Ovary

Ovarian Cysts

① Functional cysts (there is hormonal production)

- most common type

* 1- Follicle cyst (Follicular)

- follicle does not break open → fluid inside forms cyst on ovary
- if cyst is filled with blood and it ruptures → shock

* 2- Corpus luteum Cysts

- sac doesn't dissolve, opening of sac follicle seals → additional fluid develops inside sac → cyst

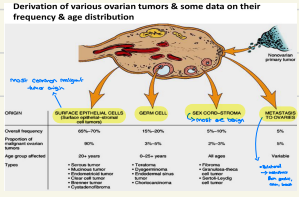
- Symptoms (appear as cyst grows) :-
  - abdominal bloating / swelling
  - pelvic pain before / during menstrual cycle
  - painful bowel movements
  - painful intercourse (dyspareunia)
  - pain in lower back or thighs
  - breast tenderness
  - nausea
  - vomiting
- Complications :-
  - most are benign and resolve on their own
  - doctor may detect cancerous cystic ovarian mass during routine examination (rare)
  - ovarian torsion → large cyst → ovary twist / move → blood supply is cut off → damage or death to ovarian tissue
  - ruptured cyst → intense pain + internal bleeding, ↑ infection risk, life-threatening if untreated

Ovarian Neoplastic Tumor

- 5th most common cancer in women, 5th leading cause of cancer death in women
- 3 origins for primary ovarian tumors :-
  - (1) multipotential surface (coelomic) epithelium (75% of primary, malignant forms → 90% ovarian ca)
  - (2) totipotential germ cells
  - (3) multipotential sex chord / stromal cells

→ less frequent, 25% of ovarian T, 10% ovarian Ca

* Derivation of various ovarian tumors & some data on their frequency & age distribution



- Pathogenesis (familial cases) ⇝ only 5-10 % are familial
  - Risk factors : nulliparity , family history , Oral contraceptives ↓ risk
  - mutations in BRCA 1 and BRCA 2 genes ⟶ ↑ risk for both ovarian and breast cancers
- Pathogenesis (Sporadic cases) :-
  * - BRCA 1 mutation ⟶ 10 %
  * - P53 mutation ⟶ 50 % of all ovarian cancers
  - HER2 / NEU overexpression ⟶ 35 %
  - K-RAS protein overexpression ⟶ 30 % (mostly mucinous cystadenocarcinomas)
- Clinical correlation of all ovarian tumors :-
  - Clinical presentation : - pain - gastrointestinal implants - frequency
  - Ascites ⟶ fibromas + malignant serous tumors
  - Functioning ovarian tumors ⟶ hormonal production of Estrogens or androgens
  - most asymptomatic until well advanced (+ metastasis)
  - 30 % ⟶ incidental discovery on routine gynecologic examination

* Surface Epithelial Tumors

* Types :-
1-Serous
2-Mucinous
3-Endometrioid
4-Clear cell
5-Brenner

- Benign lesions ⟶ Cystadenoma , or Cystadenofibroma
- malignant Tumors ⟶ Cystadenocarcinoma , or Carcinoma (or both)
- Intermediate = Borderline = tumors of low malignant potential ⟶ better prognosis than fully malignant

(1) Serous Tumor (most frequent ovarian tumors)

- 60 % ⟶ benign , 15 % ⟶ borderline , 25 % ⟶ malignant / most common malignant ovarian tumors
- Genetics :- - BRAF + K-RAS ⟶ borderline and low-grade
  - P53 + BRCA 1 ⟶ high-grade serous carcinomas
- Grossly :- - large , spherical / ovoid cysts - 25 % of benign are bilateral
  - Serosa covering benign ⟶ smooth + glistening - serosa of carcinoma ⟶ irregular nodular
  - Cystic spaces filled with clear serous fluid
  - Papillary projections (more marked in malignant)

- morphology / types :-

1- Benign : - lined by single layer of tall, ciliated or obese shaped secretory columnar epithelial cells
- Psammoma bodies on tips of papillae
- large cystic, bilateral, filled with clear serous fluid
- smooth inner surface

- Frank Carcinoma : - anaplasia of lining cells - invasion of stroma + capsule

2- Borderline : - milder cytologic atypia - little / no stromal invasion
- more complex architecture
- might be associated with peritoneal implant
- intermediate prognosis (survival with peritoneal metastasis : 75 %)
- Cystadenoma → papillary tumor growths
- Cystadenocarcinoma → large bulky tumor mass

3 - Malignant : - Anaplasia and stromal invasion
- poor prognosis

- Malignant spread through : - metastatic seeding
- lymphatics to regional LN (para-aortic), distant is rare

