BREAST PATHOLOGY

- Developmental anomalies
  1. milk line remnants
  2. Accessory axillary breast tissue
  3. Nipple inversion
- Benign epithelial lesion.
  1. Non-proliferative changes
  2. proliferative breast disease without atypia
  3. c atypia
- Carcinoma of breast.
  1. Carcinoma In-situ
     a) ductal
     b) lobular
  2. Invasive
- Inflammatory disorders
  1. acute mastitis.
  2. squamous metaplasia of lactiferous ducts Zuska disease
  3. ductal ectasia
  4. Fat necrosis
  5. Lymphocytic mastopathy
  6. Granulomatous mastitis.

  PREP
- Stromal tumors.
  1. fibroadenoma
  2. phyllodes tx
  3. lesions of interlobular stroma

Stromal tumors

FIBROADENOMA m/c female breast benign tumor.

age group - 20-30.

clinical presentation - multiple. bilateral (mostly)
palpable mass (Young)
mammographic density (old)

FIBROADENOMA

m/c female breast benign tumor.

age group - 20-30.

clinical presentation - multiple, bilateral (mostly)
palpable mass (young)
mammographic density (old)

- epithelial component is hormonally responsive
↑ size → infarction, inflammat^{n}

morphology -
- <1cm — large.
- well circumscribed
- rubbery, greyish-white nodules
- bulge above surrounding tissue.
- slitlike spaces ⊕
- delicate & myxoid stroma
- epithelia ① surrounded by stroma - pericanalicular pattern
② compressed & distorted intracanalicular pattern.
- older woman → densely hyalinised atrophic epithelium.

drug a/w - cyclosporin A

Phyllodes Tumor

- arise from intralobular stroma.

age - 60-70s

palpable mass >
mammography -

genetics - gains chromosomal 1q
↑ HOXB13

genetics - gains chromosomal 1q
↑ HOX B13.

morphology - few cm → large
- bulbous protrusions — leaflike
- nodules of proliferative stroma (covered by epithelium
  → cystic space.
- from fibroadenoma, ↑ cellularity, ↑ mitosis, ↑ nuclear polymorphism infiltrate borderes.

Prognosis - low grade - do not metastasise
high grade/medium - lymphatic spread.

Benign Epithelial Lesion

① Non-proliferative Breast changes / Fibrocystic changes. (1/3 ↑ cancer risk)

→ lumpy, bumpy breast on palpation
→ dense breast densities on radiography

morphology

3 principal changes

① cysts - - dilation of lobule → small cyst
↓
coalesce → large cyst

- contain turbid, brown-blue colored ~~semi-translucent fluid~~ - blue dome cyst

① cysts - ◦ dilation of lobule → small cyst
↓
coalesce → large cyst

◦ contain turbid, brown-blue colored semi-translucent fluid - blue dome cyst

◦ lined by atrophic epithelium or metaplastic apocrine cells.
↳ abundant granular eosinophilic cytoplasm

◦ calcification → mammography

disapearance of mass after FNAC of its contents.

② Fibrosis - rupture of cyst
↓
secretory material into adjacent stroma
↓
chronic inflammation
↓
fibrosis
↓
palpable nodularity

③ Adenosis - ↑ acini number pere lobule (in pregnant)
calcification within lumen.

acini lined by columnar epithelium
↳ del^n 16q
flat epithelial atypia

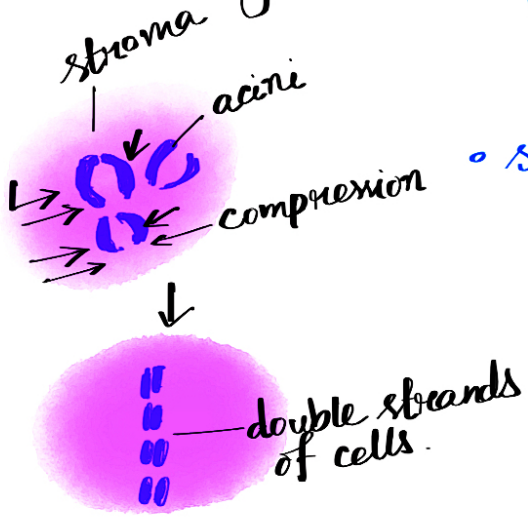
2> Proliferative Breast Disease without Atypia (1.5-2)

