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TOPIC : 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.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:

01.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]

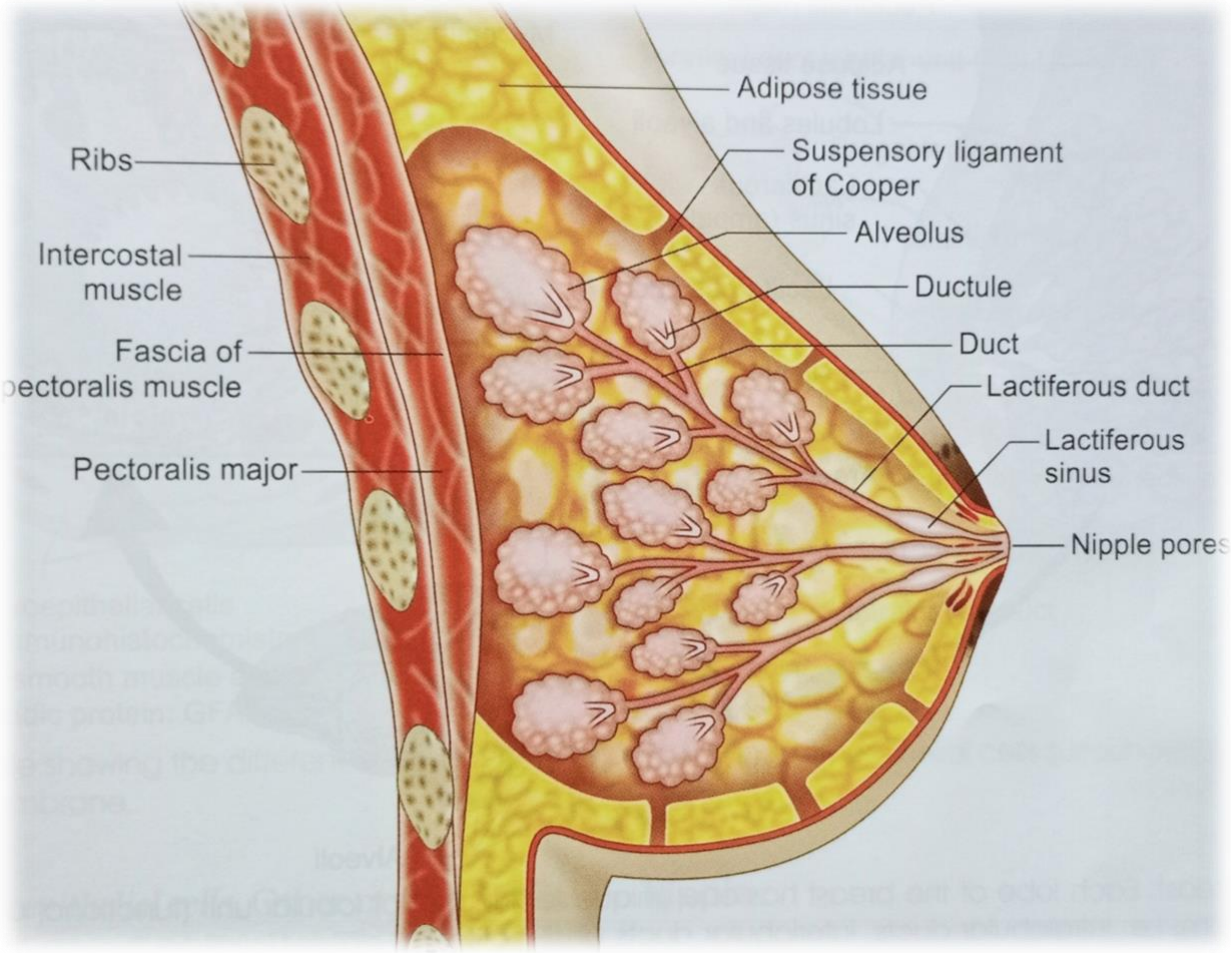


Diagram:A:Structure of the adult female breast.

02.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 differen-tiation 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.

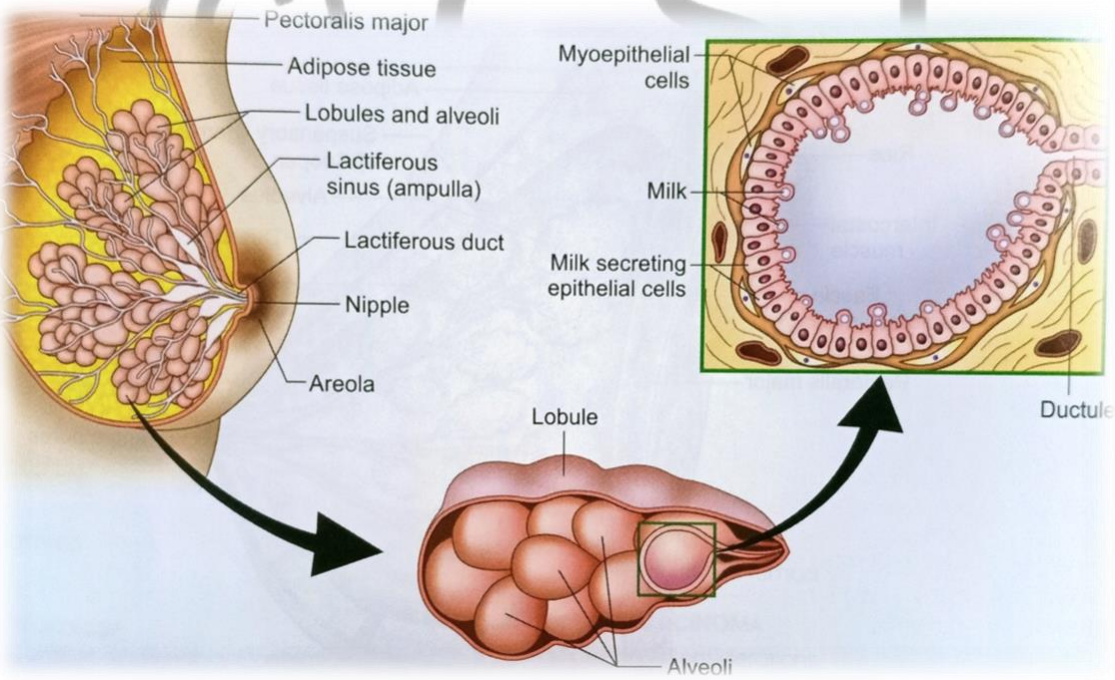


Diagram:B:structure of female breast & Branching system.

BLOOD SUPPLY

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

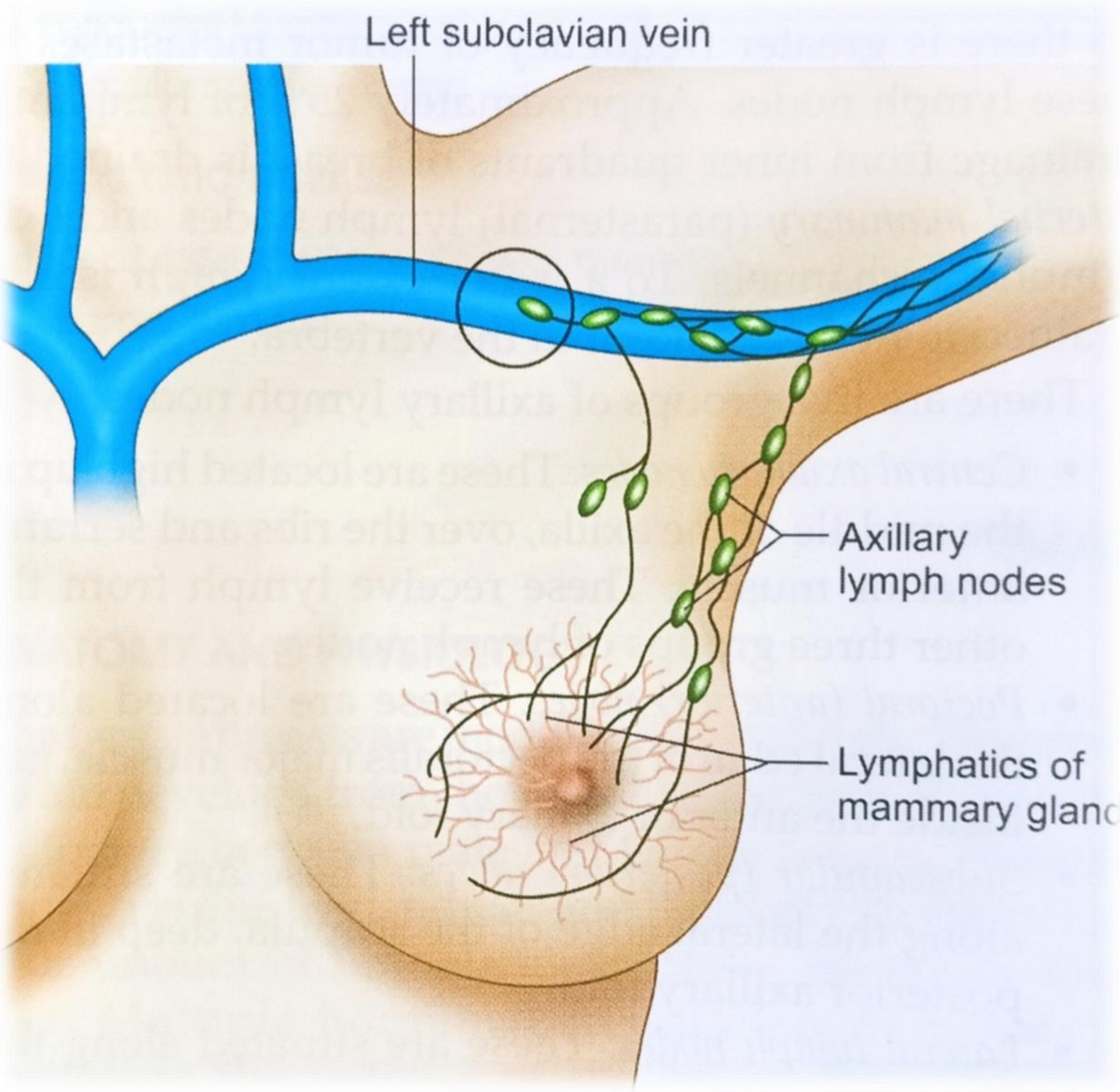


Diagram:C:Indicate a chain of the lymph nodes near the axilla and breast.Another point of contact between the two circulations (lymphatic and venous circulation).

03.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 develop- ment 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.

