Breast

Embryology:

- The Breast Develop from Ectodermal Ridge (Milk line), which extend from Anterior Axillary fold into Groin.
  - ↳ Amastia → No Breast (Nipple & tissue)
  - ↳ Athelia → No Nipple.
  - ↳ Amazia → present Nipple but no Breast tissue.

Anatomy:

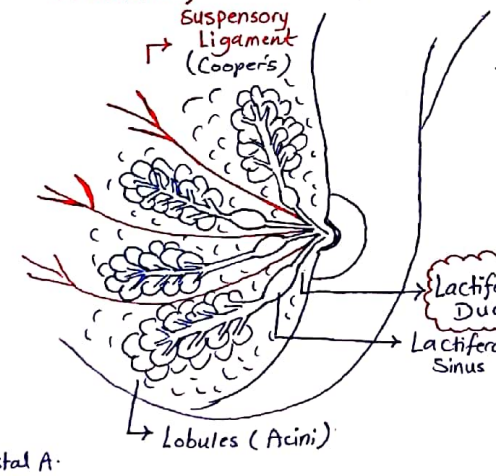
- The Breast is a modified sweat gland, consist of:
  1. Mammary Glands → Lobules (15-20) ⊕ Ducts
  2. Fat
  3. Connective tissue
  4. Lymphatics
- It extends from 2nd to 6th rib, from Lateral border of sternum to Mid Axillary line.
- Axillary tail ⇒ Peirce deep fascia & enter axilla between Latissimus Dorsi & pectoralis major muscle.

* Blood Supply:

- Arterial Supply: 1. Subclavian A. → Internal Thoracic → Intercostal A.
  2. Axillary A. → Lateral thoracic.
- Venous Drainage: - Drained by corresponding veins → Azygus vein
  → Vertebral veins (Breast Ca can early metastisize to the vertebra)
- Lymphatic Drainage:
  - upper quadrant → Apical LN
  - Lateral quadrant → Anterior Axillary LN ⇒ 85%
  - Medial quadrant → Internal thoracic LN. ⇒ 25%
  - Lower quadrant → peritoneal & Abdominal LN (Sister-Mary-Joseph Nodule)

Developmental Abnormalities

1. Ectopic Breast (Hekrotopia) - The most common-
   → Most common sites → chest wall, Axilla, valva.
   → It could be only Nipple (Polythelia) or Glandulartissue (Polymastia)
   → More prone to malignant changes & Breast ca. at earlier age.
2. Breast Hypoplasia → Iatrogenic → Trauma or Radiotherapy.
   → Congenital → 1. ulnar-mammary syndrome 2. Poland syndrome
   (↑ Breast Ca.) 3. Turner syndrome 4. CAH ⊕ Abscent Pectoralis major muscle. ⊕ Brachysyndactyly.



* Primary secretory unit is Alveoli

⇒ lined with single layer of epithelium surrounded with myoepithelial cells to move secretion along the duct.

Inflammatory Lesions

	① Mammary Duct Ectasia (Periductal mastitis, Plasma cell mastitis)	② Fat Necrosis
Pathology	- Dilation of major Breast ducts in subareolar region with Accumulation of eosinophilic granular secretion & foamy Histiocytes within lumen → Inspissated luminal secretion can undergo calcification.	- Benign, non-suppurative inflammatory Process of Adipose tissue. - Anuclear fatty cells surrounded by Histiocytes.
Presentation	- Age: Middle age - elderly (Parous), Usually Asymptomatic. - Nipple Discharge → Greenish, Tooth Paste like, or Bloody. - Palpable Subareolar mass (Scarring around the duct) - Non-Cyclic mastalgia - Nipple retraction * Usually detected by Mammogram due to Micro-Calcification.	- Ill-defined, speculated dense mass. - skin retraction - Ecchymoses, Erythema - skin thickness - On Ultrasound: Hypoechoic mass with well defined margins - On mammogram → ill defined, Irregular/speculated mass ± Calcification → with time become more defined (oil cyst)
Causes	- Unknown. - Associated with young smokers.	① Trauma (Radiation, Accidental, Surgical) ② Secondary to Breast Pathology: Carcinoma, Duct ectasia, Fibrocystic Disease with large cyst formation.
Management	- Core needle Biopsy (if clinically or mammographically suggestive for Cancer) - Don't ↑ Risk for Breast Cancer- - Conservative management (Generally) - Surgical Excision of main duct.	- Conservative - Excisional Biopsy if Carcinoma can't be Ruled out.

③ Mastitis :

A- Acute Mastitis :

- Defined as : Cellulitis in interlobular connective tissue.
- Etiology : - Occur in first 3 months postpartum (2-24% of lactating) (from Breastfeeding)
  - ↳ Improper Nursing ⇒ fissures, Milk stasis → enter of Mo. → Staph. Aureus (Mc), Coagulase -ve staph., B-Hemolytic strep., Ecoli, Strep. fecalis.
  - ↳ Sleep depreviation & stress ⇒ ↓ Immunity & inhibit milk flow → Breast Engorgement
- Presentation : - Signs of inflammation ⊕ Nipple discharge
  - Abscess formation (10%.) → Always R/o in recurrent mastitis with Us / MRSA → Clinda or vancomycin.
  - Septicemia.
  - Duration between symptoms & treatment is the Only Risk factor.
- Management : (Weaning ↑ Breast Abscess)
  1. Continue Breastfeeding → ↑ Frequency of feed ⊕ Manual Pumping between feeds. Initiate feeding with unaffected Breast then change Positions at different feeds.
  2. Analgesia (Bruphen)
  3. ↑ fluid intake & Nutrition, Non-Constricting Bras.
  4. Warm Breast Compressor ⇒ ↑ Breast Drainage
  5. Emperical Abx → Outpatient (for 14 days) → Amoxicillin-Clavulanate, Dictoxicillin, if B-lactam Allergy Clarithromycin, if MRSA Clindamycin, Doxycycline. CI in Breastfeeding
     - Inpatient → IV Nafcillin, Oxacillin, in MRSA or B-lactam Allergy use Clindamycin or Vancomycin.
- In non-peurperal mastitis → R/o Cancer, Ruptured Cyst (self-limited)

