Objectives

- Appreciate the potentially overlapping clinical presentations of benign and malignant breast diseases
- Describe selected common benign breast diseases
- Understand the pathology of breast cancer, and their prognostic and predictive factors

Outline

I. Anatomy, Developmental Disorders and Clinical Presentation

a. **Normal Anatomy and Microanatomy**
b. **Disorders of Development:** *Milk line remnants, Accessory axillary breast tissue*
c. **Clinical Presentations of Breast Disease:** *Pain, Mass, Nipple discharge*
d. **Mammographic Screening:** *Densities, Calcifications*

II. Inflammatory Disorders

a. **Mastitis:** *Acute, Periductal, Granulomatous*
b. **Duct Ectasia**
c. **Fat Necrosis**
d. **Lymphocytic Mastopathy (diabetic mastopathy)**

III. Benign Epithelial Lesions

a. **Non-Proliferative Breast Changes:** *Fibrocystic changes*
b. **Proliferative Breast Disease Without Atypia:** *Usual ductal hyperplasia, Papilloma etc.*
c. **Proliferative Breast Disease With Atypia:** *ADH, ALH*

IV. Breast Carcinoma

a. **Carcinoma in-situ:** *DCIS, LCIS, Paget's disease*
b. **Invasive Breast Carcinoma**

V. Lesions of the Male Breast

a. **Gynaecomastia**
b. **Invasive Breast Carcinoma**

VI. Stromal Tumours and Miscellaneous

a. **Fibroadenoma**
b. **Phyllodes Tumour**
c. **Lesions of Interlobular Stroma:** *Lipoma, Angiosarcoma etc*.
d. **Other Malignant Tumours:** *Metastasis, Lymphoma, Skin Tumours etc.*

References

Kumar V, Abbas A, Aster J. *Robbins & Cotran Pathologic Basis of Disease*. 9th ed.
Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van de Vijver MJ (Eds.): WHO Classification of Tumours of the Breast. IARC: Lyon 2012

Image credits

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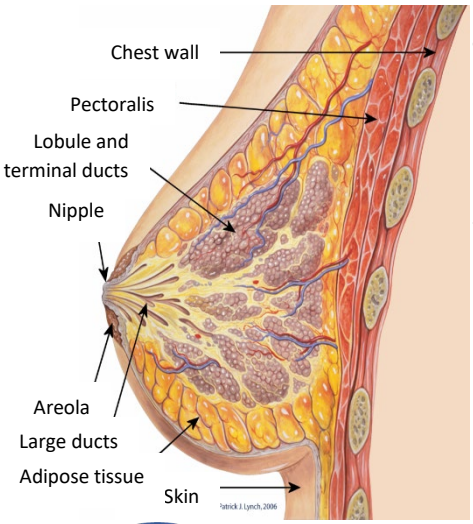
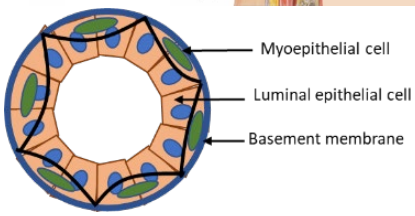
***Note**: Pathweb Study Notes are based on the key topics covered in the lectures in the Yong Loo Lin School of Medicine, as well as additional topics covered in major texts. For more comprehensive discussion on specific pathology topics, readers are advised to refer to the recommended texts in your respective courses.*

I. ANATOMY, DEVELOPMENTAL DISORDERS AND CLINICAL PRESENTATION

Normal anatomy and microanatomy



Original author: Patrick J. Lynch.



- Breast comprises **ducts** and **lobules** (each lined by a peripheral layer of **myoepithelial cells** and an inner luminal layer of **epithelial cells**) with 2 types of **stroma**: interlobular and intralobular. Both benign and malignant lesions can arise from each element
- 6-10 major duct orifices open onto the skin surface at the nipple (the superficial portions of these major ducts are lined by keratinizing squamous epithelium). Successive branching of the large ducts eventually leads to terminal ducts (in prepubertal females and males) which further branch into a grapelike cluster of small acini to form a lobule (**terminal duct lobular unit** - TDLU) in adult women
- The breast structure changes with different age periods, especially during the female reproductive years, as well as with the menstrual cycle (number of acini per lobule increases in the latter half due to rising estrogen and progesterone levels, and the intralobular stroma becomes more oedematous, before regressing upon menstruation). As the major function of the breast is **nutritional support of the infant**, the breast only comes completely mature and functional with the onset of pregnancy. There is an increase in number and size of lobules compared to stroma, which is necessary for the production of colostrum and subsequently milk after parturition. Only some lobule regression occurs upon cessation of lactation, hence there is a permanent increase in the size and number of lobules after pregnancy. Involution of the lobules and specialized intralobular stroma starts after the third decade (long before menopause), and the interlobular stroma converts from radiodense fibrous stroma to radiolucent adipose tissue

Disorders of development

Milk line remnants (supernumerary nipple/breast): persistent epidermal thickenings along the milk line which extends from the axilla to the perineum. Hormone-responsive, therefore often presents with painful premenstrual enlargements

Accessory axillary breast tissue: normal ductal system may extend into the subcutaneous tissue of the chest wall or axillary fossa. Because breast tissue may not be removed in these areas, prophylactic mastectomies markedly reduce but do not completely eliminate the risk of breast cancer