04.Breast lumps and their anatomical correlation:

04.01.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]

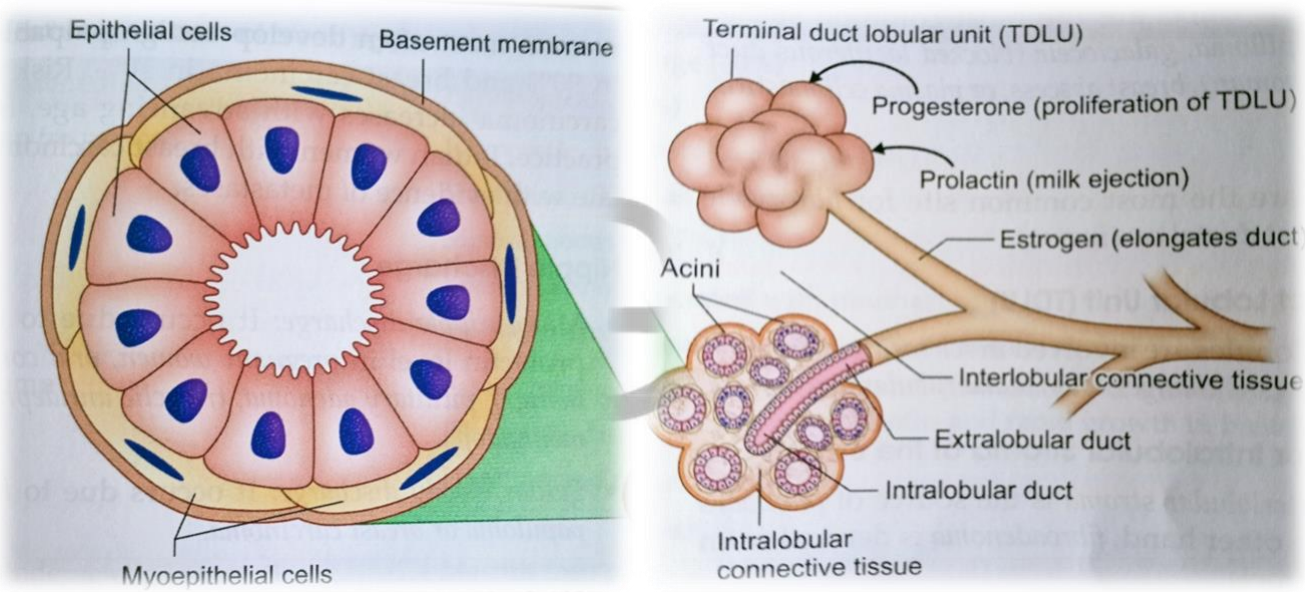


Diagram:D:Two Deep structure of females breast & about membranes.

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

04.03.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]

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

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

04.06.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]

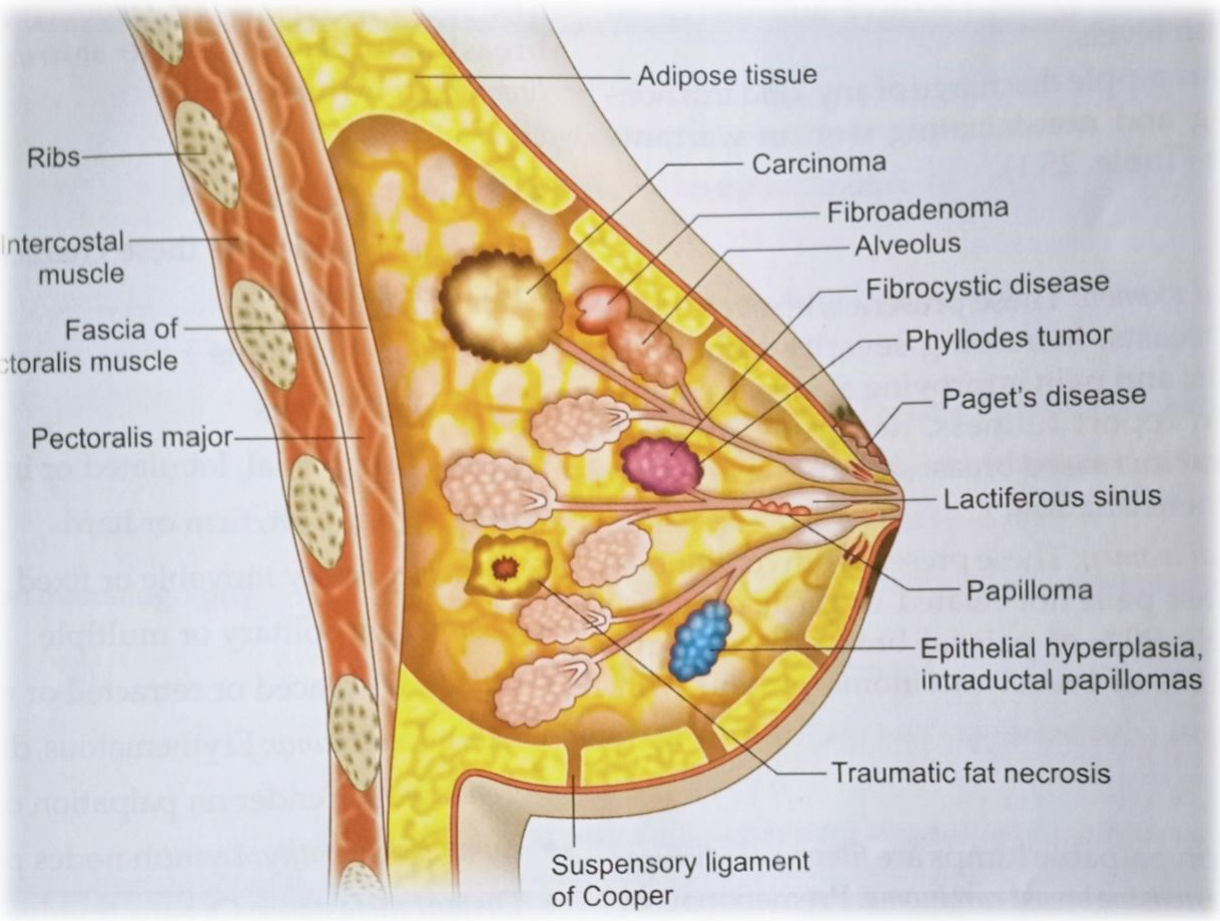


Diagram:E:Structure of the adult female breast showing major components and location of various lesions.

05.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]

06.Breast symptoms in disease conditions:

06.01.Painful Breasts:

1.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]

2.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]

06.02.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]

06.03.Nipple Discharge:

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

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

3.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]

06.04.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]

06.05.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]

07.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

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)

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]

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 todetermine 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.

01.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]

01.01.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]

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

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

02.PERIDUCTAL MASTITIS:

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

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

02.02.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.

03.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]

03.01.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, inflam matory 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.

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

04.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]

04.01.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]

04.02.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]

04.03.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.

05.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]

05.01.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.

06.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]

07.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 includo 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

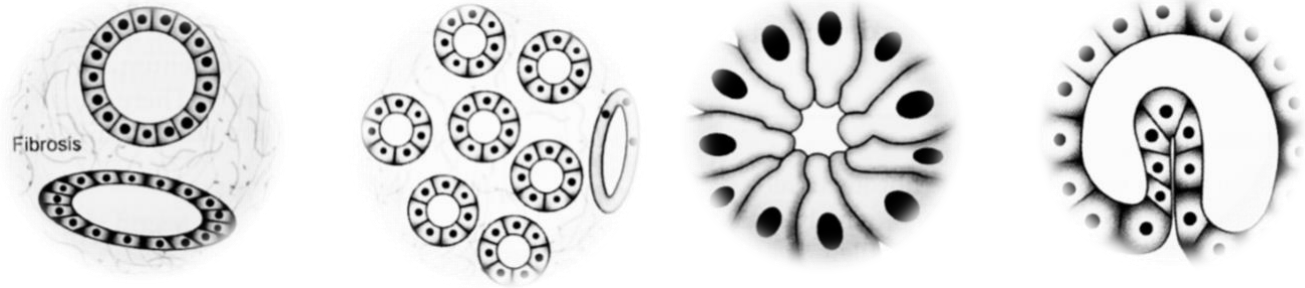
- Fibrocystic changes occur in glands and stroma,Which include fibrosis, duct ectasia, apocrine metaplasia, duct hyperplasia and sclerosing adenosis.
- Histology of fibrocystic disease shows cystic diltation of the terminal ducts with increased surrounding collagen fibers.
- Fibrocystic changes may be nonproliferative 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 blue domed cysts.
- These cysts vary in size with the menstrual cycle.
- These are most often enlarged and tender one week before menstruation.

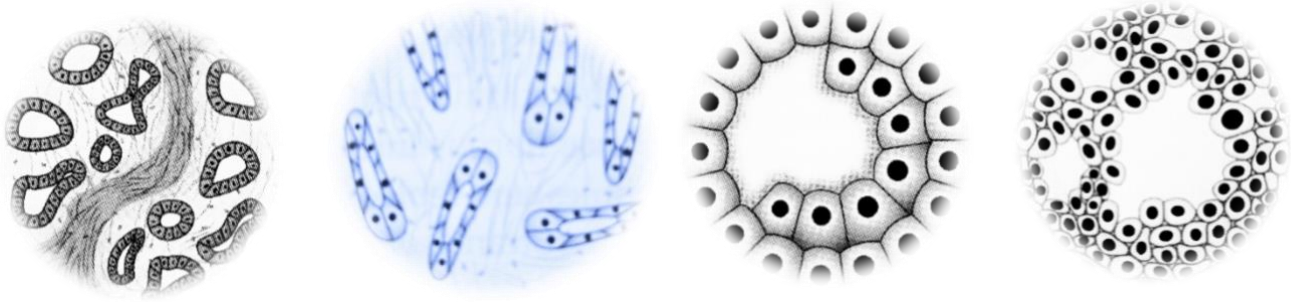
01.Histopathological Changes:

01.01.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



A. Cyst formation **B.Adenosis** **C.Apocrine metaplasia** **D. Papilloma**

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.