C- Foreign Body :

- Silicon, Paraffin (following reconstruct or Augmentation)
- Siliconoma (Silicone Granuloma)
  - ↳ after direct injection or Rupture of implant.
  - ↳ Painful hard mass → 2ndry fibrosis

D- Recurring Subareolar Abscess → Zuska's Disease :

- ↳ Benign Bacterial Infection of Breast (Rare)
- ↳ Triad of : 1) Draining fistula from subareolar tissue.
  2) chronic, thick pasty discharge from nipple
  3) Hx of recurrent mammary Abscess.

* 90% Are Smokers.

- ↳ Pathology :
  - Smoking → Squamous metaplasia of Lactiferous duct → Keratin plug obstruct the duct → Infection & Rupture.
  - ⇒ Abscess underneath the nipple & fistula open at the margin of Aereola.
- ↳ Management :
  1. Stop smoking.
  2. Surgical Drainage (To stop Acute inflamm)
  3. Fistulectomy (Hadfield operation) → Complete excision of affected duct & sinus. (Can Recur)

B- Granulomatous Mastitis : (Rare Benign Inflammatory Breast lesion)

- Etiology :
  1. Idiopathic Granulomatous Mastitis :
     - ↳ Non-Caseating Granulomatous lesion, limited to Lobule.
     - ↳ Unknown Cause (Autoimmune response to protein / fat rich secretion in ducts) - non-well formed Granuloma -
     - ↳ Associated with Post partum Period. (Mean Interval is 2 years from pregnancy)
     - ↳ May have Assoc. fat Necrosis & Abscess.
  2. Foreign Body. (Siliconoma)
  3. Sarcoidosis → widespread distribution, well formed Granuloma, lack inflammation, Rarely have Necrosis & Abscess.
  4. Wegner's Granulomatosis
- Presentation :
  1. Ill defined Painful mass (Unilateral), in any Quadrant
  2. Skin thickness, Abscess, Sinus formation. Nipple retraction
  3. Axillary LN (Mistaken for Breast cancer)
- Treatment : (Spontaneous Resolution may occur)
  - Complete surgical Excision ⊕ Steroids → 30 mg/day Prednisolone (Orally) / Topical
  - Antibiotics (Emperical)
  - PPI

Prognosis :

- 50% have → Persistance / Recurrence ⇒ So Long-term follow-up needed.
- Complications → Abscess, Fistula, Chronic Suppuration

Fibrocystic changes

- Most frequent Benign Breast Disorder.
- Age ⇒ Premenopausal (20-50 yrs)
- Can be multifocal & Bilateral (Lumpy Breast)
- Most Common Presentation ⇒ Painful Breast (related to mens) & multiple tender nodularities)
- Pathogenesis: Unknown, but related to Hormonal Imbalance (Estrogen)
- Detected 50% Clinically & 90% Histologically.

*** Determination of Breast Ca. Risk:**

1. Histologic features
2. Age at Biopsy (If young women with Atypical epithelial proliferation Bc risk is twice a women > 55 yrs)
3. Degree of family hx of Bc. (↑ Risk)

Dupont & Page classification

	Examples.	Notes.
Non-Proliferative Lesions.	- Cysts - Papillary apocrine changes - Epithelial related calcification - Mild Epithelial Hyperplasia - Duct Ectasia - Periductal fibrosis, Non-sclerosis Adenosis	- 70% of cases - No ↑ Risk for Breast Ca.
Proliferative lesion without Atypia.	- Moderate or florid duct Hyperplasia - Sclerosing Adenosis - Radial Scar - Intraductal Papillomatosis	- Breast cancer ↑ 1.3-1.9 x
Proliferative lesion with Atypia.	- Atypical Ductal Hyperplasia - Atypical Lobular Hyperplasia.	- Bc ↑ 4-13 x - > 80% don't develop Invasive Breast Ca. during their lives.

Breast Cyst

- Fluid filled Oval, Round structure.
- Age: 35 - 50 years.

Classification

Size

- Subclinical (Microcyst) ↓ Majority.
- Palpable (Gross) ↓ 20-25%
  - Generally simple cysts.

Structure

- **Simple** ↓ Not Assoc. with malignancy ↓ Routine follow up.
- **Complicated** - 5% of all Breast examination
  - Internal echo, thin septation, thick/Irregular wall abscent Posterior enhancement.
  - ↓ Malignancy rate 3% → follow up with imaging study.
  - If with internal mass/nodule → CNB or surgical excision.

Breast ca. Progression.

Normal Duct → Epithelial Atypia → DCIS → fills the duct ⇒ Invasive Ductal Ca.

The most common form of proliferative Breast Ecc.

Epithelial Hyperplasia

Ductal Hyperplasia ⇒ E-Cadherin +ve.

- ↑ Number of cells lining Breast Duct.