Congenital nipple inversion: failure of nipple to evert during development; common and may be unilateral. Usually corrects spontaneously during pregnancy or by simple traction. Acquired nipple retraction is more concerning as it may indicate an underlying disease (cancer or inflammation)

Clinical presentations of breast disease

Symptoms are non-specific - both benign and malignant diseases can present similarly. Evaluation of breast diseases thus depends on the **triple assessment**: clinical examination, imaging and pathology

- **Pain** (mastalgia/mastodynia): may be **cyclic** (with menses) or **noncyclic**. Diffuse cyclic pain may be due to premenstrual oedema. Noncyclic pain is usually localized and may be due to ruptured cysts, physical injury, or infections although often no specific lesion identified. Although almost all painful masses are benign, ~10% of breast cancers present with pain
- **Palpable mass**: Benign masses (e.g. cysts, fibroadenomas) are most common in premenopausal women; the likelihood of malignancy increases with age. 1/3 of breast cancers are first detected as palpable masses (~2-3 cm), by which time the majority would have likely metastasized; screening by breast examination thus has little effect on reducing mortality
- **Nipple discharge**: clinically worrisome when **spontaneous** and **unilateral**; risk of malignancy also increases with age. A small discharge produced by breast manipulation is often normal. Milky discharge (**galactorrhoea**) is associated with elevated prolactin levels (e.g. pituitary adenoma), hypothyroidism, endocrine anovulatory syndromes, or certain medications; not with malignancy. **Bloody or serous discharges** are most commonly due to large duct papillomas, cysts, or during pregnancy

Mammographic screening

Introduced in US in 1980s to detect small non-palpable asymptomatic breast carcinomas (as small as 1 cm), and is currently the most common means to detect breast cancer. The sensitivity and specificity of mammography increases with age (as the breast tissue becomes more fatty and radiolucent). ~10% of invasive carcinomas are not detected by screening mammography, usually because the tumour is obscured by surrounding radiodense tissue (esp.in younger women), very small, has a diffuse infiltrative pattern with little or no desmoplastic response, or is located close to the chest wall or in the periphery of the breast. In such cases, other imaging modalities e.g. ultrasound or MRI may be needed. Principal mammography radiologic signs of breast carcinoma are densities and calcifications:

- **Densities**: when breast lesions replace adipose tissue with radiodense tissue. Rounded densities are most commonly benign e.g. fibroadenomas or cysts; invasive carcinomas are generally irregular
- **Calcifications**: can occur in secretions, necrotic debris or hyalinized stroma. Can be associated with benign lesions e.g. clusters of apocrine cysts, hyalinized fibroadenomas and sclerosing adenosis. Calcifications associated with malignancy are usually small, irregular, numerous and clustered. Screening has increased the detection of ductal carcinoma in-situ (DCIS), since it is most commonly detected as mammographic calcifications

Earlier diagnosis due to mammography has decreased deaths from breast cancer. However, the beneficial effect of screening is limited – 70-80% of cancers detected by mammography are already invasive and likely have already metastasized. In addition, the cancers most likely to cause death are those least likely to be detected by mammography – young women of pre-screening age, or rapidly

growing cancers that present during the interval between mammograms. Conversely, ~10-30% of cancers detected by mammography) have indolent behaviour and are clinically unimportant

II. INFLAMMATORY DISORDERS

Rare outside of the lactational period (accounts for <1% of breast symptoms). Can be caused by infections, autoimmune disease, foreign body-type reactions to extravasated keratin or secretions. **DDx**: inflammatory breast cancer – can also cause swollen erythematous breast by obstructing dermal vasculature with tumour emboli

Mastitis

- **Acute (bacterial) mastitis**: erythematous painful breast +/- fever. Usually during 1st month of breastfeeding, caused by a local bacterial infection (*Staphylococcus aureus* or streptococci) when the breast is most vulnerable due to cracks and fissures in the nipples. Treatment: antibiotics and continued expression of breast milk
- **Periductal mastitis (squamous metaplasia of lactiferous ducts, recurrent subareolar abscess)**: painful erythematous subareolar mass +/- inverted nipple (due to underlying inflammation); if recurrent, may form a fistula tract. More than 90% of cases are smokers (?due to relative vitamin A deficiency associated with smoking or substances in tobacco smoke that alter the differentiation of the ductal epithelium). **Pathogenesis**: Keratinizing squamous metaplasia of the nipple ducts, with plugging of the ductal system by shed keratin, causing dilatation and eventual duct rupture with associated chronic granulomatous inflammatory response. Recurrences can have secondary supervening bacterial infection causing acute inflammation. **Treatment**: en bloc surgical removal of the duct and any fistula tract; simple incision of the abscess cavity alone drains any abscess but does not remove the keratinizing epithelium which allows for recurrences
- **Granulomatous mastitis**: umbrella term – can be manifestation of **systemic** granulomatous disease (e.g. granulomatosis with polyangiitis), or **localized** breast disorders (e.g. granulomatous lobular mastitis, adjacent foreign objects e.g. breast prostheses ('paraffinoma','siliconoma') /piercings, rare infections). **Granulomatous lobular mastitis**: uncommon, only in parous women. The granulomas are closely associated with the breast lobules, suggesting that it is a hypersensitivity reaction to antigens expressed during lactation. Treatment with steroids sometimes effective