E.Fibrosis ***F.Sclerosing*** ***G.Typical epithelial Hyperplasia*** ***H.Atypical***

01.02.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]

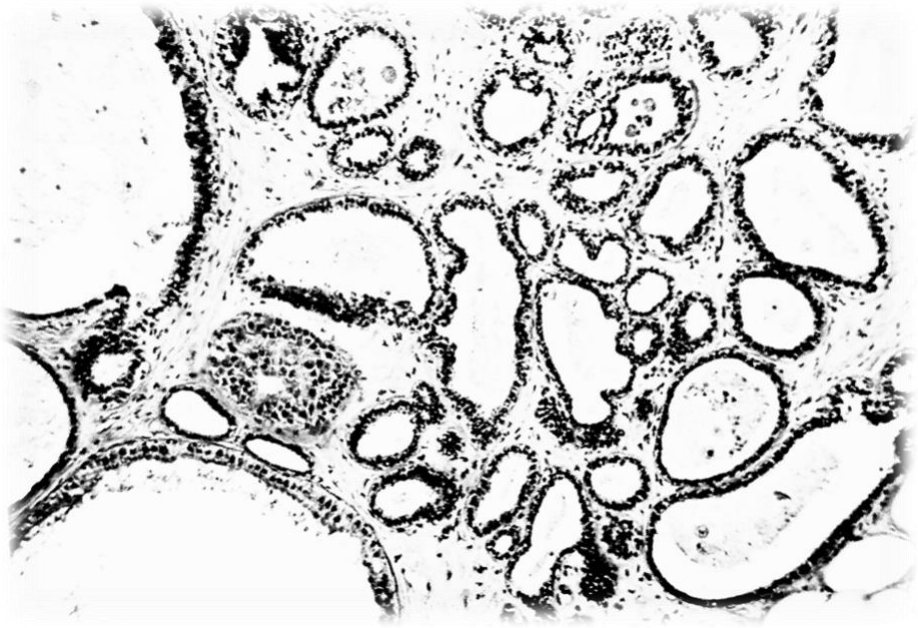
•**Fibrosis:** Rupture of cysts with extravasation of fluid in the stroma results in inflammation and fibrosis, Dense fibrous interlobular stroma expands into the lobules, and replaces the loose intralobular connective tissue.Strands of fibrous tissue constrict the ducts, so that the normal secretions 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]

02.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 lobulesTubules 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]

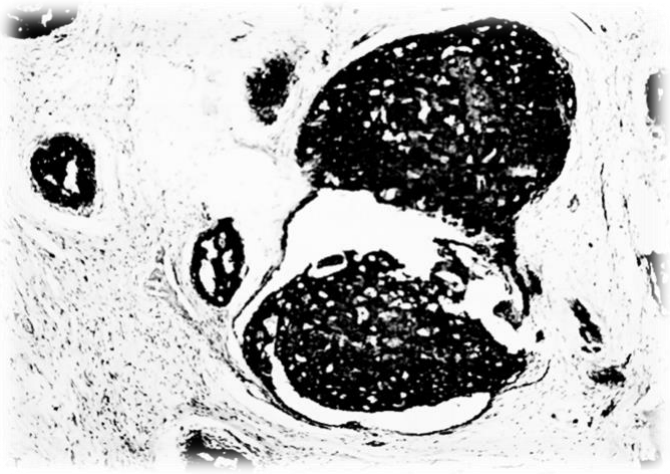
• **Ductal epithelial hyperplasia:** As the ducts are estrogen sensitive, florid ductal epithelial hyperplasia occurs within areas of fibrocystic changes.[4]



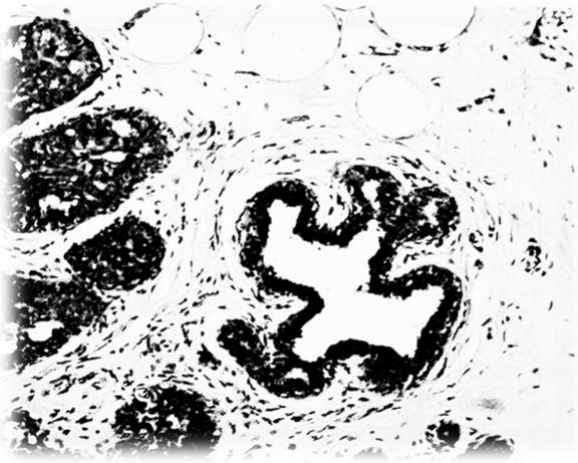
StructureA:Spectrum of morphological changes in fibrocystic disease of the breast showing duct dilatation, adenosis, fibrosis (intralobular and interlobular), and apocrine change (400X).

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.

03.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]



StructureB.Fibrocystic disease shows typical ductal hyperplasia.



StructureC:Fibrocystic disease shows atypical ductal hyper- plasia (arrow) (100X),

04.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 exami- nation distinguishes benign from malignant changes.[39]

Histological features	Ductal hyperplasia	Atypical hyperplasia/DCIS
Size	•Variable size,rarely extensive when associated with papilloma or radical scar.	•May be extensive, rarely <3 mm.
Cellular composition	•Epithelial cells along with spindle cells,lymphocytes,macrophages.Myoepithelial cell hyperplasia around periphery.	•Single cell population.Absence of spindle cells.Myoepithelial cells around periphery.

Architecture	•Variable.	•Well-developed micropapillary,cribriform or solid patterns.
Lumina	•Lumina irregular often ill-defined slit-like spaces common.	•Lumina well-delineated,regular,punched out in cribriform pattern.
Cell orientation	•Streaming pattern with long axis of nuclei arranged 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 cribriform type with nuclei oriented towards the luminal type.
Nuclear spacing	Uneven	Even
Epithelial cell character	Small ovoid with variation in shape	Small uniform monotonous appearance.
Nucleoli	Indistinct	Single small
Mitoses	Infrequent	Infrequent, abnormal form
Necrosis	Rare	If present, confined to small particulate debris in cribriform and/or luminal spaces.

Research Paper Overview

TOPIC:BREAST CARCINOMA

1]GENERAL CONSIDERATIONS:

The most important disease is breast carcinoma especially in postmenopausal women.It is second most frequent cause of death in women. Most breast diseases present as palpable lump.It is important to distinguish cases of breast carcinoma from benign breast disease.True nature of a breast lump is ascertained by histopathological examination of many areas of the excised lump.Good idea of nature of breast lump before surgery may be obtained by clinical features (size, texture, relation to adjoining tissues), mammographic examination of the affected breast, and cytological examination of smears obtained by fine needle aspiration cytology.Early detection is the most important factor in breast carcinoma survival. Most important risk factors for breast carcinoma are estrogen stimulation of breasts by ovarian hormones and advancing age.Breast carcinoma arises by accumulation of DNA mutations.[39][3][2]

Clinical Features

Breast lump is the presenting symptom in 85-90% of patients with breast carcinoma.Approximately 60% of breast masses are discovered by patient on self examination.Clinical breast examination is a necessary complement to screening mammography.

Distribution

Most glandular tissue is located in the upper outer quadrant and beneath the nipple.Thus, breast carcinoma is most commonly located in upper outer quadrant.It occurs most commonly in the left breast than right.

Origin

Breast carcinomas are derived from the epithelial cells that line the terminal duct lobular unit.These are classified according to their site of origin into ductal and lobular.Ductal carcinoma is the most common subtype followed by lobular carcinoma second most common (most often bilateral) with distant meta- stases.

Location

Breast carcinoma in decreasing frequency is located in upper outer quadrant (50%), central region beneath nipple (20%), lower outer quadrant (10%), upper inner quadrant (10%) and lower inner quadrant (10%), respectively.

In situ (noninvasive) breast carcinoma:*Ductal carcinoma in situ and lobular carcinoma in situ feature neoplastic cells confined within the basement membrane of ducts and lobules, respectively.Myoepithelial cells can be demonstrated in carcinoma in situ unlike invasive carcinoma.Noninvasive breast carcinomas include ductal carcinoma in situ, lobular carcinoma in situ, mixed intraductal carcinoma and lobular carcinoma in situ and papillary carcinoma and comedocarcinoma ductal carcinoma in situ with central necrosis).Ductal carcinoma in situ is detected by screening Mammography.[4][2][1]*

Invasive breast carcinoma:*When ductal/lobular carci- noma breaches basement membrane and invades the normal breast parenchyma, it is termed as invasive carcinomas are usually breast carcinoma.Lobular multifocal in origin.CA 125 is a cell surface glycoprotein originally identified in mucinous epithelial ovarian tumors.It is also expressed in carcinomas of endometrium, gastrointestinal tract, thyroid, and breast.[4]*

Histological type	Frequency
Carcinoma in situ	
Ductal carcinoma in situ	3.6%
Lobular carcinoma in situ (LCIS)	1.6%
Intraductal and lobular carcinoma in situ	0.2%
Comedocarcinoma with central necrosis	0.3%
Invasive carcinoma	
Ductal carcinoma (not otherwise specified)	70-75%
Lobular carcinoma	5-15%
Ductal and lobular carcinoma	1.6%
Tubular carcinoma	5%
Mucinous (colloid) carcinoma	2-3%
Medullary carcinoma	1-2%
Micropapillary carcinoma	1-2%
Metaplastic carcinoma	1%
Papillary carcinoma	0.8%

Markers of breast carcinoma
Serum tumor markers
CA 15.3 -PTHrP
CA 27.29-Mammoglobin
CEA-Gross systic
-Disease fluid
PS2 – protein 15 BRCA -(GCDFP-15)

Immunohistochemistry

ER-Galectin 3

PR-Cathepsin D

Srp27-Her2 neu

P53-Lactalbumin

Key Facts: Myoepithelial 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 (GFAP) and keratin 14.

•Myoepithelial cells are most often demonstrated in benign breast tumors and carcinoma in situ.

2]POSITIVE FAMILY HISTORY:

Incidence of breast carcinoma is greatly increased in first-degree female relatives of patients (mother, sister, or daughter) with carcinoma of the breast at a younger age.Family members may also transmit the abnormal susceptible gene (autosomal dominant with limited penetrance) without developing breast carcinoma themselves.Approximately 5% of cases are associated with a penetrant dominant genetic predisposition.Prophylactic mastectomies are performed in familial positive history of breast carcinomas.[14][11][10]

I]BRCA1 Tumor Suppressor Gene Mutation:

All families with strong family history of breast carcinoma may have mutation of BRCA1.It is a tumor suppressor gene located on chromosome 17p2.It regulates DNA repair by binding to RAD51, a molecule that mediates DNA double-strand repair breaks.BRCA1 gene mutation is responsible of 52% familial and rare cases of sporadic breast carcinomas (medullary carcinoma and metaplastic carcinoma).This is also associated with development of carcinoma of the ovary and prostate.[9][2][1]

II]BRCA2 Tumor Suppressor Gene Mutation:

BRCA2 gene is a tumor suppressor gene located on Chromosome 13q12-13. It regulates DNA repair by binding to RAD51, a molecule that mediates DNA double-strand repair breaks.BRCA2 gene mutation is responsible for 32% familial breast carcinoma.BRCA2 gene mutation is rarely demonstrated in sporadic breast carcinoma.[16][11]

III]Tumor Suppressor Gene Mutation p53;

Approximately 5% of families with breast carcinoma have mutation of p53 tumor suppressor gene.[12]

3]GENETIC DISORDERS: Women with genetic disorders are at increased risk of development of breast carcinoma. These are described as under;

1)Li-Fraumeni Syndrome:

Germline mutations of TP53 tumor suppressor gene cause Li-Fraumeni syndrome.Patients may develop multiple cancers such as breast carcinoma, leukemia, sarcoma, brain tumors, adrenal tumors, laryngeal and lung cancer.

2)Cowden Disease:

PTEN gene is located on chromosome 10q.Phosphatase and tensin homologue are proteins of PTEN gene.Normally, PTEN gene products inhibit AKT/PI3K signaling pathway.PTEN gene mutation leads to Cowden disease characterized by fibroadenomas, fibrocystic lesions, ductal epithelial hyperplasia, and nipple malformations.There is increased risk of breast carcinoma in Cowden disease.