① Usual (Simple)	② Atypical Hyperplasia
- Can be: 1. Mild (3-4 layer) 2. Moderate (4 layers & Bridging of luminal Space) 3. Florid (distended or obliterated lumen)	- Uniform population of cells - Mimic low Grade DCIS - Occur in late Premenopause - Atypia. Have higher Risk than Postmenopause - Risk for BC ↑ 4-5 folds in 10 years & ↓ Risk after 15 years
- Occur in late Premenopause	+ ③ DCIS (↑ Risk 9-10 folds)
- No Atypia	(2+3 called Ductal Intraepithelial Neoplasia)
- Risk for Bc (x2 folds)	
- 30% of Breast Biopsy	

Lobular Hyperplasia

Have the same Histologic features ← (Intra-acinar proliferation of small uniform cells) (E-Cadherin -ve in 85%)

	① Atypical LH	② LCIS
* Extent of Proliferation	- Proliferation not occluding lumen - Acini involvement is < 50%	- Lumen is occluded. - Acini involved > 50%
* Risk for Breast Ca.	4-5 x ↑	8-10 x ↑
* Site of Breast Cancer	Ipsilateral: Contralateral 3 : 1	Risk is equal in Both Breast
* Management	- Systemic follow up & Risk Assessment	- R/o Synchronous DCIS or Invasive Ca. - Negative margins are required - Bilateral mastectomy if high Risk for Breast ca.

* Both LCIS & ALH can coexist in same specimen

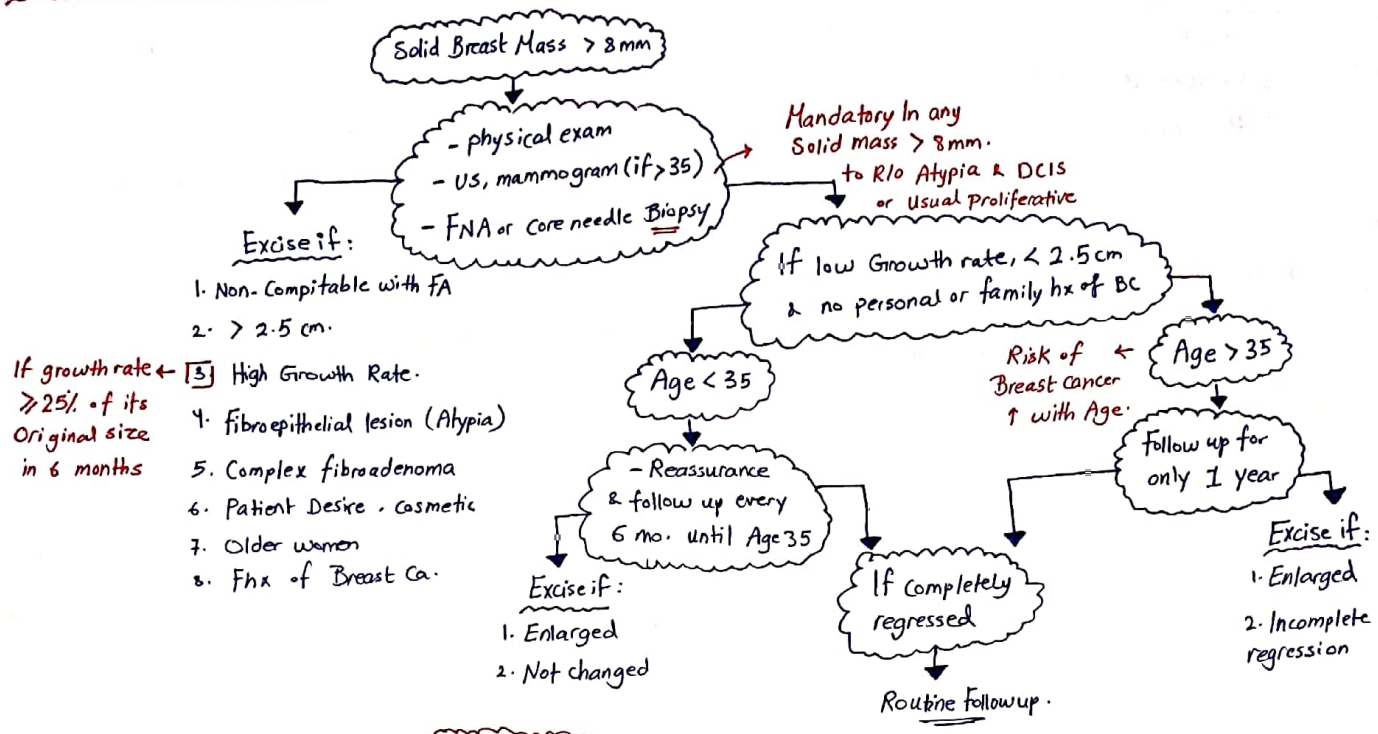
*Important

Benign Breast Tumors

5 lipoma 6 Granular cell T. (Nerve sheath T.)
7 Hamartoma 8 Radial scar.