(2) Mucinous Ovarian Tumor

- mucin secreting cells
- 80 % → benign , 10 % → borderline , 10 % → malignant (less likely bilateral)
- large , multilocular , no psammoma bodies found
- prognosis depends on stage
- * Bilateral mucinous Ca → signet-ring appearance, must be differentiated from metastatic adenocarcinoma in ovaries (Krukenberg tumor) → ovarian masses
  - ↳ metastasis of mucinous Ca of GIT to ovaries, may mimic primary ovarian
- Pseudomyxoma peritonei → implantation of mucinous tumor cells in peritoneum + production of copious amounts of mucin
  → caused by metastasis from GIT tumors (primarily appendix)
- Grossly :- - similar to serous but filled with mucin
- dominant papillation, serosal penetration, solid areas → malignancy

3 Endometrioid Tumors

- Solid or cystic, develop as mass projecting from endometriotic ovarian cyst wall filled with chocolate-coloured fluid, usually malignant
- 15-30% → have concomitant endometrial carcinoma of the endometrium
- mutations in PTEN suppressor gene

* Germ-Cell Tumor

- Teratomas → 20% of ovarian tumors
- majority of teratomas are benign in ovaries (malignant in testes)
- immature malignant variant is rare (5-10%)

1 Benign (mature) Cystic Teratomas

- full differentiation from totipotential germ cells into mature tissues
- all 3 germ cell layers: ectoderm (hair + skin), endoderm (glands), mesoderm (bone + cartilage)
- young women (1-20 years) → ovarian masses or incidentally found (x-ray)
- Grossly:-
  - cyst filled with sebaceous secretion + hair, bone + cartilage, epithelium, or teeth
  - malignant → 1%
  - torsion → 10-15%
  - unilateral → 90%
  - mostly incidental discovery
- * Struma ovarii → composed entirely of mature thyroid tissue, unilateral brown ovarian masses, hyperfunction → thyrotoxicosis

2 Dysgerminoma

- 2nd-3rd decades (young)
- All malignant, only 1/3 → aggressive + spread
- All radiosensitive → 80% cure
- unilateral, solid, small-large, potato-like grey masses

* Sex Cord Tumors (most are benign)

(1) Granulosa - thecal cell (5-10% ovarian tumors)

- postmenopausal, unilateral
- morphology (mixture of):-
  - (1) Cuboidal granulosa cells (mostly benign (malignant granulosa → 5-25%))
  - (2) Spindled / plump lipid-laden thecal cells → elaborate ↑ estrogen amounts → promote endometrial / breast cancer

→ vaginal bleeding in case

(2) Thecoma - fibroma

- Benign, unilateral, solid grey
- morphology :- - fibrocytes - yellow (lipid-laden) plump thecal cells
  - most are hormonally inactive
- * 40% produce ascites + hydrothorax + fibroma ⇒ Meig's syndrome

(3) Sertoli - leydig cell

- unilateral, small, grey to yellow-brown, solid
- Stimulate testis development, tubules / cords + plump pink sertoli cells
- masculinizing or defeminising - rarely malignant

* Metastasis to Ovary

(1) Krukenberg tumors

- older ages, bilateral
- Solid, grey-white mass (20 cm, 1 Kg)
- Anaplastic tumor cells in cords, glands dispersed though fibrous background
- may be → Signet-ring, mucin-secreting adenocarcinoma
- primary tumor : - GIT - Breast - Lung

Fallopian Tubes

(1) Ectopic Pregnancy (implantation of fertilized ovum outside uterus) (1%)

- 90% → Fallopian tubes
- Predisposing factors :- - tubal obstruction (50%) - tumors
  - PID - endometriosis - IUCD
- 50% → no anatomic cause demonstrated
- Early :-
  - normal early embryo development
  - formation of : placental tissue, decidual changes, amniotic sac
- Later :-
  * - placenta burrows through tubal wall → intratubal hematoma (Hematosalpinx) + intraperitoneal hemorrhage
  * - rupture of ectopic pregnancy → intense abdominal pain + signs of acute abdomen → sever hemorrhage + hypovolemic shock → prompt surgical intervention (life saving)
- histological diagnosis + confirmation → visualization of placental villi, embryo (rarely)
- Until rptve it is indistinguishable from normal pregnancy (amenorrhea + ↑ serum and urinary hCG)
- hCG → Aries stella reaction (50%), but there are no chorionic villi in the uterus
- Absence of ↑ hCG → does not exclude diagnosis (because poor attachment with placental necrosis is common)

(2) Tubal malignancy

- rare, most common histological type → Serous Carcinoma
- ↑ in BRCA mutations
- frequently spread to omentum and peritoneal cavity at time of presentation (advanced)
  ↳ due to access of Fallopian tubes to peritoneal cavity

- Diseases of pregnancy :-
  (1) Ectopic pregnancy
  (2) gestational trophoblastic disease