Duct ectasia: palpable periareolar mass often associated with thick, white nipple secretions +/- skin retraction (can mimic invasive carcinoma clinically and radiologically). Unlike periductal mastitis, pain/erythema is infrequent, and is not associated with smoking. **Pathogenesis**: Ectatic dilated ducts filled with inspissated secretions and numerous lipid-laden macrophages, that can rupture causing a marked periductal and interstitial chronic inflammatory reaction (+/- granulomas around cholesterol clefts) and fibrosis, producing an irregular mass with skin and nipple retraction

Fat necrosis: painless palpable mass +/- skin thickening or retraction, mammographic densities or calcifications (can mimic cancer). ~50% have history of breast trauma or prior surgery

Lymphocytic mastopathy (diabetic mastopathy): single or multiple hard palpable masses or mammographic densities (can mimic cancer). Atrophic ducts and lobules have thickened basement membranes and are surrounded by a prominent lymphocytic infiltrate. Most common in women with type 1 diabetes or autoimmune thyroid disease -? Autoimmune basis

III. BENIGN EPITHELIAL LESIONS

Include **non-proliferative** breast changes, and **proliferative** breast diseases **with or without atypia**, each with a differing attendant risk of subsequently developing breast cancer. Usually detected by mammography (densities, calcifications) or incidentally in surgical specimens

Non-proliferative breast changes (fibrocystic change) *(No increased risk of breast cancer)*

Common breast lesion, often during reproductive age. Usually presents as lumps/nodularity; sometimes detected as calcifications on screening mammography (in association with cysts or adenosis)

- **Cysts**: dilatation of lobules which may coalesce into larger cysts. Lining epithelium can either be flattened/atrophic or show apocrine metaplasia (abundant granular eosinophilic cytoplasm and round nuclei)
- **Fibrosis:** cysts frequently rupture, releasing secretory material into the adjacent stroma with resulting chronic inflammation and fibrosis
- **Adenosis**: increase in number of acini per lobule. Normal in pregnancy; may occur as a focal change in non-pregnant females. Acini are lined by columnar cells, which may appear benign or show nuclear atypia (i.e. flat epithelial atypia (FEA) – a clonal proliferation thought to be the earliest recognizable precursor of low grade breast cancers, but does not convey an increased cancer risk presumably because other steps in cancer development are rate limiting). **Lactational adenomas**: palpable masses in pregnant or lactating women, consisting of normal-appearing breast tissue with lactational changes (possibly an exaggerated local response to gestational hormones)

Proliferative breast disease without atypia *(1.5-2x predictor of risk of breast cancer in either breast; not direct precursors of cancer as they are non-clonal)*

- **Usual ductal epithelial hyperplasia**: increased numbers of both luminal and myoepithelial cells that fill and distend ducts and lobules. Usually incidental
- **Sclerosing adenosis**: increased numbers of acini (adenosis) that are compressed and distorted in association with stromal fibrosis (sclerosing). Palpable mass, radiologic density or calcifications
- **Complex sclerosing lesion/radial scar**: lesions with components of sclerosing adenosis, papillomas and epithelial hyperplasia. Can mimic invasive cancer mammographically, grossly and histologically
- **Papilloma**: intraductal papillary proliferation with multiple branching fibrovascular cores and frequently superimposed epithelial hyperplasia and apocrine metaplasia. Can be **large duct** (usually solitary, in the lactiferous sinuses, present as serous nipple discharge from intermittent blockage and release of normal breast secretions, irritation of the duct +/- blood if the stalk undergoes torsion and causes infarction) or **small duct** (multiple, deeper within the ductal system, present as small palpable masses, or as densities or calcifications on mammograms)

Proliferative breast disease with atypia *(4-5x increased risk of breast carcinoma)*

Clonal proliferation having some but not all of the histologic features required for a diagnosis of carcinoma in-situ (CIS) – includes **atypical ductal hyperplasia (ADH)** and **atypical lobular hyperplasia (ALH)**. ADH is usually detected by calcifications, while ALH is often an incidental finding. Despite the increased cancer risk, <20% with atypical hyperplasia develop breast cancer; patients may therefore prefer careful clinical and radiologic surveillance over intervention (surgery or estrogen antagonists).

IV. BREAST CARCINOMA

More than 95% of breast malignancies are adenocarcinomas that first arise from cells within the terminal duct-lobular unit (TDLU) as carcinoma in-situ (CIS); at the time of clinical detection, the majority (at least 70%) will have breached the basement membrane and invaded the stroma.

Carcinoma in-situ (CIS) *(8-10x increased risk of breast carcinoma*)

Neoplastic clonal proliferation of epithelial cells confined to ducts and lobules by the basement membrane – the myoepithelial cell layer is preserved. Includes **ductal carcinoma in-situ (DCIS)** and **lobular carcinoma in-situ (LCIS)** based on their growth patterns i.e. resemblance of the involved spaces to normal ducts or lobules, reflecting their different tumour cell genetics and biology