1 Fibroadenoma	2 Phyllodes Tumor (Cystosarcoma phyllodes) ↑ Cyst within large mass	3 Gynecomastia	4 Intraductal Papilo
- Incidence: 25%	Rare, < 1% of all Breast tumors	—	- 2-3% Assoc. with Duct Hyperplasia, ADH,
- Epidemology: Occur at any age but mostly 20-30 Juvenile FA → 14-15 yrs.	- Occur in women Aged 35-55, could be Juvenile (14-15 yrs) - White American & Asian - Rarely in men & Assoc. with Gynecomastia	- Could be Neonatal, Aldoscent 13-14 or Adult.	- Age 30-55 - Typically small (few mm) & may grow to several cm.
- Histologically: Biphasic Tumor (Epithelial & stromal) Arise from TDLU or Bcl2 +ve mesenchymal cells - Slowly Growing	- Biphasic Tumor, leaflike Architecture result from enhanced Intracanalicular growth pattern (dilated lobules), Large Cleftlike spaces & Hypercellular stroma - Rapidly Growing mass (lesion apparent for years & suddenly ↑ in size)	- Hypertrophy in male Breast Glands - Pseudogynecomastia: Excess fat deposition without ductal proliferation. ↳ Soft Breast, Bilateral.	- Develop within mammary ducts, composed of epithelium Supported by underlying stroma ↳ fibrovascular core. - Atypical features carry high Risk of malignancy.
- Pathogenesis: 1) Unknown 2) Hormonal Stimulation (Estrogen sensitivity - OCP, & pregnancy) 3) EBV in Immuno-Compromised.	—	- Neonatal: Transplacental transfer of mother's estrogen. - Aldoscent: Peripheral Aromatization of circulating Androgens - Adult: Idiopathic 25%, physiological (Senile) due to ↓ Circulating Androgen (↓ Production 10-20% or ↑ conversion Peripherally), medication related (Liver failure 8%, RF 1%, Testicular Ca 3%, Pituitary Adenoma, Hyperthyroid., Obesity, Ectopic Hormone release.)	—
- Clinical Presentation: - Mostly Asymptomatic - If Symptomatic: firm, Painless (unless large become discomfort or Pressure), mobile - Multiple, Bilateral in 20%	- Rapidly Growing longstanding mass - Large mass (Avg. 4 cm), 20% grow larger than 10 cm (Giant phyllodes Tumor) - Mostly unilateral, Rarely with nipple retract - Non-ulcerating, but Assoc. with dilated veins & Blue discoloration. - Fixated to skin & Pectoralis major (Rarely Invade structure even if malignant) - Mostly In upper Outer Quadrant (Higher Density of Glands)	- Breast exam should be done. - Look for signs of liver disease: Jaundice, Spider Nevi, Palmar erythema muscle wasting, Ascites, Hepatomegally fetor hepaticus, Hair distribution, Testicular Atrophy, Caput medusa) - Assess Regional LNs. - Frequently Bilateral * Distinguishing Clinical feature is Concentric Enlargement.	- Central: Spontaneous Bloody nipple discharge (30%) - Most Common cause of Bloody nipple discharge - DDx: Mastitis, Duct Ectasia, BC - Peripheral: Asymptomatic, Incidental on Imaging. - Higher Assoc. with malignancy esp. if with Atypia & multiple
- Radiological findings: ① Us (modality of choice) → Round, oval, Lobulated well-defined Hypoechoic mass. ② Mammogram: Done if >35, Fhx of BC, suspecious lesion	① Us → Cystic Areas within solid mass. ② Mammogram → Rounded Border & Lobulated.	- Should Always do Ultrasound to R/o masses. - Mamogram in males is sensitive in 92% & specific in 90% - Labwork-up: LFT. KFT. TSH prolactin, B-HCG, LH. Testosterone	① Us: Intraductal mass, complex Cystic lesion with dilated ducts. ② Ductogram: Obstructed duct, filling defects, wall Irregularity & Duct expansion & distortion ③ Mammogram: Occult in central. - Peripheral: Architecture distortion. Nodules, mass ± Calcification.
- Classification: 1. Size ↕ < 5 cm, ≥ 5cm (Giant) 2. Microscopic → Intra vs. Peri-canalicular ↳ Simple vs. *complex* (Hyperplasia, Metaplasia, Sclerosing Adenosis) * High Risk lesion * 3. Rare Types ↳ Tubular (Pure Adenoma) → Prominent Adenosis with very little Stroma ↳ Lactational Adenom → lactational changes in glands in Pregnant or lactating women	- Benign, Borderline, Malignant Based on: Stromal cellularity & Atypia, Stromal Overgrowth, Mitosis & Tumor margins. ⇒ ↑ features in malignant	- Neonatal: Transient, Resolve spont. after 1st week. - Aldoscent: Transient, resolve by age of 18 yrs, 8% continue to Adulthood → Embarassment, fear of malignancy. - Adulthood ↳ Florid Phase (Reversible) - Non-surgical Treatment ↳ Fibrotic phase (Irreversible) - Only surgical treatment	1. Number ↕ solitary, Multiple (papillomatosis) 2. Central (subareolar) vs. Peripheral.
	- Management: - Mainstay of treatment is surgical excision with at least 1cm free margin ± CT or RT (no improvement in prognosis if we use them) * Local Recurrance if inadequate resection. High mitotic rate, cellular Atypia. - Any 2 features mandate Core Biopsy: - Clinical: Sudden ↑ in size, > 3cm or > 35 yrs - Imagin: ↑ see Above - FNA: Hypercellular stroma. Indeterminate.	- Treat underlying cause. - If pubertal persist after Age of 18 yrs → surgical excision. * Alarming features: Unilateral, Eccentric, skin / Nipple change, discharge Lymphadenopathy, Fhx of Breast ca → lymphoma or sarcoma.	- Treatment: Surgical excision - 0-29% transform into CIS or Invasive Ca. ↳ Less in: 1. lesions with no microcalcifications 2. Abscent Atypia 3. Microscopic lesion 4. Sufficient amount of tissue on core Biopsy. ④

Treatment of fibroadenoma:



Breast Cancer

- Most Common non-skin cancer in women worldwide.
- 2nd leading Cancer-killer in women (1st is Lung Ca.)
- Lifetime Risk to Develop Breast ca. Is 1 in 8 (12.5%)

- Breast Ca → 80% sporadic.
  - 15% familial → No well-known Gene mutation
  - 5-10% Genetic → well known Gene mutation.