2) Proliferative Breast Disease without Atypia (15-20%) (5-10%)

diagnosed by calcification in mammography
incidental biopsy finding
not genetic, not clonal
↑ cancer risk but not true precursor of cancer.

① Epithelial hyperplasia: ↑ number of luminal and myoepithelial cells
- distended ducts and lobules.

② sclerosing adenosis: ↑ acini number
↳ compressed in central portion of lesion.
- stromal fibrosis
↳ compress lumen of acini
↳ appear solid cord or double strand of cells in dense stroma



③ Papilloma: - within duct
- have fibromuscular core
- epithelium hyperplasia + apocrine metaplasia +

large duct papilloma → in lactiferous sinus → single of nipple

small duct papilloma → deeper ducts → multiple.

>80%.
↳ nipple discharge — palpable mass

large duct papilloma → in lactiferous sinus → single of nipple

Small duct papilloma → deeper ducts → multiple.

>80%
↳ nipple discharge
- may be bloody
- stalk torsion → infarction
- blockage

palpable mass

④ Complex sclerosing lesion.

sclerosing adenosis + papilloma + epithelial hyperplasia.

Radial scar
central nidus of entrapped glands in hyalinized stroma by long radiating proces

(3) Proliferative breast disease ≡ Atypia (4-5%) (13-17%)

clonal proliferation having some histological features required for diagnosis of CIS.

Atypical ductal hyperplasia - resemble DCIS
- monomorphic proliferation of regularly spaced cells
- cribriform spaces
- partially fills ducts.

Atypical lobular hyperplasia - resemble LCIS.
cells dont fill / distend >50% acini within a lobule.

Atypical lobular hyperplasia - resemble LCIS -
cells dont fill / distend > 50% acini within a lobule -

atypical cells may lie between ductal basement membrane & overlying luminal cells.

Gynecomastia - type of proliferation without atypia -
m/c ♂ breast benign lesion.
button-like subareolar enlargement - unilateral / bilateral
m/e - ↑ dense collagenous connective tissue
epithelial hyperplasia
duct lined c̄ tapering micropapillae

Reason - ↑ estrogen ↓ androgen
Age - puberty, old age.
may occur c̄ liver cirrhosis (↓ estrogen breakdown)
drugs decreasing androgen (alcohol marijuana)

XXY - Kleinfelter
testicular neoplasm

small ↑ breast cancer.

CARCINOMA OF BREAST

TYPES. 1) luminal - ER⊕ (HER2⊖)
2) HER2⊕ (ER⊕/ER⊖)
3) Triple negative - TNBC (ER⊖, HER2⊖, PR⊖).

Risk factors - sex (99% ♀)

CARCINOMA OF BREAST

TYPES. 1) luminal - ER⊕ (HER2⊖)
2) HER2⊕ (ER⊕/ER⊖)
3) Triple negative - TNBC (ER⊖, HER2⊖, PR⊖).

Risk factors - sex. (99% ♀)
age
lifetime estrogen exposure. - early menarche
late menopause
nulliparity
late 1st pregnancy
estrogen therapy

genetic inheritence
environmental exposure
└ organochlorine pesticide
certain plastics.
] assumed (not proven)

high penetrance gene mutation (mc - sporadic P53)
obesity
alcohol consumption.

Genetics

✓ Familial Breast Carcinoma

BRCA1 - (17q21).] tumor suppressor gene.
BRCA2 (13q)
↳ DNA repair
↓
loss of funct^n
mutation.