- **DCIS**: rarely palpable; almost always detected by mammography usually due to calcifications associated with secretory material or necrosis (diagnosis thus increased when mammographic screening was first introduced). Less commonly, periductal fibrosis surrounding DCIS forms a mammographic density or vaguely palpable mass. May rarely present as nipple discharge or incidentally. **Histology**: clonal epithelial cell proliferation within duct/lobules with different architectural patterns (e.g. solid, cribriform, micropapillary) and low to high nuclear grades. Can spread throughout the ductal system and produce extensive lesions. **Prognosis and treatment**: If untreated, women with small low grade DCIS develop invasive carcinoma at a rate of ~1%/year, usually in the same quadrant and with similar grade and ER/Her2 expression pattern as the associated DCIS. Local excision is recommended, as subsequent invasive carcinomas usually occur at the same site. Mastectomy is curative in >95% of women, while breast conservation has a slightly higher risk of recurrence – about half of which are DCIS and half invasive carcinoma. The major risk factors for recurrence are 1. High nuclear grade and necrosis 2. Extent of disease 3. Positive surgical margins. Complete excision is difficult as the extent of DCIS may not be always be reliably predicted by imaging and it is usually not grossly evident at surgery. Post-op radiotherapy and tamoxifen can reduce the risk of recurrence
- **LCIS**: Almost always an incidental biopsy finding since classic LCIS is not associated with calcifications or stromal reaction. Bilateral in 20-40% of cases (vs 10-20% of cases of DCIS). **Histology**: uniform epithelial cell proliferation expanding ducts/lobules +/- mucin-positive signet-ring cells. The cells appear discohesive and rounded, mostly due to loss of cellular adhesion via acquired loss / dysfunction of the transmembrane tumour suppressor protein E-cadherin (e.g. through mutation of the E-cadherin gene *CDH1*). Cells of ALH, LCIS, and invasive lobular carcinoma are morphologically

identical. Pagetoid spread, the presence of neoplastic cells between the basement membrane and the overlying luminal cells, is commonly seen in the breast but not the nipple skin. Almost always ER/PR+, Her2-. Rare variants of LCIS (e.g. pleomorphic LCIS) have high grade nuclei and central necrosis, and may be ER-, Her2+. Natural history of these subtypes is limited, although some believe they are more aggressive than classic LCIS. **Prognosis and treatment**: LCIS is both a risk factor and a non-obligate precursor for invasive carcinoma in either breast. 25-35% of women develop invasive carcinoma over 20-30 years, or at a rate of ~1%/yr, similar to untreated DCIS. However, unlike DCIS, LCIS confers an almost similarly high risk in the contralateral breast as in the ipsilateral breast. The invasive carcinoma is 3x more likely to be lobular carcinoma, but most are of other morphologies. Treatment choices include bilateral prophylactic mastectomy, tamoxifen, or more typically close clinical follow up and mammographic screening

- **Paget disease**: rare manifestation of breast cancer (1-4%); presents as a unilateral erythematous eruption with scaling, crusting +/- pruritus (mimicking eczema). 50-60% of women have a palpable mass, usually indicative of an underlying invasive carcinoma; those without a palpable mass usually have only DCIS. **Histology**: Malignant Paget cells extend from DCIS within the ductal system via the lactiferous sinuses into nipple skin without crossing the basement membrane → can be detected by nipple biopsy. The tumour cells disrupt the normal epithelial barrier, allowing extracellular fluid to seep out onto the nipple surface. **Prognosis**: Depends on the features of any underlying carcinoma (usually poorly differentiated, ER-, Her2+), and is not affected by presence or absence of DCIS involving the skin when matched for other prognostic factors

Invasive breast carcinoma

Neoplastic epithelial cells penetrate through the basement membrane into the stroma, where they have potential to invade into the vasculature and metastasize to regional lymph nodes and distal sites.

- Most common non-skin malignancy in women, second only to lung cancer as a cause of cancer deaths. Almost all breast malignancies are **adenocarcinomas** and are divided based on **molecular and morphologic characteristics** into several subgroups with important associations with clinical features, response to treatment and outcomes. The **3 major molecular subtypes** are based on expression of ER and Her2: **ER+ Her2-** (50-65%), **Her2+** (10-20%) and **ER- Her2-** (10-20%), which can be determined via immunohistochemistry +/- *Her2* gene amplification studies. **Morphologically**, ~1/3 of breast cancers can be classified into **special histologic types** (some of which have associated clinically relevant biologic characteristics) while the remainder are labelled **'no special type'**
- **Risk factors**:
    - **Hereditary factors:**
        - **Germline mutations**: 5-10% of breast cancers occur in persons with germline mutations in tumour suppressor genes e.g. *TP53*
        - **1st degree relatives with breast cancer**: 15-20% have affected first degree relative but do not carry an identified breast cancer gene mutation. Increased risk is probably due to the interaction of low-risk susceptibility genes and shared environmental factors