Risk Factors

Non-Modifiable

1. **Gender** (Female Is the most Important Risk Factor)
2. **Age** (BC not related to any Age But Risk ↑ with Age & mortality ↑)
   - ↳ Median Age for Diagnosis Is 61.
3. **Race (Ethnicity)** - Higher Incidence in white women, But Blacks have Higher mortality rates & Incidence at early Age.
   - → Due to Late presentation from poor access to medical care, Biology of Tumor Is more aggressive. / ↑ in Jewish.
4. **Family hx of BC** - Esp. first degree & if relative had it at younger Age.
   - ↳ 1 1st degree relative → x2 higher risk
   - ↳ 2 1st degree relative → x3 higher risk
   - ↳ 3 1st degree relative → x4 higher risk
5. **Personal hx of BC** - x2 times higher Risk to develop metachronous Breast ca.
6. **Menstral cycle** - ↑ Risk In early menarche & Late menopause, strongly related to ER+ve Breast Cancer.
7. **Radiation** - Any Girl who had chest radiation due to papillary thyroid Ca. or Hodgkin lymphoma Should start screening 8 years after it & not before 25 yrs.
8. **Dense Breast**
   - ↳ Increased in: Pregnancy, late menopause, Obesity, HRT.
   - ↳ Decreased in: ↑ Age (post-menopausal) & Tamoxifen
9. **Bone Mineral Density**
   - High BMD in postmenopausal Osteoperosis screening Indicate that there's cummulative ER exposure & Assoc. with ER+ Breast ca.
10. **Genetics**
    - ↳ BRCA1/2 Gene Mutation
      - Not all will develop Breast ca. 70% of BRCA1, 40% of BRCA2 (BRCA2 Assoc. with Male BC)
      - Ovarian Ca. → 40% in BRCA1 & 15% in BRCA2.
      - Cummulative lifetime Risk for metachronous contralateral BC is 60% in BRCA1/2.
    - ↳ Le-Fraumeni syndrome
      - P53 Gene Mutation → BC + sarcoma
    - ↳ Cowden Syndrome
      - PTEN mutation → BC + Colon Ca.

Modifiable

1. **Obesity**: ↑ Peripheral conversion of Androgen to Estrogen → ↑ Breast Density (not fat) - Controversial-
   - ↳ Protective in Premenopausal & ↑ Risk in Post-
2. **Nulliparity** - women who are nulliparous or have 1st Child > 35 yrs have high Risk for BC (1st child before Age of 20 have 50% reduced lifetime Risk)
3. **Fertility Drugs** - Ovulation stimulating Drugs have no Assoc. with BC (↑ Risk in >12 clomiphen cycles)
4. **Breastfeeding** - for a year or more decrease Overall Risk for BC. (↓ Risk 4% for every 12 mo. BF)
   - → ↓ menstruation → ↓ Hormone Exposure.
5. **Combined OCP & HRT** - Slight ↑ in Risk for BC (Progestin-Only don't ↑ the risk).
6. **Smoking** → ↑ the Risk of BC.
7. **Physical Activity** - Active women have 10-25% Lower Risk than Inactive women.
8. **Diet** - Fruits & vegetables ↓ the Risk, Fatty food & soy (has Estrogenic effect) Increase the Risk.
9. **Alcohol** - ↑ the Risk for BC. (↑ER+ve BC)
10. **Occupation** - Night-shift workers → ↑ stress, ↓ melatonin → ↑ Risk for BC.

Factors that don't ↑ Risk of Breast ca.

1. Abortion
2. Environmental Pollution
3. Hair dyes
4. Breast Implants → Don't ↑ Risk for Breast Ca. but rare Breast lymphoma
   ↳ Don't affect Mammo. sensitivity Because its under muscles & Glands
   But Mammo. can damage the implant so we use MRI for screening

BI-RADS for Breast Density

1- Grade1 (Fatty) - < 25% Density
x 1-2↑ risk. [2- Grade 2 (scattered) - 25-50%
x 2-4↑ Risk [3- Grade 3 (Heterogenous) - 51-75%
[4- Grade 4 (Extremely Dense) - > 75%
} Need MRI for screening

Stage

Presentation:

- Most Common Presentation Is Breast mass, But nowadays In developed country its discovered during screening.
- Usually Asymptomatic, if Symptomatic → Advanced Stage.
- Symptoms ⇒
  1. Breast Pain
  2. Axillary LN
  3. Skin thickening
  4. Nipple Discharge (Bloody)
  5. Skin dimpling (Peau d Orange)
  6. Nipple changes → retraction, erosion
  7. Inflammation → Breast Erythema more than 2/3 of Breast surface (Inflammatory BC)
  8. Breast mass

Breast Ca. In Jordan

- Highest Incidence of all ca. (37%)
- Median Age is 51 years.
- 1260 New Cases recorded yearly 34% of them In childbearing Age.
- 80% of cases from south are locally Advanced & 50% of cases In Amman are locally Advanced.

Breast Cancer Screening:

- Start Radiological Screening at Age 40 Annually till Age 52 then every 2 years.

- Individualized Based on: 1. Age 2. Estimated Risk 3. Individual Risk factors 4. Family hx 5. Genetics.
  ↳ If 1st degree relative has BC start screening 10 years before the Age of relative's Presentation.

① Mammography:

↳ Low dose x-ray Procedure allow visualization of internal structures.
↳ Most effective method for early detection.
↳ Used In Screening & Diagnosing.
↳ Film Mammography (Patient Can take film Home) vs. Digital Mammography (Saved on screen, Higher Resolution) vs. Breast Tomosynthesis (3D Digital mammography, Advanced).

80% sensitive.

2 views ↔ Mediolateral → See Pectoralis major muscle.
CranioCaudal → Semi-circle view.

Factors Impact Sensitivity:
1. Breast Density
2. Post menopausal HRT
3. Breast Implant.