Placenta

* Gestational Trophoblastic Tumors

- Divided into 3 categories: (1) Benign, complete, partial Hydatidiform moles (HM)
  (2) Invasive mole
  (3) Choriocarcinomas (Chorio Ca) ~> highly malignant
- * all elaborate hCG (detected in blood + urine, used for pregnancy diagnosis) at titers higher than of found during pregnancy (titers progressively rise from HM → invasive mole → chorio Ca)
- * fall / rise hCG in blood / urine → monitor treatment effectiveness
  ↳ judging hCG is more important than anatomic segregation to study response to therapy

(1) Hydatidiform Mole (HM): Complete and Partial

- grape-like structure (Swollen, cystically dilated chorionic villi → Coved by varying amounts of normal to highly atypical chorionic epithelium)
- due to abnormal contribution of paternal chromosomes in gestation

* 1- Complete HM

- emty egg fertilized by 2 spermatoza or diploid sperm
- diploid Koryotype (46, XX or 46, XY (less common)) → entirely paternal genes
- * does not permit embryogenesis → never contains fetal parts
- All chronic villi are abnormal + Chorionic epithelial cells are diploid + all chromosomes are paternal
- Mole s- (1) hydropic swelling of chorionic villi, loose edematous + myxomatous stroma
  (2) absence of villi vascularization
  (3) proliferation of cytotrophoblast + syncytiotrophoblast of chorionic epithelium
- monitoring post-Curettage blood + using β-subunit of hCG concentrations → detection of incomplete removal, or more ominous complication → Chemotherapy (Curative)

* 2- Partial HM

- normal egg fertilized by 2 spermatoza or diploid sperm
- triploid Koryotype (69, XXY) → preponderance of paternal genes
- Compatible with early embryo formation → Contains fetal parts, some normal chorionic villi (+ always triploid having 2 sets of paternal chromosomes)

- mole :- (1) Some villi → villous edema
  (2) focal + slight trophoblastic proliferation
  (3) irregular scalloped margin

	Complete HM	Partial HM
Karyotype	46,XX / 46,XY (diploid)	69, XXY (triploid)
Villous edema	All villi, no blood vessels in villi	All villi, no blood vessels in villi
Trophoblastic proliferation	Present	Absent
Atypia	Elevated	less elevated
hCG in tissue	+ + + +	+
progress to choco ca	2%	rare
uterine bleeding	massive	less

- evidence of an embryo or fetus (sometimes fully formed fetus, normally appearing except for triploid)
- incidence (US + western countries) → 1/1000 pregnancies (higher in asian countries)
- most common before 20 and after 40 years old
- history of HM increase risk in subsequent pregnancies
- usually discovered in 12-14 weeks of pregnancy
  ↳ Early diagnosis can be done by :-
    (1) ultrasound → absence of fetal parts or fetal heart sounds
    (2) detecting hCG ↑ in maternal blood
- Grossly :- - early → normal sized uterus
  - fully developed HM → large uterine cavity filled with delicate, friable mass of thin-walled translucent cystic structures
- Prognosis :- - 80-90 % → do not recur after thorough curettage
  - 10 % of complete HM → invasive
  - 2-3 % of complete HM → give rise to choio ca
  - partial HM → rarely give rise to choio ca

(2) Invasive mole

- complete HM that are locally invasive but do not metastasize
- retains hydropic villi → may embolize to distant organs (are not true metastasis, and regress spontaneously)
- microscopically :- - atypical hyperplastic cytotrophoblast + syncytiotrophoblast proliferation
  - deep penetration of uterine wall ----> rupture, hemorrhage
- local spread to broad ligament or vagina may occur
- difficult to fully remove by curettage (due to depth of myometrium invasion)
  ↳ Serum hCG remains ↑ → requires further chemotherapy → Curative

3 Choriocarcinoma (Chorio ca)

* - very aggressive, malignant, more common in Asian + African countries (x15 fold)
- Arises from :- (1) gestational chorionic epithelium (more frequent) ⇝ better chemotherapy response
  -or-
  (2) totipotential cells within gonads ⇝ poor response to chemotherapy *
  ⟶ difference in prognosis may be due to presence of paternal antigens on placental chorio ca but not on gonadal lesions (paternal antigens help chemo)
- risk → before 20 + after 40 years old
- 50% from complete HM / 25% after abortion / 25% during normal pregnancy
- discovered by apperence of : (1) bloody uterine discharge
  (2) ↑ β-hCG in blood + urine
  (3) absence of marked uterine enlargement
* - Grossly :- - hemorrhagic, necrotic mass
  - primary lesion may self-destructs ⟶ metastasis tells the story
  - invades myometrium + into BV, lymphatic invasion is uncommon
* - Microscopically :- - chorionic villi not formed (never seen)
  - composed of cytotrophoblast + syncytiotrophoblast
  - when discovered ⟶ widely disseminated via blood
    ↳ most often to lungs (50%), vagina (30-40%), brain, liver, kidneys
- Can be 100% cured by chemotherapy, even with spread beyond pelvis and vagina
  ↳ some cases gave birth to healthy infants after