TNBC
ER+

↳ a/w ↑ breast cancer.

also a/w ovarian cancer.

also of ovarian cancer.

p53 - Li fraumeni syndrome
↳ breast, brain, bone, blood cancer

PTEN - (Ch 10) - COWDEN SYNDROME
↳ breast cancer
thyroid cancer
trichilloma
Endometrial cancer

STK11 - Peutz Jaghers syndrome.
↳ colon cancer

CDH1 - E-cadherin → polyps. Invasive carcinoma. diffuse gastric cancer.

ATM - Ataxia telangectasia.

CHECK2 - Radiation induced breast carcinoma.

PALPB2.
monallelic loss → breast Prostate.
biallelic loss. → Fanconi anemia.

Sporadic breast cancer
related to risk factors.

Sporadic breast cancer

Related to risk factors.

Molecular mechanism of Carcinogenesis

① ER+ HER2- ≫ BRCA2 germline mutation
a/w 1q gain
16q loss
↓
PI3KCA activation mutation
↓
↑ signal pathways
↑ growth factor ®
↓
Atypical ductal hyperplasia
↓
DCIS
↓
ER+ HER2- cancer
Luminal type
(because cancer cells resembles normal breast luminal cells in terms of their mRNA expression dominated by genes regulating estrogen

② HER2+ ≫ TP53 mutation
↓
HER2 or 17q amplification

② HER2+ ⇒

TP53 mutation
↓
HER2 on 17q amplification
↓
atypical apocrine adenosis
↓
DCIS
↓
HER2 enriched breast cancer

③ ER−, HER2− ⇒

BRCA1 mutation
↓
T53 mutation
↓
DCIS
↓
basa like breast cancer

Carcinoma-In-Situ

Ductal Carcinoma In-situ

- a malignant clonal proliferation of epithelial cells limited to ducts and lobules by the basement membranes.

✓ "ductal" because when it involves lobules, the expanded acini resemble small ducts.

✓ No epithelial cells observed

Carcinoma-In-Situ

Ductal Carcinoma In-situ

- a malignant clonal proliferation of epithelial cells limited to ducts and lobules by the basement membranes.

- "ductal" because when it involves lobules, the expanded acini resemble small ducts.

- Myoepithelial cells preserved.
- DCIS spread through ducts & produce extensive lesions.
- bilateral 10-20%

diagnosed by mammographic calcification

architectural subtypes

Comedo DCIS

Central necrosis + tumor cells c pleomorphic, high grade nucleus

↓

vague nodularity calcification

Noncomedo DCIS

lacks either of two component

↓

- cribriform
- solid

DCIS produces true papillae c fibrovascular core.

myoepithelial cell ⊖

calcification ⊕

Pagets disease - Prep

treatment- surgical excision.

Risk of [redacted] high nuclear grade

Paget's disease - (Prep)

treatment - surgical excision.

Risk of recurrence ↑ ① high nuclear grade & necrosis
② extent of disease
③ positive surgical margins

Lobular carcinoma in situ

clonal proliferation of cells within ducts and lobules that grow in a discohesive fashion, usually due to an acquired loss of E-cadherin.

- "lobular" because cell expand but do not distort involved spaces and thus underlying lobular architecture is preserved.

- calcification ⊖ ⇒ no mammographic density
- Incidental finding —
- bilateral 20-40%
- cells of atypical lobular hyperplasia.
- CDH 1 mut^{n} → E-cadherin ↓

morphology - • uniform population of cells ↑ round-oval nuclei & small nucleoli
• mucin + signet ring ⊕
• No cribriform
• pleomorphoid spread.
• No necrosis, stromal rxn
↓ calcification ⊗

- pterigoid spread.
- No necrosis, stromal rxn
  ↳ calcification ⊗
- No nipple skin involvement
- ↑ER, ↑PR, ~HER2.

develops invasive lobular carcinoma 25-35% within 20-30 y.