3)Inherited Ataxia-telangiectasia:

Under physiological state, ATM gene is a caretaker tumor suppressor gene located on chromosome 11p22.It downregulates tyrosine kinase activity.Patients with ATM gene mutation have reduced capacity to repair DNA breaks resulting in accumulation of numerous genetic mutations overtime.Patient develops inherited ataxia-telangiectasia characterized by cerebral ataxia, immunodeficiency and dilations of small blood vessels.There is increased risk of breast carcinoma, gastric carcinoma, leukemia and lymphomas.

EXCESSIVE EXPOSURE TO ESTROGENS

•Postmenopausal estrogen therapy and oral contra- ceptive use increase the risk of breast carcinoma.Use of oral contraceptives for >4 years by younger women before their first term pregnancy almost increases risk of postmenopausal breast caracinoma.

• Risk of breast carcinoma increases in women, who receive hormonal replacement therapy for a period of 10-15 years.Hormonal replacement therapy increases breast density, which make detection of breast carcinomas more difficult.

• Hormones via blood circulation interact either with nuclear estrogen receptors of breast terminal duct lobular unit.The hormone-receptor interactions cause activation of DNA response elements leading to proliferation and differentiation factors.

ATYPICAL DUCTAL HYPERPLASIA

Presence of atypical changes in ductal epithelium in fibrocystic disease does increase the risk of breast carcinoma.

HISTORY OF BREAST CARCINOMA IN OPPOSITE BREAST

It is associated with increased incidence of involving opposite breast.

HISTORY OF ENDOMETRIAL CARCINOMA

Women with history of endometrial or ovarian carcinoma are at increased risk for breast carcinoma.

RADIATION EXPOSURE

During Second World War, risk of breast carcinoma among teenage girls has been observed due to low level ionizing radiation later in life.

DIETARY FACTORS

Diet high in animal fat increases five times risk of breast carcinoma in the United States than in Japan.

BREASTFEEDING

Longer period of breastfeeding reduces the risk of breast carcinoma. Lactation suppresses ovulation and may trigger terminal differentiation of luminal cells.

MOLECULAR GENETICS

Approximately 12% of breast carcinomas occur due to inherited gene mutations. Most of the genes play interrelated roles in maintaining genome integrity.

4]TSG[Tumor Suppressor Gene]:

A]BRCA1 Tumor Suppressor Gene:

• Location:BRCA1 is a tumor suppressor gene located on chromosome 17p21.

• Function:BRCA1 regulates DNA repair by binding to RAD51, a molecule that mediates DNA double-strand

• Gene mutation:It is responsible for 52% familial and repair breaks. 1-2% of all breast caracinomas. Risk is increased in age group by 70 years.Mutation of BRCA1 occurs by methylation.BRCA1 gene mutation is rare in sporadic medullary carcinoma and metaplastic carcinoma.[39]

Associated carcinomas:BRCA1 gene mutation may occur in cancers of ovary, male breast, prostate, pancreas and fallopian tube; but less than BRCA2.

B]BRCA2 Tumor Suppressor Gene:

•Location: BRCA2 is a tumor suppressor gene located on chromosome 13q12-13.

•Function:BRCA2 regulates DNA repair by binding to RAD51, a molecule that mediates DNA double-strand repair breaks.

•Gene mutation:BRAC2 gene mutation is rare in sporadic cases.

•Associated cancers:BRCA2 gene mutation also occurs in cancers of ovary, male breast, prostate, pancreas, stomach, gallbladder, bile duct, pharynx and melanoma.

C]TP53 Tumor Suppressor Gene;

•Location:It is tumor suppressor gene located on chromosome 17p13.1.

•Function:TP53 gene product halts cell cycle ihase by inhibiting nuclear transcription factor, until the DNA is repaired.It activates BAX gene induced cell suicide (apoptosis).It interacts with at least 17 cellular and viral proteins.

•Gene mutation:TP53 is responsible for 3% of familial and 20% in sporadic breast carcinomas.There is increased risk of breast carcinoma in 90% cases by the age of 70 years.

•Associated cancers:TP53 gene mutations are also demonstrated in pancreas (50-70%), lung, colon, and breast.TP53 gene mutation also occurs in Li-Fraumeni syndrome (breast carcinoma, sarcoma, leukemia, brain tumors and adrenal gland cancer).

D]CHEK2 Tumor Suppressor Gene:

•Location:CHEK2 is a tumor suppressor gene located on chromosome 22q12.1.

•Function:CHEK2 induces cell cycle arrest.It repairs damaged DNA.It activates BRCA1 and p53 tumor suppressor genes by phosphorylation.

•Gene mutation:Gene mutation is responsible for 5% of familial as well as sporadic breast caracinomas.Due to gene mutation, there is increased risk of breast caracinoma in 10-20% cases by 70 years of age especially after radiation exposure.It is worth mentioning that gene mutation is also demonstrated in cancers of prostate, thyroid and kidney.

E]RB Tumor Suppressor Gene;

•Location:It is a gatekeeper tumor suppressor gene.It is located on long arm of chromosome 13p14.Normal people have two alleles of the RB gene.

•Mechanism:RB gene codes for PRB protein, master brake on cell cycle.Dephosphorylated RB gene inhibits cell division.When the Rb gene is phosphorylated, cell division takes place.

•Associated cancers:Rb gene mutation is demonstrated in breast carcinoma, familial/acquired retinoblastoma, and familial/acquired osteosarcoma.Rb is also associated with cancers of colon, prostate and urinary bladder.

F]FGF3 (Fibroblast Growth Factor 3):

•Physiological state:FGF3 belongs to growth factor category.Many cancer cells, acquire the ability to synthesize the same growth factors to which they are responsive, generating an autocrine loop.

•Associated cancers:Amplification of FGF3 is associated with breast carcinoma, osteosarcoma, stomach carcinoma, bladder carcinoma and melanoma.

G]INT2 Oncogene:

•Physiological state:INT2 belongs to growth factor category.Many cancer cells acquire the ability to synthesize the same growth factors to which they are responsive, generating an autocrine loop.

•Associated cancers:Increased baseline activity of INT2 has been demonstrated in breast carcinoma and melanoma.

H]ERBB2 (Her2 neu) Oncogene;

•Physiological state:ERBB2 (Her2 neu) belongs to growth factor receptor family.It encodes for an epithelial growth factor receptor on the cell membrane that delivers continuous mitogenic signals to the cells.

•Gene mutation:Amplification of ERBB2 (Her2 neu) delivers continuous mitogenic signals to the breast carcinoma cells even in the absence of growth factor in the environment.It is most often observed in ductal carcinoma and rarely in lobular carcinoma.

•Immunohistochemistry:ERBB2 (Her2 neu) is demons- trated by immunohistochemistry on the cell membrane or using fluorescent in situ hybridization (FISH).It is marker of aggressive breast carcinoma.

I]Notch1 Oncogene;

•Physiological state:Notch1 gene belongs to Notch signal transduction protein category.

•Gene mutation:Point mutation or translocation of Notch1 gene is associated with breast carcinoma, leukemia and lymphomas.

J]RAS (RAT Sarcoma) Oncogene:

•Physiological state:It activates several intracellular signal transduction pathways and activation of the transcription factors ‘fos’ and ‘jun’.

•Associated cancer:RAS gene mutation is associated with breast carcinoma.

K]C-MYC Oncogene (Nuclear Transcription Factor):

•Physiological state:C-MYC is nuclear regulatory protein that controls the expression of several genes.

•Associated cancer:Mutation of C-MYC is demonstrated in breast carcinoma.

L]BCL-1 Cell Cycle Regulatory Gene;

•BCL-1 codes for cyclin D1, acts as stimulatory protein of the cell cycle.Mutation of BCL-1 causes loss of regulation of cell cycle resulting in breast carcinoma.

M]Cyclins and Cyclin-dependent Kinase:

•Physiological state:CCND1 and cyclin D1 are cell cycle regulators.

•Gene mutation:CCND1 and cyclin D1 are activated by translocation and amplification.Deregulation of cyclins due to mutation is associated with breast carcinoma.

N]E-Cadherins:

•Physiological state:E-Cadherins belong to CDH1 category.E-Cadherins are inhibitors of invasiveness and metastases.

•Gene mutation:E-Cadherins are irreversibly lost in invasive lobular breast carcinoma, but expressed in invasive ductal breast carcinoma.Germline and somatic mutations of cadherin play an important role in the pathogenesis of gastric carcinoma (diffuse type).

O]PTEN Tumor Suppressor Gene;

•Physiological state:PTEN gene is located on chromo- some 10q.It is inhibitor of mitogenic signaling pathway.

•Gene mutation and thyroid gland:PTEN gene mutation is associated with Cowden disease characterized by fibroadenoma, fibrocystic disease, ductal epithelial hyperplasia, nipple malformations, breast carcinoma and endometrial carcinoma.

P]Galectin 3;

•Physiological state:Galectin 3 is a member of lectin family.It is encoded by LGALS3 gene located on chromosome 14, locus q21-q22.It is expressed in the nucleus, cytoplasm and extracellular space.

•Overexpression:Its overexpression promotes neo- plastic transformation and the maintenance of trans- formed phenotypes as well as enhances adhesion of tumor cells to the extracellular matrix in breast carcinoma.