- Clinical Case :-
  - severe bleeding
  - metastasis to lung, liver, bone
  - ↑ β-hCG
  - theca-lutin cysts in ovary

⟶ Uterus Chorio ca

Breast

Breast Disease

* Clinical presentation

- underlying cause > 90% ⟶ benign (likelihood of malignancy increases with age)
- most aggressive tumors are in the young age group
- women with cancer :- - 45% symptomatic
  - palpable mass >>> pain > nipple discharge > inflammatory changes
  - screening test (show remove of signs)
- Mammographic screening :-
  - detects early, non-palpable, asymptomatic breast cancer metastasis
  - invasive carcinoma sized detected at 1 cm, where only 15% of cases have metastasized to regional lymph nodes
  - sensitivity and specificity increases with age
    ↳ due to replacement of the fibous, radiodense tissue (young women) with fatty, radiolucent tissue (older women)

(1) Pain

- cyclic ⟶ diffuse, premenstual edema + swelling
- non-cyclic ⟶ localized, ruptured cyst or physical trauma or infection
- * All painful cancers are benign

(2) Inflammation

- edematous + erythmatous breast
- mostly due to infections (during lactation + breast feeding)
- mimic inflammatory breast cancer

(3) Palpable masses (95% ⟶ benign)

- all require evaluation, detected when 2-3 cm in size
- Common lesions : - cysts - fibroadenomas - invasive carcinomas

4. Nipple Discharge
   - Milky discharge (Galactorrhea)
     ↳ ↑ prolactin levels (pituitary adenoma), hypothyroidism, endocrine anovulatory syndromes, OCPs, tricyclic anti-depressants, methyl dopa, phenothiazines
   * - Bloody or serous discharge
     ↳ - bloody are most commonly due to intraductal papilloma (large duct papillomas + cysts)
     - During pregnancy → due to rapid growth + remodeling of breast
     * - Spontaneous, unilateral bloody discharge → concern for malignancy

5. Gynecomastia
   - only common breast symptom in males
   - imbalance between estrogens and androgens (estrogen stimulate, androgens counteract

Congenital Anomalies

- Some women have sufficient irregularity of normal breast → seek clinical attention

1. Supernumerary nipples / breast
   - along embryonic bridge (milk line, especially axilla)
   - subject to same diseases that affect the definitive breast

2. Congenital Inversion of the Nipple
   - normal, present since childhood
   - Similar changes may be produced by breast cancer

* 3. Galactocele
   - painful, cystic dilation of obstructive duct that arises during lactation
   - may rupture → local inflammatory reaction + fibrosis
     ↳ may arouse suspicion of breast cancer

Inflammatory Lesions

- rare, caused by infection, autoimmune disease, or foreign body-type reactions
* - Clinically :- - erythema - pain - pain - focal tenderness
- most infectious agent ⟶ Staphylococcus aureus
  ↳ enters via fissures in nipple during first weeks of breastfeeding ⟶ lactational abscesses
- if untreated ⟶ tissue necrosis ⟶ fistula tracks opening onto skin
- treatment : (1) antibiotics (3) Continued expression of milk
  (2) Surgical incision + drainage (rarely)
- possibility of symptoms being caused by inflammatory carcinoma
  ↳ because inflammatory diseases are rare

* Inflammation of the breast (none involved with ↑ risk of cancer)

- uncommon, during acute stages ⟶ pain + tenderness in involved areas

(1) Acute Mastitis

- bacteria access to breast through ducts (when there is inspissation of secretions)
- develop during early weeks of lactation, or from forms of dermatitis involving the nipple
* - Staphylococcal infections : - Single or multiple abscesses
  - Small, if large ⟶ heal with scarring
* - Streptococcal infections : - Spread through entire breast
  - pain, swelling, tenderness, heal by resolution

(2) Mammary Duct Ectasia (peri-ductal or plasma cell mastitis)

- non-bacterial, Chronic inflammation of breast
- Associated with :
  (1) inspissation of breast secretion in main excretory ducts
  (2) ductal dilation + rupture ⟶ inflammatory changes in surrounding tissue
- uncommon condition, usually 40s + 50s who have children

* - Grossly :- - ↑ tissue firmness - thick, cheesy sections
- dilated rope-like ducts

* - Histopathology :- - dilated ducts, filled with: granular debris + WBCs (lipid-laden macrophages)
- destroyed duct epithelium lining
- prominence of lymphocytic + plasma cell infiltration

- leads to induration of breast substance or retraction of skin / nipple mimicking changes caused by breast cancer (more significant)

(3) Traumatic Fat necrosis

- uncommon. Produces mass mimicking breast cancer
- most report some antecedent trauma to breast
- Grossly : - sharply localized, small (< 2 cm), tender
- Histopathology : - focus of necrotic fat cells surrounded by neutrophils + lipid-laden macrophages
- later → enclosed by fibrous tissue + mononuclear leukocytes
- eventually → focus replaced by scar tissue, or debris becomes cystic, or surrounded by scar
- Calcifications