recurrence, contralateral carcinoma ≫ DCIS

INVASIVE CARCINOMA

Molecular subtypes

Defining Features	Luminal (ER-Positive/HER2-Negative)		HER2 (HER2 Positive)	TNBC (ER-Negative/ HER2-Negative)[a]
Percent of breast cancers	~40%–55% (low to moderate proliferation)	~10% (high proliferation)	~20%	~15%
Most similar group defined by mRNA profiling[b]	Luminal A Ki67 <14%.	Luminal B Ki 67 >14%.	HER2-enriched (ER-negative), luminal B (ER-positive)	Basal-like
Most common gene mutations	*PIK3CA* (45%), *TP53* (12%)	*PIK3CA* (29%), *TP53* (29%)	*PIK3CA* (39%), *TP53* (70%–80%)	*PIK3CA* (9%), *TP53* (70%–80%)
Typical special histologic types morphology	Tubular, grade 1 or 2 lobular, mucinous, papillary	Grade 3 lobular	(50%) Some apocrine, some micropapillary (40%) Poorly differentiated.	Medullary features, Poorly diff. metaplastic[c] circumscribed pushing border & necrotic, fibrotic core.
Typical patient groups	Older women, men, cancers detected by mammographic screening	*BRCA2* mutation carriers	Young women, *TP53* mutation carriers (ER positive)	Young women, women of African heritage, *BRCA1* mutation carriers
Complete response to chemotherapy	<10%	~10%	ER positive ~15%; ER negative ~30%–60%	~30%
Metastatic pattern	Bone (70%), more common than viscera (25%) or brain (<10%)	Bone (80%) more common than viscera (30%) or brain (10%)	Bone (70%), viscera (45%), and brain (30%) all are common	Bone (40%), viscera (35%), and brain (25%) all are common
Relapse pattern	Low rate over many years, long survival possible with bone metastases	Early peak at <10 years, late recurrence possible	Bimodal with early and late (10 years) peaks	Early peak at <8 years, late recurrence rare, survival with metastases rare

[a]TNBC lacks expression of ER, progesterone receptor, and HER2.
[b]The three major groups of cancer identified by protein expression or mRNA profiling largely overlap but are not identical. "Luminal B" can refer to ER-positive cancers with high proliferation with or without HER2 expression.
[c]Some rare special histologic types have a more favorable prognosis than this group as a whole (e.g., adenoid cystic carcinoma, secretory carcinoma, low-grade adenosquamous carcinoma).
ER, Estrogen receptor; *mRNA*, messenger RNA; *TNBC*, triple negative breast cancer.

Invasive carcinoma ~~→ mammography~~ ← dem calcification

Invasive carcinoma → mammography → <1cm calcification hard, radiod
absense of mammography → <2-3 cm

on cut → grating sound
due to pinpoint chalky white desmoplastic stroma & calcification.

may invade pectoralis muscle

Nottingham histologic score

Grade I -
- carcinoma grow in tubular pattern
- small round nuclei
- low proliferative rate

Grade II
- carcinomas may show - 1) tubule formation
  2) solid clusters
  3) single infiltrating cells.
- ↑ nuclear pleomorphism
- mitotic figure

Grade III -
- carcinoma as solid sheets, nests
- enlarged irregular nuclei
- ↑ proliferative rate
- tumor necrosis.

Histological types

- Lobular carcinoma
  - CDH1 mutation
  - E-cadherin ↓
  - tumor in dishoesive manner
  - no tubule formation - indian file pattern
  - ↓ desmoplasia, calcification
    ↳ difficult to detect by imaging. not hard/unpalpable
  - metastasis to peritoneum.

- metastasis to peritoneum, retroperitoneum, meninges (carcinomatous meningitis)
- signet cells - mucin drops
- targetoid & pagetoid spread.

- Mucinous (colloid) carcinoma -
  - consistency & appearance - grey blue gelatin
  - soft / rubbery
  - tumor cells in clusters in large lakes of of mucin
  - borders - pushing / circumscribed.