Breast Imaging Reporting & Data System (BIRADS)

Category		Management	Cancer Risk
0	Need further imaging	Additional Image	N/a.
1	Negative	Routine Screening	0%
2	Benign	Routine Screening	0%
3	Propably Benign	follow up every 6 mo.	0 - 2%
4	Suspecious	Tissue Diagnosis	-4a → low (2-10%) -4b → mod. (10-50%) -4c → High (50-95%)
5	Highly suggestive for malignay	Tissue Dx	> 95%
6	Known Biopsy Proven	surgical excision	n/a.

② Ultrasound:

↳ Used for women with Dense Breast only if with MRI in screening.
↳ Not recommended to be used instead of mammogram.

③ MRI:

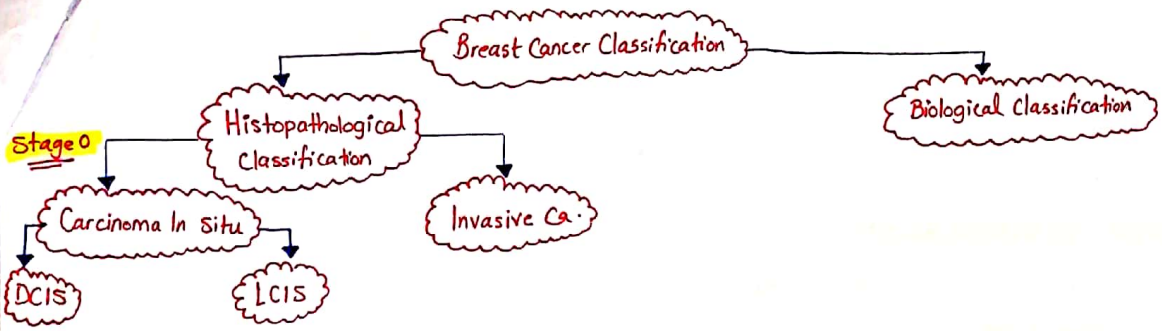
↳ Should supplement but not replace mammography.
↳ In women with lifetime Risk >20-25% ⇒ should start screening at age of 30 with Annual MRI & Mammogram.

* See Indications Slide 83

④ Clinical Breast Exam: ⇒ The Role of screening Is to detect tumor before Invasion & Symptoms, so if its detected by exam its in advanced stage (at least 1-2cm)

Not part of screening program.

- No Longer recommended because don't improve prognosis
But we still encourage women to do it because we don't have established screening. (Day 7-10 of cycle)



Ductal Carcinoma In Situ: (Most Common Premalignant lesion of BC)

- 20-25% of newly diagnosed Breast ca. (↑ Incidence from 4% due to mammogram)
- Malignant Proliferation of Ductal cells Confined to Ductal wall & not Invading Basement membrane or vessels.
- Considered a Precancerous Lesion but non-obligate precursor (Only 50% progress to Cancer in 10 years.)

- Classification

1. Subtypes → Comedo (Areas of Necrosis)
   → Non-Comedo (less aggressive)
   ↳ Papillary, Micropapillary, Solid, Cribriform.
   ↳ Can Involve more than one quadrant.
2. Nuclear Grading → Low - Intermmediate - High
   ↳ Based On Nucleus, cell, Nucleoli, Chromatic, Mitosis Microcalcification, Necrosis.
   ↳ Low Grade have +ve ER/PR & -ve HER2neu
   ↳ High Grade have -ve ER/PR & +ve HER2neu.

Imp. in recurrance

Diagnosis:

① Clinical Presentation:
- Asymptomatic, Rarely come with palpable mass (<10%)
- Very low Propability for Axillary metastasis. (<1%)
- very unlikely to be the cause of mortality. (1-3% & related to microinvasion)

② Radiological Assessment: (If type 3 or 4 Breast)
- Mammogram then MRI are the modalities of choice in detecting Microcalcifications (Not detected by US)
- Also detect soft tissue density or Asymmetry.
  ↳ linear-Branching Microcalcification → High Grade or Comedo type
  ↳ fine Granular Microcalcification → Low Grade or non-Comedo type

95% Accurate ③ Diagnostic Biopsy: ⇒ (Core Needle Biopsy to differentiate Between DCIS & Invasive Ca).

Multifocality vs. Multicentricity:
- Multifocality: DCIS in 2 or more foci in same quadrant
- Multicentricity: DCIS in ≥2 different quadrants.

5-10% of DCIS # Microinvasive DCIS: Invasion of ductal cells of BM in few mm.
↳ Size > 25mm, High Grade, Comedo, palpable mass, nipple discharge

- Prognosis of DCIS:
  - Very Good Prognosis
  - Aim to maximize local control with least aggressive treatment

Recurrance
1. Young Age < 50
2. High Grade (has 2 folds ↑ Risk of metachronous Breast cancer)
3. Large size (> 3cm)
4. Comedo type
5. +ve margins.

- Treatment of DCIS:

1- Mainstay of treatment is Surgical

→ Lumpectomy (wide local excision) ⊕ Radiotherapy (decrease chance of local recurrance - 28% without RT & 13% with RT - per year)
(with 2mm safe margin) → No invasive cell

Usually there's no need to do Sintinel LN Biopsy
Except in: 1) Diffuse DCIS (involve all Breast)
2) If large > 5 cm
3) High Grade DCIS, Comedo type.
4) If patient is doing mastectomy
5) DCIS with Micro Invasion.