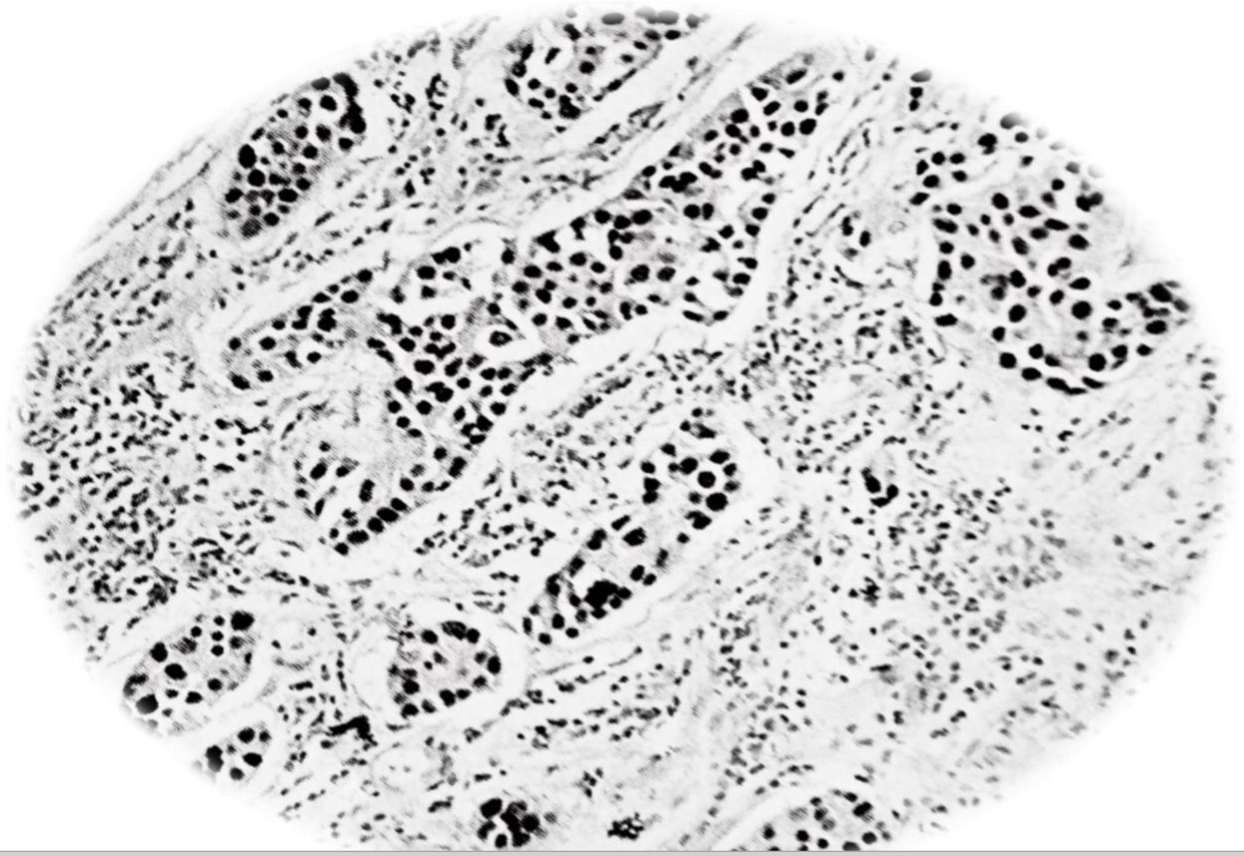
5][Major Molecular Pathway In Evaluation]:A]ER Positive Molecular Pathway (Luminal A &Luminal B):

Immunohistochemistry

Immunohistochemistry of luminal type A and B breast carcinoma.

Immunohistochemistry of luminal type A breast carcinoma shows positivity for ER/PR and cytokeratin (8; 18).

Marker	Luminal type A	Luminal type B
Estrogen receptor (ER)	+++	+
Progesterone receptor (PR)	++	+
Her2 neu	-	-/+
Cytokeratins (8; 18)	+	+



Structure:A1 [Microscope]Breast cancer-infiltrative duct carcinoma shows progesterone receptor positivity (100X).

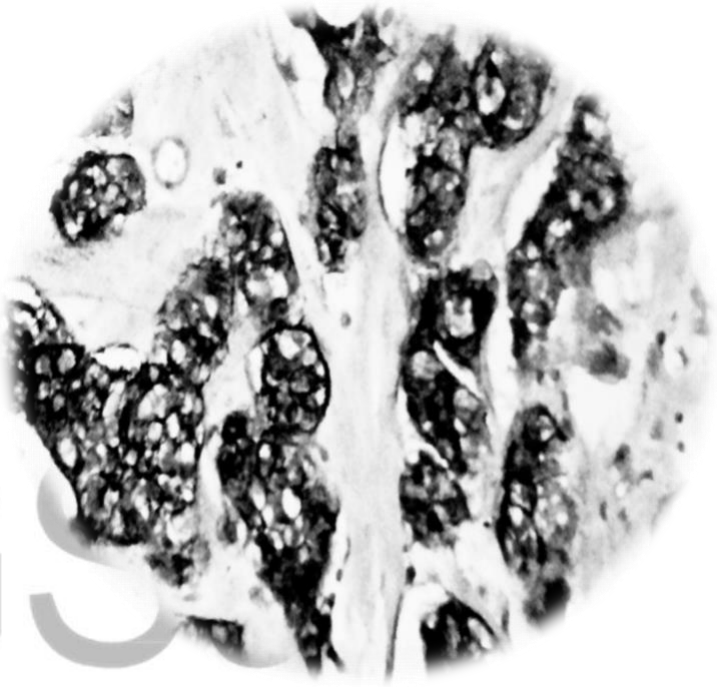
B]HER2 NEU ENRICHED MOLECULAR PATHWAY :

Salient Features:Her2 new is located on chromosome 17q.Amplification of Her2 neu is responsible for 20% cases of breast carcinomas.It is the most common type of breast carcinoma in patient with germline mutations in TP53 (Li-Fraumeni syndrome).Patient develops atypical ductal hyperplasia progressing to ductal carcinoma in situ resulting in invasive breast carcinoma.[41][28][4][1]

Clinical Course:Her2 neu enriched invasive duct carcinoma is high- grade tumor with higher proliferative rate and poor prognosis.It most often shows involvement of axillary lymph nodes.

Immunohistochemistry

Immunohistochemistry of Her2 neu enriched mole- cular pathway of breast carcinoma shows Her2 neu positivity. Tumor cells may be ER positive/negative.



Structure B2:Breast cancer-infiltrative duct carcinoma shows Her2 neu positivity. These patients are treated with herceptin (400X).

Marker	Expression
Her2 neu	Positive
Estrogen receptor (ER)	Positive /Negative

Treatment : These patients respond to herceptin and anthracycline based chemotherapeutic agents.

C]ER AND HER2 NEU NEGATIVE MOLECULAR PATHWAY:

Salient Feature:It is least understood pathway due to inheritance of BRCA1 gene mutation responsible for 15% of breast carcinomas.These tumors have a basal-like pattern of mRNA expression in normal myoepithelial cells.Basal cell type of breast carcinoma has high proliferative rate with positive lymph nodes and high recurrence rate.TP53 gene mutation is very common.These breast carcinomas show high expression of basal epithelial genes and TP53 gene mutations, dysfunction of BRCA1 gene.Ki-67 is expressed in <14% cases.[5][2]

Progression of DCIS to Invasive Breast Carcinoma:TP53 gene mutation and inactivation of BRCA1 directly cause ductal carcinoma in situ progressing to invasive breast carcinoma.

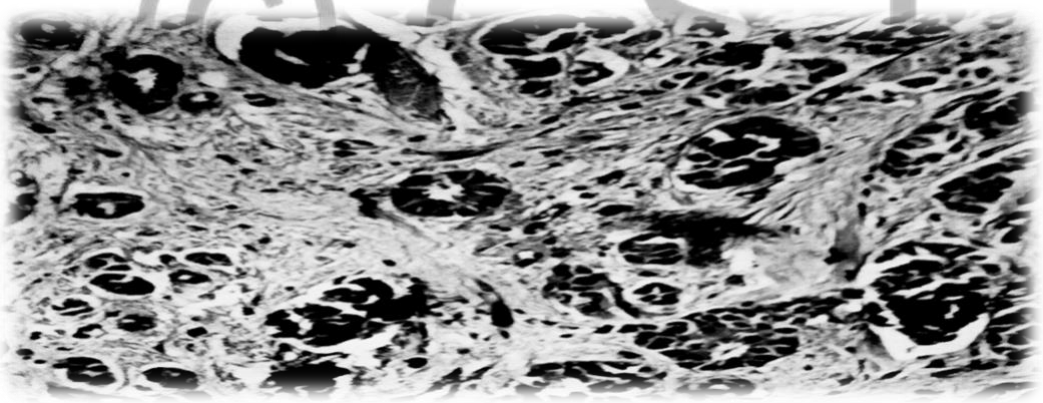
•Immunohistochemistry:These tumors are triple negative, i.e. ER/PR and Her2 neu negative.

•Estrogen receptor (ER)- Negative •Progesterone receptor (PR)- Negative •Her2 neu- Negative

Treatment:These patients do not respond to endocrine therapy (tamoxifen), aromatase inhibitors or herceptin. Prognosis is poor.Trials are going onto treat these patients with platinum-based chemotherapy or PARP inhibitors.[6]

D]DUCTAL CARCINOMA;

Ductal carcinoma in situ has two histological variants:comedocarcinoma and non-comedocarcinoma.Tumors may be low, intermediate and high-grades.Low-grade DCIS shows monomorphic cells with nuclei polarized towards luminal spaces, occasional mitosis.Nuclei are not polarized towards luminal spaces.



Structure D:Breast carcinoma shows invasive ductal carcinoma with microcalcifications.Tumor is composed of pleomorphic atypical cells with hyperchromatic nuclei, The cells are arranged in clusters

High-grade DCIS is composed of pleomorphic cells with vesicular hyperchromatic nuclei prominent nucleoli.

E]INVASIVE DUCTAL CARCINOMA (NOS):

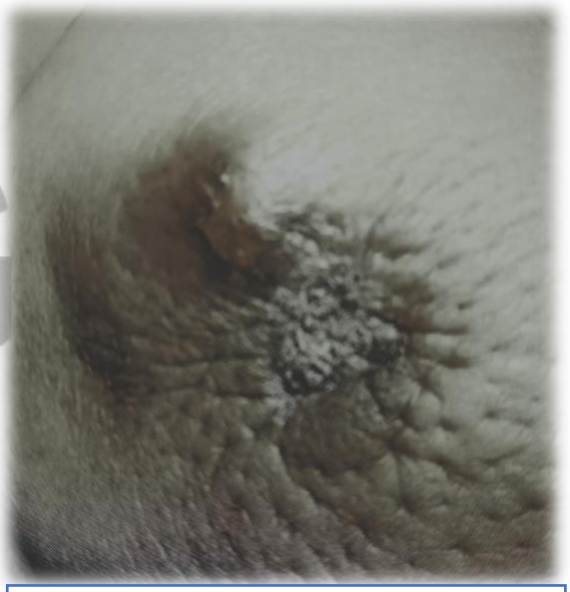
Invasive ductal carcinoma (not otherwise specified) is commonest type of breast carcinoma.Most invasive ductal carcinomas may evoke a dense fibroblastic response (proliferation of fibroblasts producing collagen fibers) in the host tissue that adds to the lesion's bulk.[4]

It replaces normal breast fat.Prognosis is stage dependent.Tumor has firm to hard consistency (schirrhous), and chalky white discoloration due to desmoplasia.Nipple retraction due to desmoplasia in an underlying advan- ced breast carcinoma is a late feature of breast carcinoma.[6]

Clinical Features:Patient presents with poorly defined solitary, non- tender breast lump of variable consistency and mobility with nipple retraction.It is solid hard, dense and fixed to the underlying tissues or skin due to invasion of breast carcinoma.[5]

Nipple Retraction;A recent retraction suggests breast carcinoma, which causes fibrosis of the whole duct system and pulls in the nipple, known as retraction of the nipple.Fibrosis also contracts the suspensory ligament, that pulls the nipple inward is known as dimpling (also called a skin tether).

Structure E1:Show Nipple Retraction (Outer).



