vary in size with the menstrual cycle.
- These are most often enlarged and tender one week before menstruation.

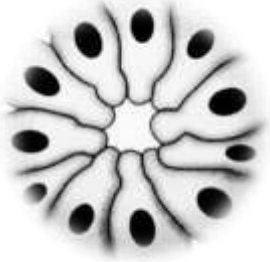
Histopathological Changes:

Nonproliferative Fibrocystic Changes: Nonproliferative fibrocystic changes include dense fibrous stroma encompassing a number of variable size cystic dilatation of the terminal ducts (duct ectasia) and mild hyperplasia. Alteration of epithelial lining is termed as apocrine metaplasia. Apocrine cells are large and more eosinophilic than that usually line the ducts and resemble apocrine sweat gland epithelium. On clinical examination, the breasts are lumpy. There is no risk of development of breast carcinoma.



A. Cyst formation

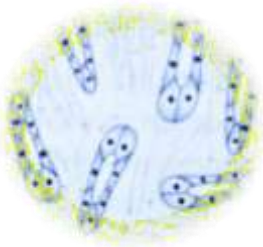
B. Adenosis



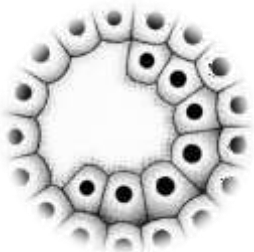
C. Apocrine metaplasia

D. Papilloma

E. Fibrosi



F. Sclerosing

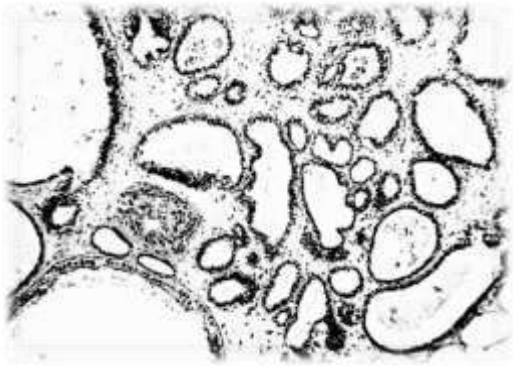


G. Typical epithelial Hyperplasia

H. Atypical

2. Proliferative Fibrocystic Changes: These are associated with epithelial hyperplasia of ducts and lobules, with or without features of atypia, and sclerosing adenosis. Atypical hyperplasia of ducts and lobules is associated with a five-fold increase in the risk of developing ductal carcinoma. When associated with a family history of breast carcinoma; the risk of development of breast carcinoma is ten- fold.[3][2]

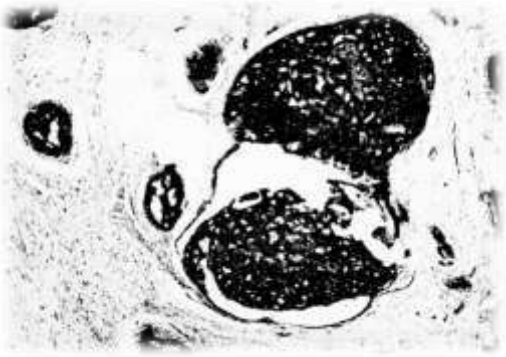
- **Fibrosis**: Rupture of cysts with extravasation of fluid in the stroma results in inflammation and fibrosis, Dense fibrous interlobular stroma expands into the lobules, and replaces the loose intralobular connective tissue. Strands of fibrous tissue constrict the ducts, so that the normal secretions cannot pass out. Terminal ducts become dilated resulting in formation of cysts containing secretions.[1]
- **Duct ectasia:** Paste-like material in subareolar ducts produces sticky purulent discharge that may be white, gray, brown, green or bloody. It is caused by stagnation of cellular debris and secretions in the ducts. Cysts filled with bluish fluid are known as blue dome cysts when examined through cyst wall. Light microscopy shows cysts lined by uniform benign cuboidal to columnar epithelial cells of variable height with microcalcifications in their lumen. These cysts do not have malignant potential. On clinical examination of breast, these lesions reveal cystic feel.[2]
- **Apocrine metaplasia:** The cells lining large cysts undergo change consisting of tall, pink, columnar benign epithelial cells with small nuclei and brightly eosinophilic cytoplasm. Chromosomal abnormalities in apocrine epithelium suggest possible precursor of apocrine carcinoma.[34][2][1]
- **Sclerosing adenosis:** Sclerosing adenosis with fibrosis of the intralobular stroma resulting in compression of the epithelial structures to give a pseudoinfiltrative growth pattern. The number of acini per terminal duct is more than double the normal found in normal lobules Tubules are lined by two layers of epithelial cells giving lobular configuration. There is more often presence of numerous microcalcifications. Sclerosing adenosis lesions have become significant in modern clinical practice, as these lesions can be confused with breast carcinoma on mammographic screening.[2]
- **Ductal epithelial hyperplasia:** As the ducts are estrogen sensitive, florid ductal epithelial hyperplasia occurs within areas of fibrocystic changes.[4]