- **Race/ethnicity**: non-Hispanic white women in US has highest incidence
- **Lifetime exposure to estrogen**:
  - **Female**
  - **Age**: risk raises throughout lifetime, peaking at 70-80 years
  - **Age at menarche/menopause**: menarche at younger than 11 years increases risk by 20% compared to older than 14 years old. Late menopause also increases risk
  - **Age at first live birth**: A full-term pregnancy before 20yo halves the risk compared to nulliparous women or women > 35yo at the time of their first birth
  - **Hormonal therapy**: Menopausal hormonal therapy increases risk (usually of small ER+ cancers), particularly when estrogen and a progestin are given together for a period of years. Oral contraceptives do not appear to increase the risk. Reducing endogenous estrogens by oophorectomy decreases the risk of developing breast cancer by up to 75%. Drugs that block estrogenic effects (e.g. tamoxifen) or the formation of estrogen (e.g. aromatase inhibitors) also decrease the risk
  - **Breastfeeding**: the longer the duration, the greater the risk reduction. Lactation suppresses ovulation and may trigger terminal differentiation in luminal cells
- **Breast characteristics**:
  - **Benign breast disease**: prior breast biopsy with atypical hyperplasia or proliferative changes
  - **Breast density**: very dense breasts on mammography has a 4-6x higher risk of breast cancer compared to women with the lowest density. High breast density clusters in families and is correlated with other risk factors e.g. older age at first birth, fewer children, and menopausal hormonal therapy. Persistently high breast density in older women may result from a failure of normal breast involution
- **Carcinoma of the contralateral breast or endometrium**: breast and endometrial carcinomas have several risk factors in common e.g. prolonged estrogenic stimulation. Approx. 1% of women with breast ca develop a second contralateral breast carcinoma per year
- **Lifestyle / environmental factors**:
  - **Diet**: moderate or heavy alcohol consumption
  - **Obesity**: obese women < 40yo have decreased risk due to anovulatory cycles and lower progesterone levels. Postmenopausal obese women are at increased risk due to synthesis of estrogens in fat depots
  - **Exercise**: probably a small protective effect
  - **Environmental toxins**: concern about estrogenic effects e.g. organochlorine pesticides, but no definite associations yet
  - **Radiation exposure to the chest**: Greatest risk with exposure at young ages and high radiation doses
- **Pathogenesis:** breast cancers are clonal proliferations of cells which have acquired multiple genetic alterations. May be **hereditary** (arising in women with germline mutations in tumour suppressor genes) or **sporadic**, with penetrance / development influenced by environmental factors.

Familial breast cancer (~12%): due to inheritance of identifiable susceptibility gene(s). More likely in patients with multiple affected first-degree relatives, early onset cancer, multiple cancers, or family members with other specific cancers. The major known susceptibility genes for familial breast cancer – *BRCA1/2*, *TP53* and *CHEK2*, are all tumour suppressor genes with important normal roles in DNA repair and maintenance of genomic integrity. Inheritance of a defective copy of these genes may mean that a single sporadic mutation in the remaining normal allele may be all that is necessary to completely lose the tumour suppressor function, resulting in a 'mutator' phenotype i.e. an increased propensity to accumulate genetic damage, thereby accelerating cancer development

BRCA1 (chr17) ***BRCA2*** (chr13)	80-90% of 'single gene' familial breast cancers and ~3% of all breast cancers. Penetrance varies form 30-90% depending on the specific mutation	BRCA1 and 2 are part of a large protein complex required for repair double stranded DNA breaks through **homologous recombination** (a normal sister chromatid is used as a template for repairing the broken stretch of DNA). It is unknown why malfunction of these ubiquitous genes are more highly associated with breast cancer than other cancers; possibilities include that breast and ovarian epithelial cells may be particularly prone to the type of DNA damage that BRCA1 and 2 are required to repair, or that the tumour suppressor function of BRCA1 involves functions independent of DNA repair *BRCA1/2* carriers are at higher risk of other epithelial cancers e.g. prostate, pancreatic carcinoma *BRCA1*: markedly increased risk of ovarian ca (20-40% of carriers) *BRCA2*: lower risk for ovarian cancer vs *BRCA1* (10-20%), but is associated more frequently with male breast cancer Identification of carriers is therefore important for increased surveillance and prophylactic mastectomy and salpingo-oophorectomy to reduce cancer-related morbidity and mortality. However, because genetic testing is difficult due to the many different mutations that can be present in each gene (some of which are inconsequential polymorphisms), testing is restricted to those with strong family history or high-risk ethnic groups *BRCA1*: breast cancers are commonly poorly differentiated, and have 'medullary' features – syncytial growth pattern with pushing borders and a lymphocytic response. Biologically very similar to ER-/Her2- breast cancers i.e. 'basal-like' by gene expression profiling *BRCA2:* breast ca also tend to be relatively poorly differentiated, but are more often ER+ vs *BRCA1* cancers.
TP53 (Li-Fraumeni syndrome) ***CHEK2***	~8% of 'single gene' familial breast ca	CHEK2 has important functions in repair of double stranded DNA breaks
PTEN (Cowden syndrome) ***STK11*** (Peutz-Jeghers syndrome) ***ATM*** (ataxia telangiectasia)	<1% of all familial breast ca	ATM senses DNA damage and with p53 and CHEK2 induces cell cycle arrest.