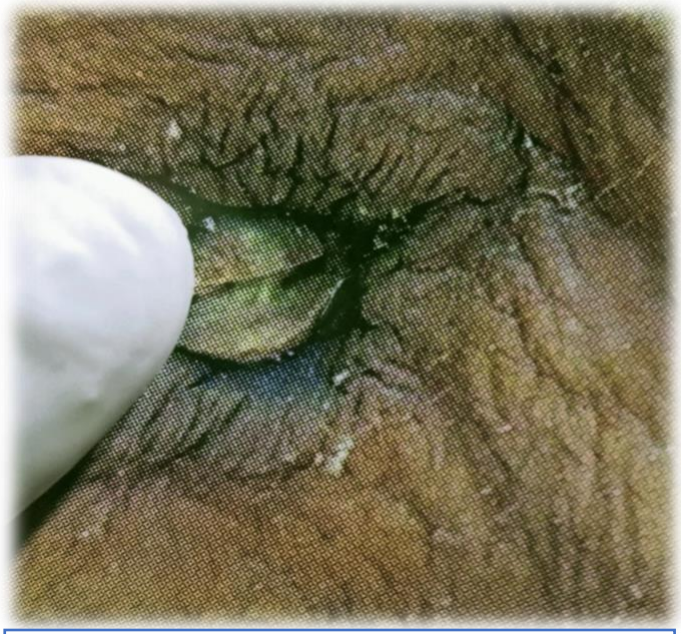
Structure E2:Peau d' orange appearance occurs due to obstruction of dermal lymphatics by tumor cells.

Gross Morphology

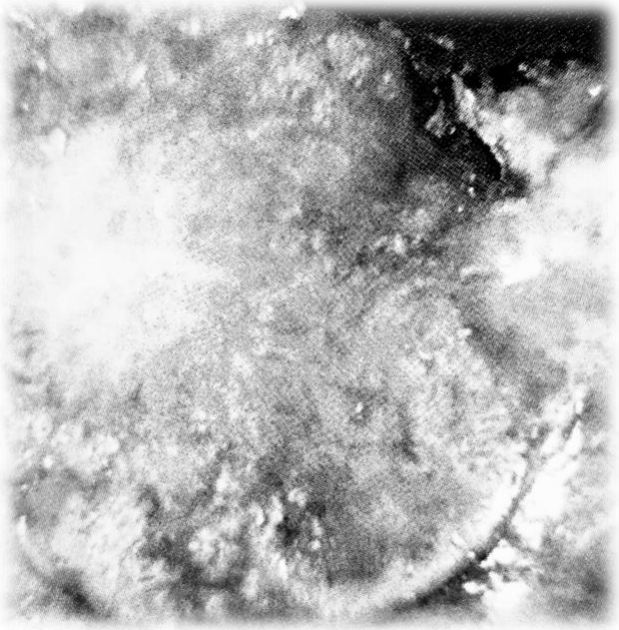
• Tumor is firm to hard, irregular, and fibrous extension into the adjacent breast stroma that create stellate (crab-like) outline measuring 1-4 cm (rarely 4-5 cm).

• Cut section reveals gray chalky white tissue yellow crab-like satellites extending into the yellow fat tissue.

• Skin surface may show retraction of nipple.



Structure E3:After cut the part these normally shrink(Surgery phase).



Structure E4:Surgery phase.

Overlying Skin:The peau d'orange (skin edema) appearance of the breast skin occurs due to obstruction of the dermal lymphatics by cancer cells.

Light Microscopy:

•Tumor comprises poorly differentiated pleomorphic cells with hyperchromatic nuclei, and abundant mitoses.

•These cells are arranged in irregular nests and cords or glandular structures within a dense fibrous stroma.

•Tumor cells invading lymphatic channels, blood vessels and perineural spaces may be seen.
•Microcalcifications may be seen.

Immunohistochemistry:

•The cadherin family of cell adhesion molecules is group of transmembrane glycoproteins located in desmosomes.

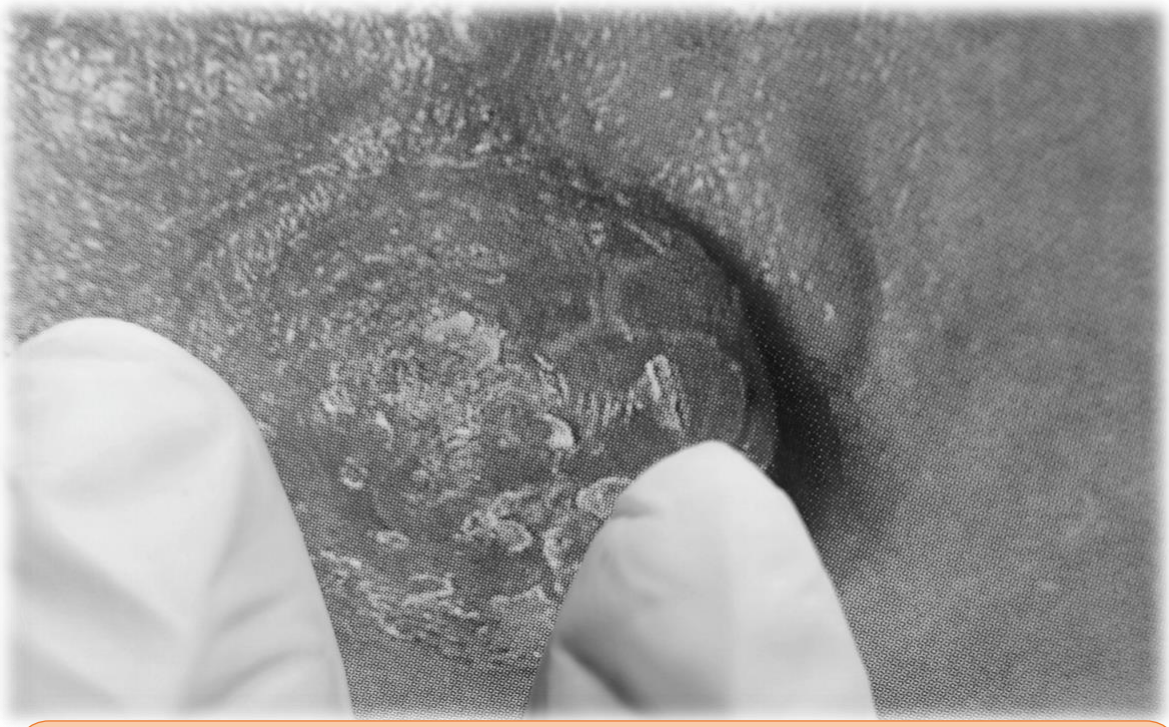
•E-Cadherins are present in ductal carcinoma and absent in lobular carcinoma of the breast.

F]PAGET'S DISEASE OF BREAST:

Paget's disease shows intraepidermal cancer cells in overlying epidermis of nipple and areola derived from an intraductal breast carcinoma.Patient presents with eczematous lesion with crusted, eroded surface over nipple and areola.Malignant cells in epidermis are known as Paget's cells.The tumor is most often poorly circumscribed.This condition is more frequently found in older women.[4][2][1]

Etiopathogenesis:The production by keratinocytes of heregulin-a, which acts via the Her2 neu receptor, may play a role in its pathogenesis.[39]

Clinical Features:Paget's disease of the breast affects the nipple from the start, whereas eczema affects the areolar region first and only rarely affects the nipple skin, which eventually leads to erosion and ulceration of the nipple in elderly women.On examination, a painless mass is palpable in the underlying breast in 50% of cases, and often associated with delay in diagnosis.



Structure F1:Eroded surface over nipple and areola.

Light Microscopy:

- Histopathological examination reveals either in situ or invasive ductal carcinoma, which involves overlying epidermis of nipple and areola.
- The tumor cells in the overlying epidermis are called as Paget's cells.

- Paget's cells within the surface epithelium of the Nipple and areola are large cells with abundant clear cytoplasm and large nuclei with prominent nucleoli, arranged singly or in clusters; represent intraepithelial extension of an underlying ductal carcinoma in situ or invasive ductal carcinoma.[39][4]

Histochemistry:PAS stain demonstrates mucin within the Paget's cells of Paget's disease of the breast in right section.This is evidence for their origin from an underlying ductal carcinoma.[39]

Immunohistochemistry:

•By immunoperoxidase staining, they will also be cytokeratin positive (low molecular weight) and epithelial membrane antigen (EMA) positive.

•Cytokeratin (low M.W.) - Positive

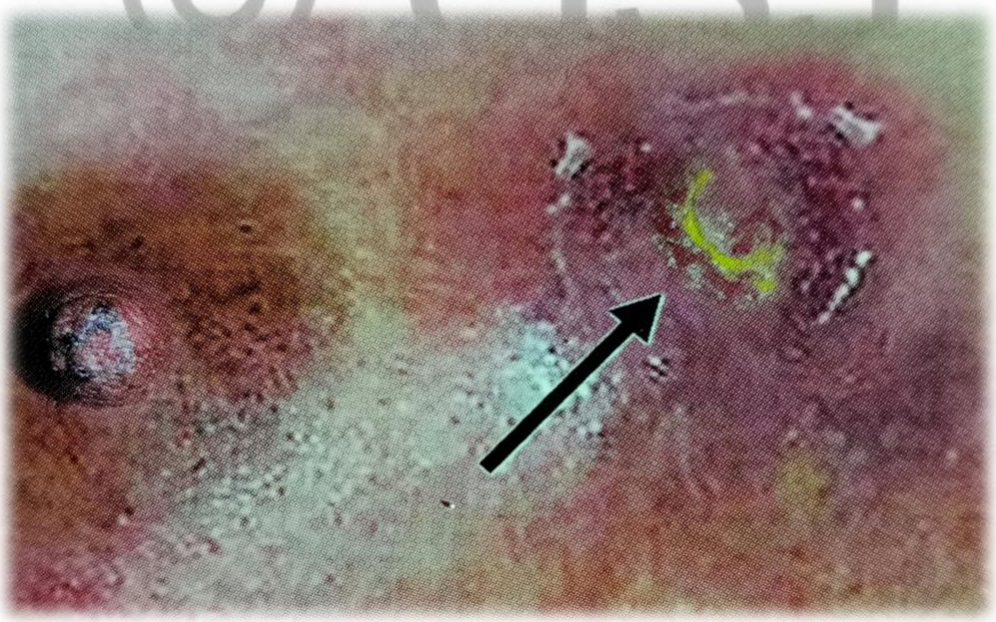
•Epithelial membrane antigen (EMA) - Positive

Mammography:If Paget's disease is suspected on clinical examination, mammography should be performed to determine if there is an underlying lesion.

Diagnosis:Diagnosis is established by cytology (e.g. smears from imprint and scrapping) or wedge biopsy of nipple.

G]INFLAMMATORY CARCINOMA:

Rapidly growing breast carcinoma metastasizing in dermal lymphatic channels results in thickened, erythematous (red), rough, swollen, hot skin as a consequence of inflammatory process.Edema usually begins in the skin around and beneath the areola, the most dependent area of breast.[24][11][2][1]



Structure G1:Breast cancer shows Inflammatory carcinoma.