- Tubular carcinoma - well formed tubules cribreiform patter +/- a/w flat epithelial atypia, LCIS calcification.

- Papillary carcinoma - fibrovascular core papillae

- apocrine carcinoma (Her2+) - cells resemble sweat gland.
  - enlarged nuclei & prominent nucleoli
  - abundant eosinophilic cytoplasm

- micropapillary ~~carcinoma~~ - hollow balls of cells float in

- Papillary carcinoma - fibrovascular core papillae
- apocrine carcinoma (Her2+) - cells resemble sweat gland.
  - enlarged nuclei c prominent nucleoli
  - abundant eosinophilic cytoplasm
- micropapillary carcinoma (HER2+) - hollow balls of cells float in intercellular fluid
  mimic true papillae

- medullary carcinoma (TNBC) - soft (W desmoplasia)
  - well circumscribed mass.
  - solid, syncitium-like sheets of large cells c pleomorphic nuclei, prom nucleoli
    >75% tumor cells
  - TT mitotic figure.
  - pushing non-infiltrative border.
  - lymphoplasmacytic infiltrate

- Secretory carcinoma - mimics lactating breast by forming dilated spaces filled c eosinophilic material.

- Inflammatory carcinoma - extensive invasion & proliferation within lymphatic

- Inflammatory carcinoma - extensive invasion & proliferation within lymphatic channels.

Male Breast Cancer

- life time risk 0.11%

Risk factors: ↑age
- first degree relative c breast cancer
- exognous estrogen exposure
- radiation.
- obesity
- infertility
- prior breast disease

Epidemiology: Test in Kleinfelter Sx
60-70 age
Western countries.

genetics - BRCA2 mutation

molecular subtype ER+ (81%)

morphology - breast epithelium of men is limited to large ducts near nipple thus cancer present as subareolar palpable mass.

≥2-3cm

nipple discharge

dissemination - axillary lymph nodes.

metastasis - bone
liver
brain
lungs

treatment - mastectomy.

Prognosis

Table 23.6 American Joint Committee on Cancer 8th Edition: Anatomic Stage[a]

Stage[b]	T: Primary Cancer (Tumor)	N: Lymph Nodes	M: Distant Metastasis	10-Year Survival (%)
0	Ductal carcinoma in situ	No metastases	Absent	97
I	Invasive carcinoma ≤2 cm	No metastases or only micrometastases	Absent	87
II	Invasive carcinoma >2 cm Invasive carcinoma >5 cm but ≤5 cm	1–3 positive LNs 0–3 positive LNs	Absent Absent	65
III	Invasive carcinoma >5 cm Any size invasive carcinoma Invasive carcinoma with skin or chest wall involvement or inflammatory carcinoma	Negative or positive LNs ≥4 positive LNs Negative or positive LNs	Absent Absent Absent	40
IV	Any size invasive carcinoma	Negative or positive LNs	Present	5

[a]In the 8th edition, prognostic stages are assigned using T, N, M, grade, ER, PR, and HER2. Pathologic prognostic stage is assigned for patients who undergo surgical excision prior to other treatment. A multigene assay, when available, can be used to assign stage in this setting. Clinical prognostic stage is assigned for all other patients including patients prior to surgery, patients not eligible for surgery, and patients undergoing systemic therapy prior to surgery.
[b]The anatomic stages listed are used only when information on grade, ER, PR, and HER2 are not available. The survival estimates include the average survival for patients with all biologic types of cancer.

ER, Estrogen receptor; *LNs*, lymph nodes; *PR*, progesterone receptor.

Factors

- Invasive carcinoma v/s CIS
- Distant metastasis
- lymph node metastases -
- tumor size
- locally advanced disease
- Inflammatory carcinoma - erythema, peau d orange.