Sporadic breast cancer: major risk factors are related to hormone (estrogen) exposure (see above), which functions as a promoter of breast cancer via several effects on the breast e.g. by stimulating breast growth and cell proliferation during puberty, menstrual cycles, and pregnancy, which increases the number of cells that can give rise to cancer and permits the accumulation of DNA damage. The temporary lull in cell division during the later part of the menstrual cycle may allow time for defective DNA repair to occur and for mutations to become fixed in the genome, which may partly account for the increased risk of breast cancer with each cumulative number of menstrual cycle a woman undergoes. Once premalignant or malignant cells are present, hormones can stimulate their growth as well as normal stromal cells that may aid tumour development

- **Molecular mechanisms of carcinogenesis and tumour progression**:
  It is hypothesized that carcinogenesis is initiated in breast tissue stem cells by a driver mutation. Most common driver mutations include proto-oncogenes *PIK3CA*, *HER2*, *MYC* and *CCND1* (encodes cyclin D1), tumour suppressor genes *TP53* and (in familial cancers) *BRCA1/2*. As mentioned above, there are 3 major genetic pathways:
  - **ER+, Her2- cancers:** dominant pathway of breast cancer development (50-65%); most common subtype in *BRCA2* carriers. Often associated with chr1q gains, chr16q loss and activating mutations in *PIK3CA*; these same genetic lesions are often found in FEA and ADH (putative precursor lesions). Also called **'luminal' cancers** as their mRNA expression pattern closely resembles normal breast luminal cells, which is dominated by estrogen-regulated genes. There are 2 major molecular subtypes (A and B) that differ in their proliferation rate and response to therapy
  - **Her2+ cancers**: arise through a pathway strongly associated with *Her2* gene amplifications (chr17q) (20%); most common subtype in germline TP53 mutation carriers (Li-Fraumeni). May be ER+/-. Putative precursor: atypical apocrine adenosis. Gene expression pattern is dominated by genes related to proliferation regulated by signaling pathways lying downstream of the Her2 receptor tyrosine kinase. Also high mutational load.
  - **ER-, Her2- cancers**: arise through a pathway independent of ER-mediated changes in gene expression and *Her2* gene amplification (15%); most common subtype in BRCA1 carriers. Sporadic tumours of this type often have loss-of-function mutations in *TP53* where *BRCA1* mutations are uncommon but may be silenced through epigenetic mechanisms. Precursor lesions: unknown. mRNA expression has a **'basal-like' pattern** that includes many genes expressed in normal myoepithelial cells.

  Once a founding tumour clone is established, genomic instability results in **subclonal heterogeneity**, contributing to both tumour progression and resistance to therapy. **Epithelial tumour-stromal interactions** in the local microenvironment are also important to tumour development and growth, although not yet fully understood. Cancers occur in the areas of greatest mammographic density, suggesting that increased amounts of fibrous stroma is both a marker of risk and biologically important for tumorigenesis; angiogenesis and tumour-associated inflammation are also commonly associated with carcinoma, including the in-situ stage. The final **transition of CIS to invasive**

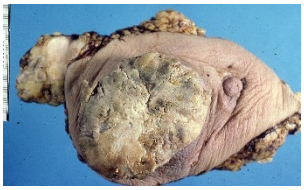
carcinoma may involve alteration of the basement membrane, increased proliferation, escape from growth inhibition, angiogenesis and invasion of stroma, as well as stromal remodeling

- **Clinical features**: Incidence is 4-7x higher in US and Europe, but rates are rising worldwide likely due to adoption of Western social lifestyles and associated risk factors. Incidence increases rapidly after age 30, with ER+ cancers continuing to increase with age, while ER- Her2+ cancers remain relatively constant, resulting in a lower proportion of ER-Her2+ cancers in older vs younger women. The number of ER+ cancers detected in older women has also risen as a result of mammographic screening (which preferentially detects these cancers) and menopausal hormonal therapy. The number of stage 1 cancers (small node-negative cancers) has also increased with screening, while the number of large node-positive or advanced stage breast cancers has fallen

  Presentation: Those detected as calcifications on mammographic screening are usually <1 cm in size; otherwise they are usually hard palpable masses of at least 2-3 cm. There can be overlying skin ulceration, dimpling or nipple retraction (if there is dermal invasion or centrally located), or be fixed to the chest wall (if there is local invasion into the pectoralis muscle). Rarely presents as axillary lymph node or distant metastasis before cancer is detected in the breast ('occult primary') – primary can may be small, obscured by dense breast tissue or fail to produce a desmoplastic response, although less common now as they can be usually be detected by MRI or ultrasound

  Prognosis and predictive factors: outcome depends on (1) extent of cancer (tumour burden / stage) and (2) underlying biology of the carcinoma (molecular or histologic type) at the time of diagnosis:

  (1) Extent of cancer:



  - **Tumour size**: larger size increases the risk of axillary lymph node metastasis although both are independent prognostic factors. Less important for Her2+ ER- cancers as they can metastasize even when small. Larger tumours are also more likely to be **locally advanced** (invade into skin and skeletal muscle) which may make surgical removal difficult
  - **Nodal metastasis**: most important prognostic factor in the absence of distant metastasis (although it may become less important as treatment decisions are increasingly based more on the molecular type of cancer). Breast lymphatic vessels drain first to 1 or 2 **sentinel nodes**, which can be identified by radiotracer/coloured dyes and biopsied – if negative for metastasis, it is unlikely that more distant nodes will be involved and the patient can be spared the morbidity of a complete axillary dissection. ~10-20% of women without axillary LN metastasis recur with distant metastasis, possibly via the internal mammary lymph nodes or haematogenously
  - **Distant metastasis**: cure is unlikely if present, although long term remissions and palliation can be achieved
  - **Lymphovascular invasion (LVI)**: ~50% of invasive carcinoma have tumour cells within vascular spaces (lymphatics or small capillaries). Strongly a/w presence of LN metastasis. Poor prognostic factor for overall survival in women without LN metastasis and a risk factor for local recurrence. **Inflammatory breast carcinomas** (with a characteristic clinical presentation and extensive dermal lymphatic invasion – see below) also have a very poor prognosis as most patients have distant metastasis