} if +ve Sentinel LN we do Axillary Dissection

→ Total Simple Mastectomy → Indications:
① If contraindicated to do Radiotherapy. (Patient refused, Pregnancy)
② If Tumor > 5cm & small Breast (Not favorable T-Breast ratio)
③ Multicentric Tumor (In 2 or more quadrants) (Previous RT in recurrent DCIS, CT disorders (Toxic))
④ Prophylactic (Angelin Joly effect) - in BRCA mutation
⑤ Persistant +ve margin after re-excision

2- Hormonal (Endocrine Therapy):
- No Role alone in treatment of DCIS.
- Used in some patients.

- Surviellance: (10% recurrance in mastectomy)
  - Should follow up patients with Annual physical exam & mammogram.
  - Recurrance is mostly within 1st 2 years.

Not all DCIS are treated <
* Follow up DCIS without any Intervention if: Elderly & low Grade DCIS (non-Comedo)
* Wide Local excision without RT if: 1. Small size 2. low Grade 3. ↑ Age (> 60) 4. Adequate margin.

Pregnant women with Breast ca:
- Contraindication for Radio. so if in 1st or 2nd trim. treat with mastectomy But if in 3rd trim. do wide Local excision & after 4 weeks of surgery Give RT (She will be delivered the Baby) or postpone BCS + RT until delivery.

Lobular Neoplasia: ⇒ Atypical Lobular Hyperplasia
⇒ LCIS (classical, Pleomorphic)

- Lobular Carcinoma in situ:
- Cells confined in Breast Lobules.
- Considered a high Risk lesion (Not Precancerous)

⇒ That means LCIS can develop into either Invasive Lobular ca., or Invasive ductal ca. or even DCIS in the same Breast (30%) or Contralateral Breast, In same or different quadrant. (But not all Procede to Cancer).

Higher Incidence.

- Multifocal in 50%
- Not detected by mamogram (Always Incidental finding in Breast Biopsies)
- Mean Age of dx 40-50 years. (Premenopausal), while Invasive lobular ca is more in Postmenopausal.

* Lobular Carcinoma in situ variants:

1. Pleomorphic LCIS → Most common form./Treated as DCIS because it's a very agressive Tumor & histologically resemble DCIS (Do excision with safe margins)
2. pleomorphic Apocrine LCIS
3. LCIS with Comedo Necrosis
4. Mixed Ductal & Lobular CIS.

only observe or Excise to R/o synchron. Breast ca.

← Classical LCIS	Pleomorphic LCIS
ER/PR +ve	ER/PR -ve
HER2neu -ve	HER2Neu +ve
P53 less frequent	P53 more frequent
E-Cadherin +ve	Ecadherin -ve
Comedo Necrosis Abscent	Common Comedonecrosis (Confused with DCIS)

- Treatment:
  - If we did excisional Biopsy & its LCIS we don't need to do excision for safe margin or give RT (except in pleomorphic) because it will still be high risk lesion.
  - Importance is in surveillance ⇒ Annual PE & mammogram
  - Bilateral Prophylactic mastectomy:
    1- If the patient have additional risk for Breast cancer
    2- Patient Desire.
    * It reduce but not eliminate the risk for BC

Invasive Breast Cancers → Most common type of Breast Ca.

* In Jordan 70% - 80% are HER2neu +ve.

Nowadays Tumors classified By the type of receptors they have:

Molecular subtype (↱ most common)	Luminal A	Luminal B	HER2neu enriched	Basal-like
Gene expression	ER/PR +ve HER2neu -ve	ER/PR +ve HER2 neu +ve	ER/PR -ve HER2 neu -ve.	Triple negative ER/PR -ve HER2neu -ve
Incidence	74% of BC	10% of BC	4% of BC	12% of BC, African, Premenopausal
Histologically	-Cells have low mitotic rate & never express HER2 neu. (Slowly Growing)	- Higher Histo. grade & mitotic rate	- Aggressive (more likely high Grade & +ve LNs)	- Very Aggressive.
Chance to have BRCA gene mutation.	low chance in ER/PR +ve	low chance in ER/PR +ve	Higher chance.	- Associated with BRCA,
Treatment response	- Respond to endocrine therapy (Tamoxifin, Letrazole (Aromatase Inhibitor) But response may differ between luminal A & B.		- Respond to Herceptic (Trastuzumab)	- No targeted receptor in treatment & patients should take chemotherapy.
Prognosis	Better than luminal B (The most favorable prognosis)	Good prognosis	Poor Prognosis Compared to luminal type.	- Poor short term prognosis

Approach to Breast cancer:

- According to NCCN Guidlines if patient is Asymptomatic, we order: 1) Simple lab. Test (CBC, LFT)
  2) chest x-ray (lung)
  3) Liver us
- Then follow up with symptoms & Radiology every 6 months.

* But in Our country we order CT & Bone Scan. (Usually for Advanced stages)

Breast Ca. Metastasis:

- Biology Plays Great role in mets.
- Most Common site for mets Is Bone (vertebral Body), but the worst type of mets Occur in Brain.
- If patient had Isolated Bone mets (Good Prognasis), & if she had other types (Lung, Liver, Brain) its Assoc. with poor prognosis.
- Luminal A, B & HER2neu mostly mets. to Bone, while patients with enriched HER2neu mets to liver, & patients with Triple -ve mets to lung & Brain (worst Prognosis)

Sintenl LN Biopsy

- Use: 1) tecnitium colloid
  2) Methylene Blue
- Inject dye near Tumor → Breast massage for 5-10 min. → Axillary Incision → Biopsy Blue LN & Send Frozen section to Histopathology → if +ve Axillary Dissection

False -ve	Methylene Blue	colloid
in 1 LN	12%	8%
2-3 LN	6-7%	1-2%

- if only 1-2 LN +ve don't do Axillary Dissection.