Fibrocystic Changes (Disease)

- Very common, ranges from innocuous to patterns associated with ↑ risk of cancer
- most → little clinical significance
- Some (stromal fibrosis + microcysts, macrocysts) → produce palpable lumps (distinguished from cancer by FNA, or biopsy + histologic evaluation)
- Small minority → forms of epithelial hyperplasia (clinically important)
- range of changes in consequence of exaggeration + distortion of cyclic breast changes that occur normally in menstrual cycle
- Estrogenic therapy + OCPs → do not ↑ incidence of these alterations
↳ OCPs may ↓ the risk

- FNA → Fine needle aspiration

Benign Epithelial lesions

- Mostly incidental, detected by mammography
- 3 groups:
  1- Non-proliferative changes (not associated with ↑ risk for cancer)
  2- Proliferative disease without atypia (polyclonal hyperplasia, X1.5-2 fold ↑ cancer risk)
  3- Proliferative disease with atypia (monoclonal, precancer, X4-5 fold ↑ cancer risk in both breast)

(1) Non-proliferative breast changes (fibrocystic changes)

- Common, 3 principal morphologic changes:
  (1) Cystic change + apocrine metaplasia (multifocal, bilateral)
  (2) Fibrosis (3) Adenosis
- Histopathology:
  - Small → multilayered cuboidal to columnar epithelium
  - large → flattened or totally atrophic
  - lined by large polygonal cells, granular eosinophilic cytoplasm
  - Apocrine metaplasia (small round deeply chromatic nuclei) → benign
  - Stroma surrounding cyst → compressed fibrous tissue
  - Stromal lymphocytic infiltration (common)

(2) Proliferative Disease without Atypia

Includes:
epithelial hyperplasia
sclerosing adenosis
complex sclerosing lesion
papilloma

- Varying degrees of epithelial cell proliferation
- Small ↑ in risk of carcinoma of breast
- not clonal
- Predictors of risk, unlikely to be true precursors of carcinoma

* 1- Epithelial Hyperplasia

- Multilayed, filling duct + acini, ↑ myoepithelial cells, no epithelial Atypia
- duct lumen filled with heterogeneous population
- Irregular slit-like fenestrations at the periphery

* 2- Sclerosing Adenosis

- back to back, cells in contact with one another (adenosis)
- stromal sclerosing fibrosis → compress + distort proliferating epithelium
- overgrowth of fibrous tissue → compress ductal + acini lumina → solid chords of cells
  ↳ pattern difficult to distinguish histologically from invasive scirrhous cancer
- acini → swirling pattern
- epithelium double-layer + myoepithelial elements → benign
- associated with only minimally ↑ cancer risk

* 3- Ductal Papillomatosis

- multiple small papillary projections into ductal lumen
- layers of intraductal epithelial proliferation → hyperplasia

(3) Proliferative Disease with Atypia

- Clonal proliferations, associated with moderately ↑ carcinoma risk
- include:
  (1) Atypical lobular hyperplasia (ALH) → resembles lobular carcinoma in situ (LCIS)
  (2) Atypical ductal hyperplasia (ADH) → resembles ductal carcinoma in situ (DCIS)
- Atypical hyperplasia
  ↳ hyperplastic cells → monomorphic + complex architectural patterns (changes approaching DCIS → Atypical)
- Difficult to define / distinguish: (1) epithelial hyperplasias with / without atypia
  (2) Atypical hyperplasia and carcinoma in situ
- IHC (aid in differential diagnosis of challenging breast epithelial lesions)
  - P63 → myoepithelial cells
  - CK 5/6 → benign / malignant epithelial cells

* Non-Invasive In-Situ Carcinoma

- Include :-
  (1) DCIS → distorts lobules into duct like spaces
  (2) LCIS (better prognosis) → expands involved lobules
  Both → arise from cells in terminal duct → give rise to lobules
  → confined by BM, do not invade stroma and lymphovascular channels

(1) Lobular Carcinoma in Situ (LCIS)

- malignancy of secretory tubules of breast, rare than DCIS
- malignant clonal proliferation of cells within lobules
- grow in discohesive fashion → acquired loss of E-Cadherin (tumor suppressive adhesion)
* - expand (not distort) → preservation of underlying architecture
- asymptomatic, incidental finding
- management :-
  - monitoring rather than excision
  * - BRCA 1 / BRCA 2 → Bilateral prophylactic mastectomy

(2) Ductal Carcinoma in Situ (DCIS)