(2) Tumour biology:

- **Molecular subtype**: determined by ER/Her2 status and proliferation
  - **ER/PR** expression: 80% of ER+/PR+ cancers respond to hormonal manipulation (vs ~40% for those either ER or PR+ only), although they are less likely to respond to chemotherapy. Conversely, ER-/PR- cancers are less likely to respond to hormonal therapy but more likely to respond to chemotherapy
  - **Her2** expression: overexpression is associated with poorer survival without therapy, but its main importance is as a predictor of agents that target this receptor
  - **Proliferative rate**: measured via mitotic count (as part of histologic grading) as well as Ki-67 immunohistochemical detection of proteins specifically expressed by actively dividing cells. Especially important for subdivision of ER+ Her2- carcinomas: high proliferation rates have poorer prognosis but may respond better to chemo
- **Special histologic types**: survival rate of women with some special types of invasive ca (e.g. tubular, mucinous, lobular, papillary, adenoid cystic) is better than women with no special type (NST), while other special types e.g. metaplastic and micropapillary ca have poorer prognosis. Note that in some special subtypes e.g. adenoid cystic ca, low grade adenosquamous ca, the histologic type is more strongly correlated with prognosis than the molecular type (tend to be triple negative)
- **Histologic grade**: highly correlated with disease free and overall survival

Treatment: Based on both local (surgery, radiation) and systemic control of disease

- **Gross**: Half of carcinomas are in the UOQ, with 10% each in the remaining quadrants and 20% in the central/subareolar region. Usually appears as a hard irregular mass due to the desmoplastic stromal reaction; can also appear deceptively well-circumscribed (if there is scant stromal reaction) or almost imperceptible (if there are scattered neoplastic glands or single tumour cells infiltrating without inciting stromal reaction)
- **Histology**: Invasive carcinomas are **adenocarcinomas**, commonly graded using the Nottingham Histologic score based on 3 features: (1) tubule formation, (2) nuclear pleomorphism and (3) mitotic rate. The points are then summated into 3 grades: Grade 1 (well-differentiated) to 3 (poorly differentiated). Most are **invasive ductal carcinomas (no special type)**; however, a third may show distinctive histologic features (special type), including:
  - **Invasive lobular carcinoma (ILC)**: subtype that has the clearest association between phenotype and genotype. The tumour cells appear similar to that seen in ALH and LCIS, and are often discohesive infiltrating single and cords of cells with no tubule formation and may demonstrate a signet-ring morphology. Their discohesion and often lack of desmoplastic stromal response is attributed to biallelic loss of expression of *CDH1*, the gene that encodes E-cadherin, although it can form hard irregular masses. Has a characteristic pattern of metastatic spread, often involving the peritoneum and retroperitoneum, leptomeninges (carcinomatous meningitis), the GIT and ovaries and uterus. Patients with heterozygeous germline *CDH1* mutations also have greatly increased risk of gastric signet ring cell ca
  - **Mucinous, tubular, micropapillary, etc**.

Inflammatory carcinomas are a distinctive clinical subtype of breast ca showing extensive invasion of lymphatic channels blocking lymphatic draining (especially the dermal lymphatics), causing erythema, swelling of the breast and skin thickening that mimics non-neoplastic inflammatory lesions. The edematous skin is tethered to the breast via Cooper ligaments, and thus mimics the surface of the orange peel (peau d'orange). Incidence is higher in African American women and younger women. The underlying ca is usually diffusely infiltrative without a discrete palpable mass. Usually high grade, do not belong to any particular histologic or molecular subtype. ~60% are ER-, 40-50% are Her2+

Correlation of molecular subtype with morphology, clinical features, outcomes and response to therapy			
ER+ Her2-		**Her2+ (ER+/-)** *(20%)*	**ER- Her2- ('triple negative', 'basal-like')** *(15%)*
Low proliferation *(40-50%)*	**High proliferation** *(10%)*		
Well-to moderately differentiated Lobular, tubular, mucinous	Poorly differentiated Lobular	Usually poorly (few are moderately) differentiated Some are apocrine, a/w Paget's disease, or micropapillary; otherwise no specific morphologic pattern	Poorly differentiated. Medullary, adenoid cystic, secretory, metaplastic. Many have circumscribed pushing borders with a central fibrotic/necrotic center. DCIS generally limited/absent
Older women, men, cancers detected by mammographic screening and those on hormone replacement therapy Mostly detected at early stage	*BRCA2* mutation carriers	Young, non-white women. *TP53* mutation carriers (ER+) Can metastasize when small	Young women, *BRCA1* mutation carriers, African-American, Hispanic. Rapid growth, likely presents as a mass between screenings, and metastasize when small
Metastasizes to bone >> viscera >> brain		Bone, viscera and brain metastases are all common	
Relapses late (>10 years); long survival possible with mets	Intermediate	Usually short relapse <10 yrs, survival with mets rare	Usually short relapse < 5 yrs, survival with mets rare
Responds well to hormonal therapy; <10% show complete response to chemotherapy. Surgery often curative (lowest incidence of local recurrence)	10% show complete response to chemo and have much better prognosis	ER+: 15% complete response to chemo ER-: >30% complete response to chemo Despite poor prognosis without therapy, 1/3 of cases respond to Her2 targeted therapy (e.g. trastuzumab/Herceptin) and have excellent prognosis; others may develop primary or acquired resistance	~30% complete response to chemo