Treatment of Breast cancer:

* Treatment selection based on → Patient factors: Age, medical conditions, expectations, Fhx, Hereditary BC
  → Tumor Factors: Stage, Histology, Biology Uni/Bilateral, primary or recurrent BC.

* Treatment Categories:

↳ Surgery → wide local excision + RT
→ Mastectomy (with or without reconstruction) → Traditional → Breast, Nipple & skin.
→ Breast Preserving → Skin sparing - reconstruct immediately
→ Nipple sparing - preserve skin & Nipple.

Axillary LN dissection → Don't Improve prognosis or 5yrs survival it only decrease Locoregional recurrance
Complications (in 28%) → lymphedema & limitation in movement & weakness/parasthesia

↳ Radiotherapy → External Beam
→ Brachtherapy (Invasive, not used)

↳ Used in:
1. Post wide local excision
2. post mastectomy (Tumor stage, Size > 5cm, margins).
3. +ve LN (1 is enough)
4. Inflammatory Breast Ca. → Indication for mastectomy because Tumor has reached sub-dermal lymphatics

↳ Systemic Therapy:

① Chemotherapy
↳ Depends on:
1. Biology (most imp.) → T_1/T_2 triple -ve.
2. Size.
3. LN status.

* The more Aggressive the tumor the better response to chemo.
(Triple -ve have the most pathologic response - complete pathologic response in 60% -)
- ER/PR +ve < 20% respond to chemotherapy.

② Hormonal Therapy (for 5yrs)
↳ Estrogen Resources:
1. Premenopausal → Ovary
2. Post menopausal → Adipose tissue
- So we fight the source:
Pre-1. Oophrectomy → surgical or medical (GnRh Analoug)
Pre-2. Tamoxifen (ER modulator) & post → Breast antagonist & Endometrial agonist.
Post-3. Aromatase Inhibitor (Letrozole) → ↓ peripheral Aromatization of Estrogen In Adipose tissue.

③ Targeted Drug therapy

⇒ Early Invasive Breast ca. (Stage 1, stage 2a, 2b):

↳ Breast Conservative surgery ⊕ RT is treatment of choice., Recurrance rate is 1% in 10 years.
* Mastectomy Recurrance rate is 10%, & lumpectomy alone 25%.
* Safe margin In Invasive Breast Cancer Is no Tumor at Ink margin.

⇒ Advanced Loco-reginal BC (Stage 3a, 3b)

↳ Chemotherapy (Neoadjurent) Is the Gold standard nowadays:
① To Assess Tumor response to chem & usually Give 2-3 regimens
↳ Tumor response:
↳ Clinical → symptoms & radiology
↳ pathological → Histopathology
either → Complete → Fibrotic specimen
→ Partial → still viable cells.
- So, Neoadjuvent don't improve Prognosis except in Complete Pathological response.
② To downstage/shrink size.

Breast Reconstruction
Immediately after Radio.
2 stages:
1. Submuscular expander
2. Replace them with implant (Prosthetic)
- Atologous uses ↳ Dorsi or Abd. flap.

Prognosis of Breast Ca.

5 years survival in females:

- Stage 0 > 100%
- Stage 1
- Stage 2 → 93%
- Stage 3 → 72%.
- Stage 4 → 25%

* In males, the Prognosis stage by stage comparing to females is Almost the same but overall worse Prognosis.

#

Paget Disease

- Unilateral erythematous, eczematous lesion of nipple & Areola.
- Subtypes: 1. Paget disease of nipple.
  90-95% { 2. Paget disease of nipple with DCIS
  3. Paget disease of nipple with Invasive Ca.
- Any female diagnosed with nipple changes should do Biopsy & Histopathology. → Treat Based on result.
- Treatment: 1. Only Paget → Remove nipple-Aereolar complex + central quadrant.
  2. paget with DCIS &/or Invasive ca → same as Above, if -ve margin add RT, if +ve margin do mastectomy (Because its usually diffuse in Invasive ca')

Commonly Used Drugs:

	Tamoxifen	Letrazole	(Trastuzumab) Herceptin.	Exemestane (Aromasin)
Action	- Estrogen Receptor Antagonist in the Breast & Agonist in Endometrium (Selective ER modulator)	- Aromatase Inhibitor → ↓ Peripheral Conversion of Androgen to estrogen in adipose tissue	- Monoclonal Ab.	- Aromatase Inhibitor (steroidal Inhibitor)
Indications	- Non-Cancerous Indication is mastalgia. - ER +ve Breast Ca. (luminal A/B) In Post & Premenopausal for 5-10 years	- ER +ve Breast Cancer (Adjunctive with Tamoxifen) In Postmenopausal. for 5-10 years.	- Used in HER2/3 +ve Breast cancers for 1year duration & in luminal A for 6 months.	- ER +ve Breast cancer In Postmenopausal
Side effects	1. ↑ Risk for Endometrial Cancers. 2. Hot flushes, mood swing, Headache 3. loss of lipido	1. Nausea/Vomiting 2. Hot flushes, sweating 3. Joint pain & tiredness.	1. Bone Pain 2. Cardiotoxicity 3. N/V 4. Joint/Back pain	1. Joint Pain 2. Menopausal symptoms 3. fatigue 4. Osteoperosis
Contraindications	1. Hx of DVT or Anticoagulation 2. Endometrial Hyperplasia 3. Bone Marrow suppression 4. Hypercalcemia	1. Osteoperosis 2. Pregnancy 3. Breast feeding	1. Arrhythmia 2. Other Cardiotoxic drugs 3. Hypertension 4. Cardiomyopathy.	1. Hypersensitivity to Drug. 2. Premenopausal (Pregnancy & Breast feeding) 3. Osteoperosis.