* - most common type of non-invasive breast malignancy
- malignancy of ductal tissue, contained within BM, 20-30% without treatment → invasive
- when invasive → axillary nodal metastasis
- malignant clonal proliferation of cells within ducts
- variety of histologic presentations
  - solid, comedo, cribriform, papillary, micropapillary
    → high Ki67 protein → proliferation
  - from low to high nuclear grade (pleomorphic)
  - extensive central necrosis (toothpaste like necrotic tissue)
  - Associated with calcifications → destruction of breast tissue

- Management :-
  - excellent prognosis (97% long-term survival after mastectomy)
  * - localized DCIS → Complete wide excision
  * - widespread / multifocal DCIS → Complete mastectomy
  - adjacent invasive CA becomes invasive if untreated (1/3 cases)

* Relationship of Fibrocystic Changes to Breast Cancer

- minimal / no ↑ risk for cancer :- - fibrosis - microscopic / macroscopic cysts - apocrine metaplasia
  - mild hyperplasia - fibroadenoma
- Slight ↑ risk for cancer (x1.5-2) : - hyperplasia without atypia - ductal papillomatosis
  - sclerosing adenosis
- Significant ↑ risk for cancer (x5) : - DAH - LAH (Bilateral + multiple)
- family history (ex: BRCA 1 / BRCA 2) → ↑ risk in all categories (ex: x10 in atypical hyperplasia)

Tumors / Lesions

① Fibroadenoma (FA)

* - most common benign tumor of the breast
  - ↑ estrogen activity → development
  - may enlarge in menstrual cycle + during pregnancy, or regress + calcify after menopause
* - young women (3rd decade)
* - Clinically :- Solid, discrete, freely-movable nodule (Breast mouse)
  - Grossly :- firm, uniform white cut-section
  - Histopathology :- - loose fibroblastic stroma containing duct-like epithelial lined spaces
    - intact + well defined BM
  - Ductal lumens :
    - Pericanalicular FA (open, round-oval, regular)
    - or -
    - Intracanalicular FA (compressed by extensive proliferation, slits / irregular star shaped)

- whatever the size, they are easily shelled out
- on mamogram → appears denser than surrounding tissue (does not contain adipose tissue)
- never become malignant, but may have LCIS or Atypia around it

* - FA
↳ proliferation in both stromal and glandular elements
- Phyllodes Tumor
↳ proliferation only in stromal elements

- infiltrative margin → malignant or Borderline
- well-circumscribed margin → Benign

2 Phyllodes Tumor

- less common, arise from peiductal stroma
- most → benign, grow to large / massive size
* - lobulated + cystic → leaflike tumors
- Some → ↑ stromal cellularity, anaplasia, high mitotic activity, rapid ↑ size, invasion
- most → remain localized, treat by excision
- malignant phyllodes (Cystosarcoma phyllodes) → may recur, but mostly remain localized
- most malignant cases (15%) → distant metastasis

3 Intraductal Papilloma

- benign papillary tumor growth within duct, solitary,
- Clinically: - serous / bloody nipple discharge
  - presence of small subareolar mass
  - nipple retraction
- Grossly: - solitary, < 1 cm, Branching papillae within dilated duct or cyst
  - firm, lobulated pale-yellow
  - granular surface, forms raspberry-like nodule
* - Histopathology: - double-layered (epithelial layer covering myoepithelial layer)
- solitary papilloma → benign / multiple papillomas → become malignant
* - papillary carcinoma must be excluded
  ↳ - lacks myoepithelial component
  - monotonous ductal epithelium or severe cytological atypia

Breast Cancer

- Divided into 2 main groups :
  - (1) Carcinoma – arise from epithelial component
    - majority of breast cancers
  - (2) Sarcoma – arise from stromal (CT) component
    - rare
    - include : phyllodes T and Angiosarcoma
- world-wide ↑ incidence
  - earlier detection
  - social changes (delayed childbearing, fewer pregnancies, reduced breast feeding, lack of access to optimal health care)
- most common non-skin malignancy in women
- 2nd most common cause of cancer deaths in women after lung cancer
- >95 % of breast malignancies are Adenocarcinoma (arise from ducts)

* - presence of myoepithelial element in periphery of duct → DCIS -or- LCIS

* Classification System

(1) Depending on hormone receptors

- 3 major groups :-
  - (1) ER positive (HER2 negative, 50-65 %)
  - (2) HER2 positive (ER positive / negative, 10-20 %)
  - (3) Triple negative (ER, PR, HER2 negative, 10-20 %)

(1) ER, PR (+), HER2 (-) → good prognosis
(2) ER, PR (-), HER2 (+) → aggressive, but targeted therapy available
(3) Triple negative → very poor prognosis

(2) Relies on Gene expression profiling

- Divides Breast Cancer into 4 major Groups :-
  - (1) Luminal A
    - low-grade
    - ER-positive, HER2-negative
    - ↓ Ki-67
  - (2) Luminal B
    - higher-grade
    - ER-positive, HER2-negative
    - ↑ Ki-67, Progestrone negative