Prognosis:Prognosis is poor in inflammatory breast carcinoma.Patient is treated by chemotherapy followed by surgery end irradiation.

H]COLLOID (MUCINOUS) CARCINOMA;

Colloid breast carcinoma accounts for 1-4% of breast carcinomas.It features abundant mucin production.

Molecular Genetics:BRCA1 gene mutation is demonstrated in some cases.Amplification of ERBB2 (Her2 neu) is seen in some cases.

Clinical Features:It is uncommon slow-growing neoplasm primarily seen in elderly women as a small well circumscribed mass.

Gross Morphology:Tumor is well circumscribed tumor with soft consistency measuring 1-5 cm in diameter with an average of 2.8 cm.

Structure H1:Colloid carcinoma of the breast. This sagittal slice of the breast shows that it is completely replaced by mucoid tumor.

•Cut surface of tumor is completely replaced by glistening gelatinous blue to gray-colored mucoid material.

Light Microscopy

• Tumor is composed of small islands or clusters of generally uniform, round epithelial cells (10-20 cells) arranged in trabeculae, nests, sheets or acini with glandular lumen, floating within extensive lakes of extracellular mucin pool synthesized by tumor cells.

- Mucin dissects into the surrounding stroma.Tumor contains >90% of mucinous component.

Immunohistochemistry

- Most tumors express hormone ER (estrogen receptors) in 80%.

Prognosis:It is low-grade malignant tumor with low incidence of metastases.It has better prognosis than conventional ductal carcinoma.

I]TUBULAR BREAST CARCINOMA;

It accounts for 1 to 4% of invasive breast carcinomas.A higher frequency (up to 19%) has been reported in small and screen-detected breast carcinomas in whites compared with blacks.It affects younger age at onset (40s).It is luminal A type low-grade invasive ductal cell carci- noma.It shows low proliferative rate.Recurrence rate is low.[12]

Molecular Genetics:Amplification of ERBB2 (Her2 neu) is unusual.

Clinical Features:Patient presents with breast lump measuring 2 mm to 1.5 cm in diameter.Most are 1 cm or less, but rarely examples of 2 cm or above is encountered.

Gross Morphology

- The tumor is usually small (<2 cm), firm to hard in consistency, and often detected on mammography.
- There is increased incidence of cancer in opposite breast in 10-40% of cases.

Light Microscopy

Diagnosis is made when 75% of neoplasm shows well-formed small duct structures embedded in cellular stroma.

Tumor shows bland-looking tumor cells arranged in tubules that possess widely patent lumens lined by low-grade single cell layer.

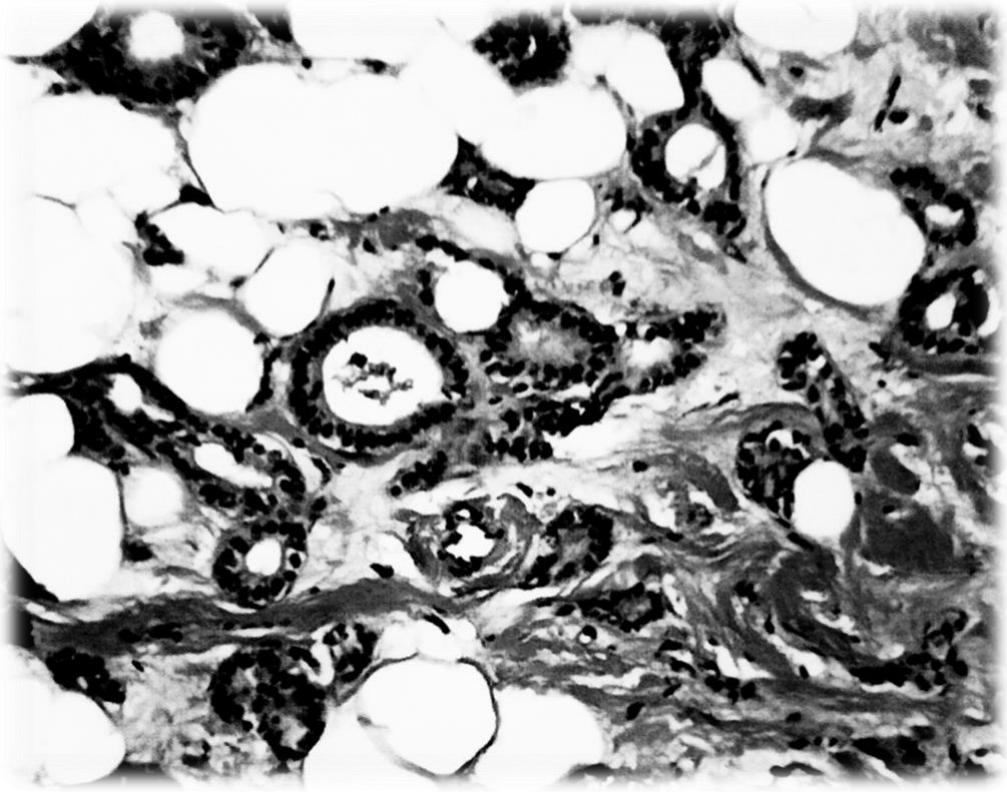
Myoepithelial cells are absent, and the malignant tubules are arranged in an irregular stellate pattern.

The intervening stroma is densely fibrotic.Mitoses are rare.

It may be difficult to separate from sclerosing adenosis or radial scar but generally spread outside the confines of enlarged lobules.

Immunohistochemistry:Virtually all tubular carcinomas express ER and PR hormone receptors and cytokeratin (8; 18).[13]

- Estrogen (ER) – positive
- Progesterone (PR) – positive
- Cytokeratin (8; 18)- positive



Structure I1:Tubular carcinoma of breast.The intervening stroma is densely fibrotic (400X).

Treatment:These patients respond to tamoxifen, aromatase inhibitors and herceptin.

Prognosis:Prognosis is better despite multifocal nature and bilateral involvement.Lymph node metastases are rare.

J]PAPILLARY BREAST CARCINOMA:

It constitutes approximately 1-2% of breast carcinoma.

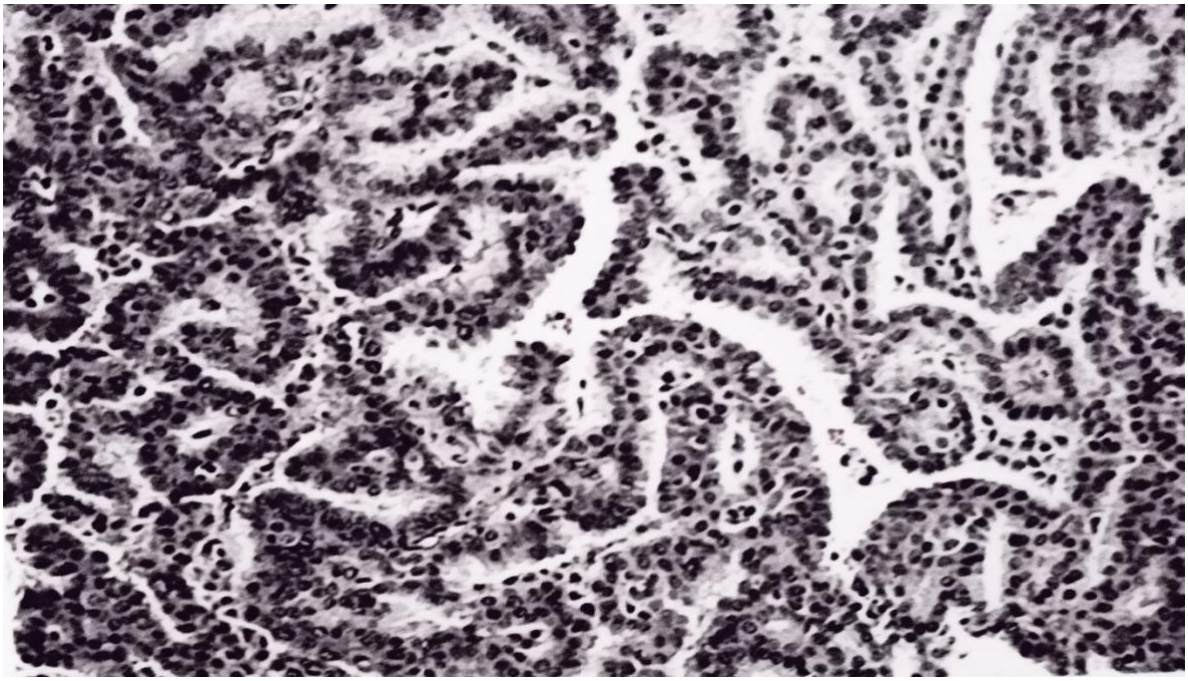
Clinical Features:Approximately 50% tumors are located beneath the nipple (associated with bloody nipple discharge).

Gross Morphology

•The tumor is usually 2-3 cm in size, and well- circumscribed.

•Cystic lesions contain brown mixture of blood clot and neoplastic tissue.

Light Microscopy:The tumor is composed of delicate fibrovascular tissue lined by atypical epithelial cells with hyperchromatic nuclei and mitoses forming papillary structures with the absence of an outer myoepithelial cell layer.It must be differentiated from papilloma that is characterized by thick fibrovascular tissue and presence of myoepithelial cells.Periphery of cystic tumor is fibrotic and distinguishing invasion may be difficult unless neoplasm reaches fat.[41][2][1]



Structure J1:Invasive papillary carcinoma breast is comprised of delicate fibrovascular tissue lined by atypical epithelial cells with hyperchromatic nuclei and mitoses forming papillary struc- tures with the absence of an outer myoepithelial cell layer (400X).