Factors

- Invasive carcinoma v/s CIS
- Distant metastasis
- lymph node metastases
- tumor size
- locally advanced disease
- Inflammatory carcinoma - erythema, Peu'd orange
- lymphovascular invasion
- molecular type
- histologic type.
- grade
- ER & PR ⊕ ✓
- HER2 ↓
- Proliferative rate. Ki67

Table 23.5 Prognostic Factors for Invasive Breast Carcinoma

Prognostic Factors	Comments
Elements of AJCC 8th Edition Staging	
Distant metastasis (M)	Metastasis beyond regional lymph nodes is the most important prognostic factor.
Regional lymph nodes (N)	Nodal metastasis (including the number of involved nodes) is the second most important prognostic factor.

Table 23.5 Prognostic Factors for Invasive Breast Carcinoma

Prognostic Factors	Comments
Elements of AJCC 8th Edition Staging	
Distant metastasis (M)	Metastasis beyond regional lymph nodes is the most important prognostic factor.
Regional lymph nodes (N)	Nodal metastasis (including the number of involved nodes) is the second most important prognostic factor.
Tumor (T)	Size, involvement of skin (e.g., ulceration or dermal metastases), invasion into chest wall, and presentation as inflammatory carcinoma are important features.
Histologic grade	Survival diminishes with higher histologic grade.
Expression of ER, PR, and HER2	Survival is highest for the most favorable combination (high ER and PR and absent HER2) and is lowest for the least favorable combination (absent ER, PR, and HER2).
Other Prognostic Factors	
Lymphovascular invasion	Tumor cells seen in vascular spaces at the periphery of carcinomas are a poor prognostic factor.
Special histologic types	Some histologic types of cancer are strongly correlated with very favorable survival (e.g., tubular, adenoid cystic).
Response to chemotherapy	The degree of response is a strong prognostic factor for TNBC and HER2 cancers, but not the majority of luminal cancers.
Gene expression profiling	The most important clinical value of these assays is to identify patients with antiestrogen-responsive cancers who do not need chemotherapy.

AJCC, American Joint Committee on Cancer; *ER*, estrogen receptor;

AJCC, American Joint Committee on Cancer; ER, estrogen receptor;

treatment

Table 23.7 Targeted Treatment of Breast Cancer

Target	Treatment	Companion Assay	Comments
ER	Estrogen deprivation (oophorectomy, aromatase inhibitors) Blockage of ER (tamoxifen) Degradation of ER (fulvestrant)	IHC for nuclear ER	Effective cytostatic (but not cytotoxic) therapy for ER-positive cancer
Cyclin-dependent kinases 4 and 6 (CDK4/6)	Kinase inhibitors (palbociclib, abemaciclib, ribociclib)		Used for ER-positive cancers, usually in conjunction with an aromatase inhibitor
HER2	Antibodies to HER2 Cytotoxic therapy linked to HER2 antibody Tyrosine kinase inhibitors Vaccines	IHC for membrane HER2 ISH for HER2 amplification DNA sequencing for *HER2* mutations	Effective for HER2-positive cancer
Defects in HRR*	Chemotherapy with agents causing DNA damage requiring HRR (e.g., platinum agents) Inhibition of alternative DNA repair pathway PARP inhibitors)	DNA sequencing to identify *BRCA1* and *BRCA2* mutations	May be effective in carcinomas with germline *BRCA1* or *BRCA2* mutations or carcinomas with somatic loss of BRCA function
PI3K/AKT/mTOR pathway	Inhibition of proteins in the pathway	Activating mutations or pathway activation—ability to predict response under investigation	>80% of breast cancers have alterations in this pathway
Immune checkpoint proteins	Blocking antibodies to PD-L1, PD-1, and other immune checkpoint proteins such as TIM-1 and LAG-3	IHC for immune checkpoint proteins—ability to predict response under investigation	Under investigation for high-grade ER-negative carcinomas

*Mutations in *BRCA1* and *BRCA2* cause defects in HRR.

ER, Estrogen receptor; *HRR*, homologous recombination repair; *IHC*, immunohistochemistry; *ISH*, in situ hybridization; *PARP*, poly-ADP ribose polymerase