* Best prognosis
(1) Luminal A
(2) Luminal B
(3) HER2-enriched
(4) Triple negative
Worst prognosis

- Ki-67 → protein that controlles proliferation → presence in ↑ amounts is not a good indicator

(3) HER2-enriched
- overexpress HER2
- ER / PR - negative
* - successfully treated with targeted therapy

(4) Triple-Negative / Basal-like
- ER / PR / HER2 - negative
- more common in :-
  - BRCA 1 / 2 mutations
  - younger - Black

* ## Risk Factors

(1) Age
- rare in under 25, incidence ↑ after 30
- >2/3 -> older than 50, 5% -> younger than 60

(2) Gender
- F > M (only 1% in male)

(3) Family History
- ↑ risk with multiple affected first-degree relatives

(4) Geographic Factors
- higher in America and Europe than in Asia and Africa
- immigration from low incidence to high incidence -> acquire rates of new home countries
  ↳ diet, reproductive patterns, breastfeeding patterns are thought to be involved

(5) Race / Ethnicity
- ↑ Europe -> ↑ ER-positive incidence
- Hispanic + African American -> develope at younger ages + more aggressive

(6) Reproductive History
- Early age of menarche, nulliparity, absence of breast feeding, older pregnancy
  -> ↑ risk (due to ↑ exposure of epithelial breast cells to estrogenic stimulation)

7. Ionizing Radiation - Chest radiation (especially during developing breast)

8. Other: - postmenopausal obesity - mamographic density
- postmenopausal hormone replacement therapy - alcohol

* Pathogenesis

1. Genetic factors

- BRCA 1 / BRCA 2 (both alleles defected → cancer)
  - BRCA 1 → ER-positive
  - BRCA 2 → triple-negative
- P53 (key role in controlling cell division and death) (gardian of genome)
  - → mutation → cancer cells grow and spread
- HER2 gene amplification (HER2 → receptor tyrosine kinase promoting cell proliferation + inhibits apoptosis)
  - → - highly proliferative cancers
    - poor prognosis (past), nowadays → improved prognosis with targeted therapeutic agents

2. Hormonal factors

- Estrogens are important hormonal factors (stimulate GFs promoting tumor growth)
  - → - estrogen receptors regulate other genes → some are important for tumor growth
    - drives proliferation from precursor → fully malignant + metastatic carcinoma
    - estrogen antagonists → reduce development of ER-positive cancer in high-risk women
      → mainstays in treatment of established ER-positive tumors

* Morphology

- upper outer quadrant (50%)
- Central portion (20%)
- lower outer quadrant (10%) - upper inner quadrant (10%) - lower inner quadrant (10%)
- 4% → bilateral primary T, or sequential lesion in same breast (multicentricity)

Breast Carcinoma

Non-Invasive

- Confined to BM, do not invade stroma or lymphovascular channels

① DCIS ..... ② LCIS .....

Invasive (infiltrating)

① Invasive Ductal Carcinoma (70-80%)

- Arise from milk duct (Cancer within duct -> in situ / breaks out ducts -> invasive)
- precancerous lesion → DCIS
  - ↳ ductal carcinoma produces desmoplastic response → replaces normal fat → mammographic densities
- mamography density : - hard, palpable, irregular mass
  - nipple retraction / fixation to chest wall → Advanced
- * Receptor profile :- (1) ER-positive (50-60%) (3) ER, HER2-negative (15%)
  (2) HER2-positive (20%) (4) E-cadhein positive

* - Invasive Ductal → Cohesive cluster of cells
- Invasive lobular → Dissohesive due to loss of E cdhein

* - Any Breast cancer test must include all 3.
  - ER
  - PR
  - Ki-67
  - HER2
  - p53

② Invasive lobular Carcinoma (10-15%)

- Arise from milk producing lobule
- precancerous lesion → LCIS
- 10-20% → multicentric + bilateral
- Clinically : - palpable masses or mammographic densities
- Single (CO) small cells in linear pattern (Targetoid apperance) → nuclei stroma, TDLU, adipose tissue
- eccentrically placed round nuclei, occasional intracytoplasmic vacules
- cells individually invade stroma, allined as single-file
- * Receptor profile :- (1) express hormone receptors, but HER2 overexpression → rare / absent
  (2) loss of E-cadhein (Specific biomarker)
- metastesis (unique) → CSF, Serosal surfaces, bone marrow, Ovary, uterus

3 Carcinoma with medullary features (5%)

- Triple-negative, Receptor profile :- (1) lack hormone receptors
  (2) do not overexpress HER2/NEU
- precancerous lesion ⟶ absent, ↑ frequency in BRCA 1 mutations
- grow as round masses ⟶ difficult to destinguish from benign tumors

4 Colloid Mucinous Carcinoma (rare)

- microscopically :- - produces abundant extracellular mucin ⟶ dissects into surrounding stroma
- Grossly :- - soft, gelatinous
- Receptor profile :- (1) ER-positive (2) HER2-negative (3) PR-positive