K]INVASIVE MICROPAPILLARY BREAST CARCINOMA;

It is luminal type B invasive breast carcinoma:It is seen in <20% of cases. It has higher proliferative rate than luminal A-type.Recurrence is high.It should be differentiated from duct papilloma.[39]

Light Microscopy:Invasive micropapillary carcinoma shows rounded groups of tumor cells with a peripheral clear rim and lacks true fibrovascular core.[4]

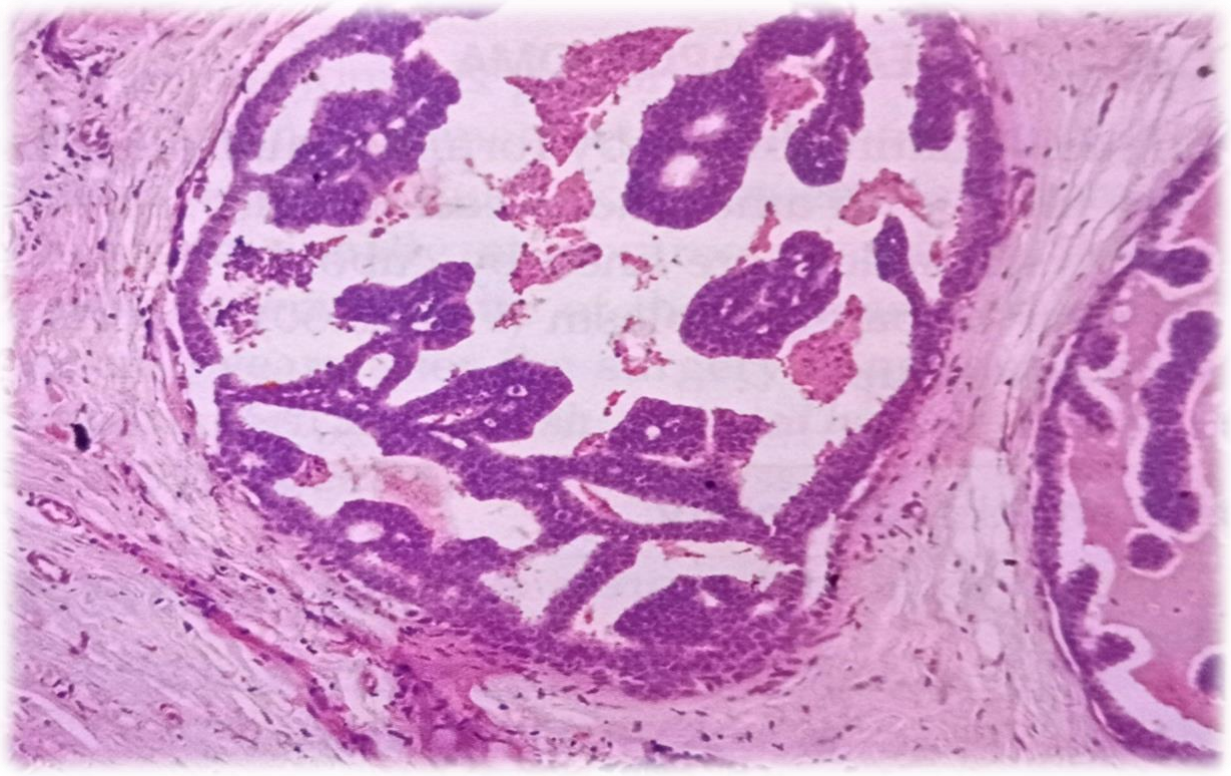
Immunohistochemistry:Tumor cells may show low expression of ER and PR.Immunohistochemistry shows cytokeratin positivity (8; 18).[3]

Estrogen receptor (ER)-Low expression.

Progesterone receptor (PR)-Low expression.

Cytokeratins (8; 18)-positive.

Prognosis:Prognosis may not be as good as in luminal type A.



Structure K1:Micropapillary carcinoma of breast.It shows large duct with micropapillary tufts of epithelial cells lacking true fibrovascular core (400X.

L]METAPLASTIC BREAST CARCINOMA:

Metaplastic carcinoma of the breast is a form of breast carcinoma that shows differentiation towards malig- nant squamous epithelium, cartilaginous, or bony tissue.This term is used to describe a heterogeneous group of Neoplasms.It is also known as carcinosarcoma.It is basal like subtype of breast carcinoma.It has high proliferative rate with positive lymph nodes.Recurrence rate is high.[40][33][21][9][4]

Molecular Genetics;

•TP53 gene mutation is very common.It shows dysfunction of BRCA1 gene.

•Ki-67 is expressed in <14% cases.

Treatment:Patients do not respond to tamoxifen, aromatase inhibitors and herceptin.Trials are going onto treat these patients with platinum-based chemotherapy or PARP inhibitors.

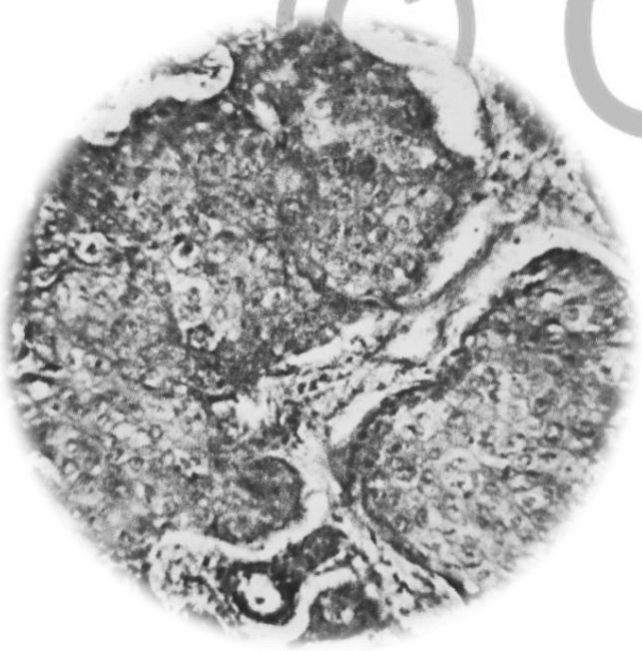
Light Microscopy:

- Metaplastic carcinoma includes monophasic or biphasic sarcomatoid carcinoma.
- Tumor is admixture of malignant epithelial component (adenocarcinoma grade 2 or 3) with malignant mesenchymal elements including cartilage, bone, and myxoid stroma, and/or squamous or spindle cell elements.

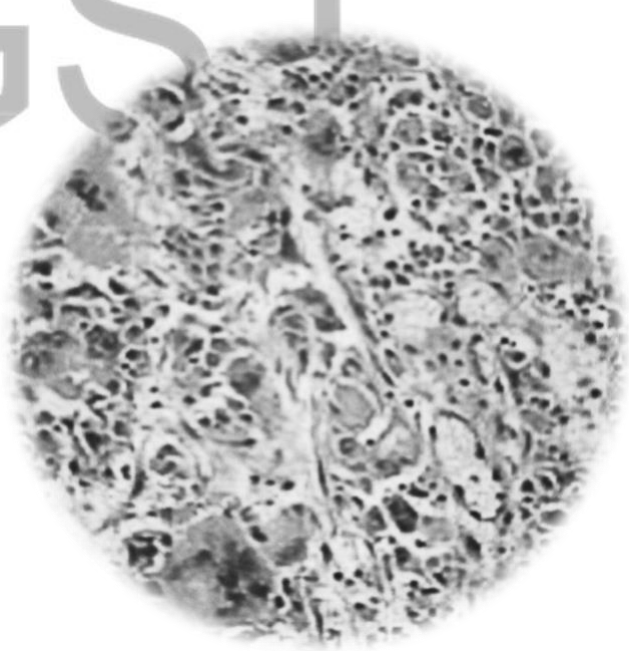
Immunohistochemistry:It shows co-expression of cytokeratin (5; 6) and vimentin in spindle cell elements of metaplastic carcinomas.[4]

Tumor cells are triple negative for estrogen and progesterone receptors as well as Her2 neu.

- Cytokeratins (5; 6)-Positive
- Vimentin-Positive
- Estrogen receptor (ER)-Negative
- Progesterone receptor (PR)-Negative
- Her2 neu-Negative



StructureATumor shows mixed squamous cell carcinoma and ductal carcinoma components.



StructureB:The intervening areas show malignant spindle cell proliferation.It is high-grade breast cancer with poor prognosis (400X).

0.6Current Update:September 12, 2023, by Sharon Reynolds:

It has become widely accepted that it's always best to find breast cancer as early as possible, when the cancer is less likely to have spread elsewhere in the body and less aggressive treatment may be needed.Studies have shown that routine screening mammography does reduce breast cancer deaths in women aged 40 to 75.Screening also comes with downsides, which include the risk of overdiagnosis and overtreatment. A new study suggests that the risk of overdiagnosis with routine screening mammography is substantial for women in their 70s and older.This overdiagnosis risk escalates with increasing age and other health problems, according to findings published August 8 in the Annals of Internal Medicine.The concept of overdiagnosis is a tricky one. It doesn't refer to false positives—test results that indicate that a suspicious mass is cancer when further tests show that it actually isn't. Instead, in overdiagnosis, a screening test does find a true cancer. But it's a cancer that will grow very slowly—or not at all—and would never cause problems during someone's lifetime.Treatment for such cancers would, by definition, be unnecessary. But since there is currently no way to tell which breast cancers found on screening mammograms will grow, and how fast, women who have such cancers almost always have surgery, and sometimes additional treatments.Because older or frail women are most likely to have a shorter remaining life span, the prospect of overdiagnosis has led to sometimes intense debate about whether it's appropriate to screen these women for breast cancer.The suggestion that screening may not be helpful [for some people] is tricky," said Ilana Richman, M.D., from Yale School of Medicine, who led the new study. We don't want our patients to think that we're giving up on them, when what we're really after is just the opposite—focusing on care that improves quality of life by avoiding tests that are unlikely to be beneficial."It can often take 10, 20, even 30 years for a slow-growing breast cancer to cause harm," added Mara Schonberg, M.D., from Beth Israel Deaconess Medical Center, who was not involved with the new study. "So, for older women with other health conditions, with frailty, ... diagnosing breast cancer and treating it [may] only cause additional problems."[New Contains]

07.Conclusions: This research paper evaluates a new approach to treating and preventing breast cancer and gives information about how to treat breast cancer Breast cancer is a complex and challenging disease that affects millions of people worldwide.Early detection, through regular screening and awareness, remains a key factor in improving outcomes.Advances in research, treatment options, and support systems offer hope for those affected by breast cancer.Continued efforts in education, research, and support are crucial in the fight against this disease, with the ultimate goal of reducing its impact and improving the quality of life for those affected.Genetic factors play a significant role, with mutations in certain genes, such as BRCA1 and BRCA2, increasing the risk of developing breast cancer.Hormonal factors, particularly estrogen and progesterone, are also implicated as high levels of these hormones can stimulate the growth of breast cancer cells.Environmental factors include exposure to carcinogens and radiation, which can increase the risk of breast cancer.Lifestyle factors like diet, alcohol consumption, and physical activity also influence the likelihood of developing the disease.Another theory is the "somatic mutation theory," which emphasizes the accumulation of genetic mutations in breast cells over time.These mutations can lead to uncontrolled cell growth and the formation of tumors.The "inflammatory theory" suggests that chronic inflammation in breast tissue may contribute to cancer development. Inflammation can cause DNA damage and promote the growth of cancer cells.In recent years, researchers have focused on the role of the immune system and the

“immune surveillance theory.” This theory suggests that the immune system plays a critical role in detecting and eliminating early-stage cancer cells, and a weakened immune response may contribute to cancer development.Breast cancer prevention involves a combination of lifestyle choices and risk reduction strategies.Breast cancer is a type of cancer that begins in the cells of the breast. It can manifest physically in various ways, including:Lump or Mass: A common sign of breast cancer is the presence of a painless lump or mass in the breast or underarm area.Changes in Breast Size or Shape: Breast cancer can cause noticeable changes in the size or shape of the breast.Skin Changes: Skin on or around the breast may become red, dimpled, or develop other unusual textures.Nipple Changes: Changes in the nipple, such as inversion, discharge, or skin scaling, can be indicative of breast cancer.[all about the research]

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_____Thank You_____