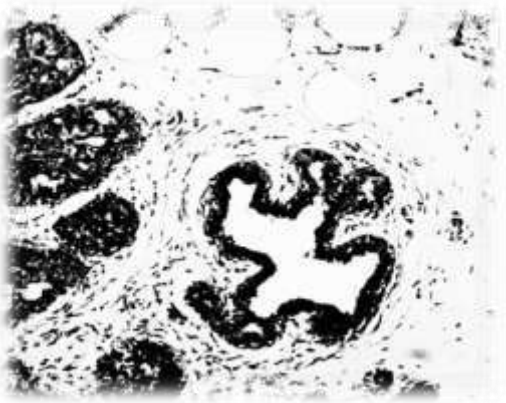
Structure A: Spectrum of morphological changes in fibrocystic disease of the breast showing duct dilatation, adenosis, fibrosis (intralobular and interlobular), and apocrine change (400X).

The epithelial cells are multilayered, filling and expanding the ducts or acini. There is a slightly increased risk (1.5 to 2 times) of development of breast carcinoma.

Atypical ductal hyperplasia: It occurs in ducts and lobules lined by multilayered pleomorphic atypical cells with hyperchromatic nuclei resembling carcinoma in situ of ducts (DCIS) or lobules (LCIS). These atypical cells do not fill the entire lumen of ducts or lobules. These atypical changes are indicative of an increased risk for subsequent breast malignancy.[39]



Structure B. Fibrocystic disease shows typical ductal hyperplasia



Structure C: Fibrocystic disease shows atypical ductal hyperplasia (arrow) (100X)

Diagnostic Tools:

Since the introduction of mammographic and ultra- sound imaging of the breast, this condition can be diagnosed without having to perform surgical excision. Ultrasonography is done to distinguish cystic fluid filled lesions in fibrocystic disease from solid masses. Fine needle aspiration cytology of bloody aspirate is done to rule out malignant change. Histopathological examination distinguishes benign from malignant changes.[39]

Histological features	Ductal hyperplasia	Atypical hyperplasia/DCIS
Size	•Variable size, rarely extensive when associatedwith papilloma or radical scar.	•May be extensive, rarely <3mm.
Cellular composition	•Epithelial cells along with spindle cells, lymphocytes, macrophages. Myoepithelial cell hyperplasia around periphery.	•Single cell population. Absence of spindle cells. Myoepithelialcells around periphery.
Architecture	•Variable.	•Well-developed micropapillary, cribriformor solid patterns.
Lumina	•Lumina irregular often ill-defined slit-likespaces common.	•Lumina well- delineated, regular, punched out in cribriform pattern.
Cell orientation	•Streaming pattern with long axis of nucleiarranged parallel to direction of cellular bridges, which often have a 'tapering appearance.	•Micropapillary structures with indiscernible fibrovascular cores or smooth, well-delineated geometric spaces. Cell bridges 'rigid' in cribriformtype with nuclei oriented towards the luminal type.
Nuclear spacing	•Uneven	•Even
Epithelialcell character	•Small ovoid with variation in shape	•Small uniform monotonousappearance.
Nucleoli	•Indistinct	•Single small
Mitoses	•Infrequent	•Infrequent, abnormal form
Necrosis	•Rare	•If present, confined to small particulate

		debris incribriform and/or luminal spaces.

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