5 Tubular Carcinoma (10%)

- Clinically :- irregular mammographic densities
- microscopically :- - well-formed tubules - low-grade nuclei - Angulated glands
- LN metastasis ⟶ rare, excellent prognosis
- * mistaken for Benign sclerosing lesions
  - opposite of tubular Carcinoma → Sclerosing adenosis (fibrocystic disease) ⟶ ducts/glands surrounded by fibrosis, some of ducts are indistinguishable from tubules, double layers, p63+ (preservation of myoepithelial elements)

6 Inflammatory Carcinoma (worst types ⟶ involvement of dermal lymphatics)

- Clinically :- - enlarged, swollen, erythmatous ⟶ blockage of dermal lymphatic spaces by Ca cells
  ⟶ Sometimes misdiagnosed as eczematous disease
  - poorly differentiated, diffusely invasive
  - true inflammation ⟶ minimal / absent
  - most have distant metastasis, poor prognosis
  - mimics surface of orange peel (peau d' orange)

Spread of Breast Cancer

- lymphatic and hematogenous channels
- Favored metastasis : - bone - skeleton - liver - adrenals
  (- brain - spleen - pituitary) ⇝ less common
- metastasis may appear years after therapuic control of primary lesion
  ⟶ Screening programs (1) mammographic screening (2) MRI
- LN metastasis (50%.) ⟶ palpable masses , <15% found by mammography
* - outter / centrally located ⟶ first to axillary nodes / inner ⟶ LN along internal mammary arteries
  ↳ Supraclavicular LN involved after axillary / internal mammary , Sometimes primary site of spread is skipped
- Distant dissemination follows , metastatic involvement of any organ / tissue
- often discoved as Solitary , painless , fixed mass , 2-3 cm , regional LN involvement ⇝ 50%

* Prognosis / Prognostic factors

- depends on biological features (molecular + Histologic) and extent of spread (stage)

* Tumor stage

- Invasive carcinoma / in situ ⟶ better prognosis ⟶ in situ
- Distant metastasis ⟶ bad prognosis (stage 4) (Cure is unlikely)
- LN metastasis ⟶ depends on involved LN (Axillary LN most important in absence of distant metastasis in invasive carcinoma) (Biopsy is necessary)
  ⟶ 10 year survival rate ⟶ no LN involvement ⟶ 70-80 %
  ⟶ 1-3 LN involved ⟶ 35-40 %
  ⟶ >10 LN involved ⟶ 10-15 %.
- Size ⟶ Best : stage 1 (< 2cm) , ↑ risk of axillary LN involvement with ↑ in size
- locally advanced disease ⟶ Better than distant , invading into skin / skeletal muscle or difficult to treat surgically and are usually large
- lymphovascular invasion ⟶ poor prognosic factor
  ⟶ Strongly associated with LN metastasis

- Molecular subtype → Luminal A < Luminal B < HER2-enriched < Triple-negative (worst)
- Special histologic types → Survival rate of (tubular, mucinous, tabular, papillary, adenoid cystic) is greater than of no special subtype
  → metaplastic carcinoma / micro-papillary carcinoma → poorer prognosis
- Histologic grade → All invasive carcinoma → nuclear grade, tubule formation, mitotic rate
- proliferative rate (measured by mitotic counts)
  ↳ ↑ proliferative → poor prognosis (may have better chemotherapy response)
- Hormone Receptors
  (1) ER / PR
  - 80% ER+PR positive → respond to hormonal therapy
  - 40% ER or PR positive → ER-positive → less likely to respond to chemotherapy
  - failure to express either → < 10% likelihood for hormonal therapy response but more likely to respond to chemotherapy
  (2) HER2
  - overexpression → poor survival
  - FISH TEST → positive HER2 → targeted therapy (take herceptin)

* Staging

Stages of breast ca

Stage 0: DCIS or LCIS, with 5-year survival rate (5YSR):**92%**
Stage I: Invasive ca up to **2 cm**Ø(including ca in situ with micro invasion) without LN involvement **(**5YSR:**87%).**
Stage II: Invasive ca up to **5 cm**Ø **with up to 3 involved axillary LNs** or invasive ca more than 5 cm without LN involvement **(**5YSR:**75%).**
Stage III. Invasive ca up to **5 cm**Ø **with 4 or > involved axillary LNs**; invasive ca more than 5 cmØ with LN involvement; invasive ca with 10 or more involved axillary LNs; invasive ca with involvement of the ipsilateral internal mammary LNs; or invasive ca with skin involvement (edema, ulceration, or satellite skin nodules), chest wall fixation, or clinical inflammatory ca (5YSR:**46%).**
Stage IV. Any Ca B with **distant metastases**(5YSR: **13%**).
Why some cancers **recur** following postoperative therapy whereas others do not? Remains unknown & a **mystery**.