V. LESIONS OF THE MALE BREAST

- **Gynecomastia:** enlargement of the male breast - the only benign lesion seen with any frequency in the male breast. **Pathogenesis**: Occurs as a result of **imbalance between estrogens** (which stimulate breast tissue) **and androgens** (which counteract these effects). May appear during puberty, in the very old, or any time there is hyperestrinism e.g. liver cirrhosis (responsible for metabolizing estrogen), drugs (e.g. alcohol, digoxin, steroids), testicular atrophy (e.g. Klinefelter syndrome (XXY karyotype)), functioning testicular neoplasms (e.g. Leydig cell tumours), prolactinomas . **Clinical features**: unilateral or bilateral button-like subareolar enlargement. Associated with a small increased risk of breast cancer (as per proliferative disease in women). **Histology**: Increase in dense collagenous connective tissue associated with epithelial hyperplasia of the duct lining, with characteristic tapering micropapillae. No lobule formation
- **Invasive breast cancer**: Usually diagnosed at 60-70 yo, presenting as a palpable subareolar mass and/or nipple discharge (because the breast epithelium in males is limited to the large ducts near the nipple). Incidence is only 1% of that in women i.e. a 0.11% lifetime risk. **Risk factors** similar to those in women (e.g. increasing age, family history, exposure to exogenous estrogens or ionizing radiation, infertility, obesity, prior benign breast disease and residency in Western countries). 3-8% are associated with Klinefelter syndrome, 4-14% due to germline *BRCA2* mutations (less often *BRCA1*). **Pathology and prognostic factors** are similar to women, although ER positivity is more common and even small carcinomas can invade the overlying skin and underlying thoracic wall due to the smaller amount of breast tissue present. Axillary LN metastases are present in ~50% of cases at diagnosis, with distant metastasis to lungs, brain, bone and liver common. Although men present at higher stages, prognosis is similar to women when matched stage for stage. Most are **treated** locally with mastectomy and axillary node dissection

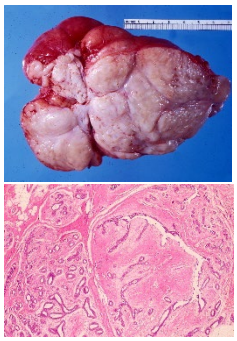
VI. STROMAL TUMOURS AND MISCELLANEOUS

The breast **intralobular stroma** is specialized, from which arises the breast-specific biphasic tumours fibroadenoma and phyllodes tumour. This specialized stroma may also elaborate growth factors for epithelial cells, resulting in proliferation of the non-neoplastic epithelial component of these tumours. The **interlobular stroma** is the source of tumours found in connective tissue in other body sites e.g. lipomas, angiosarcomas as well as tumours arising more commonly in the breast e.g. myofibroblastomas

Fibroadenoma (FA)

- Benign breast fibroepithelial lesion, probably arising as polyclonal hyperplasia of the intralobular stroma. Most common benign tumour of the female breast
- **Clinical features**: Usually in patients 20-30yo, presenting as a palpable mass (in younger women) or as a mammographic density/clustered calcifications (in older women). Can be multiple and bilateral. Size typically increases during pregnancy due to lactational changes as the epithelial component is usually hormonally responsive. Increase in size may be complicated by infarction and inflammation, and may raise a false suspicion of carcinoma. Similar to other 'proliferative changes without atypia',

FAs confer a mildly increased risk of subsequent cancer, which may be limited to complex FA (those with cysts >0.3 cm, sclerosing adenosis, epithelial calcifications or papillary apocrine change)



- **Gross**: variable size, well-circumscribed, rubbery greyish white nodules that bulge above the surrounding tissue and often contain slit-like spaces
- **Histology**: stromal component is often myxoid, resembling normal intralobular stroma, and can surround (pericanalicular pattern) or compress and distort (intracanalicular pattern) epithelial structures. Stroma typically becomes densely hyalinized, and epithelium atrophic, in older women

Phyllodes tumour (PT)

- Fibroepithelial lesion with a range of behaviour from benign to malignant. Also arises from intralobular stroma like FAs, but are much less common. A/w clonal acquired chromosomal changes
- **Clinical features**: Any age but mostly 50-60yo, presenting as a palpable mass or rarely by mammography. Most are benign – these occasionally recur locally but do not metastasize. In contrast, borderline and malignant PT often recur locally unless they are treated with wide excision or mastectomy. Regardless of grade, lymphatic spread is rare – no role for axillary LN dissection. Distant haematogenous metastasis (of the stromal component) seen in ~1/3 of high grade tumours
- **Gross**: variable size (can be massive and involve the entire breast). Larger lesions often have bulbous protrusions (phyllodes is Greek for 'leaf-like') due to the presence of nodules of proliferating stroma covered by epithelium, which may extend into a cystic space. Note that this growth pattern can also be seen in larger FAs and is not an indication of malignancy
- **Histology**: distinguished from FA on the basis of higher cellularity, higher mitotic rate, nuclear pleomorphism, stromal overgrowth, and infiltrative borders. Malignant lesions may also have foci of malignant heterologous differentiation e.g. resembling liposarcoma

Lesions of interlobular stroma

Less common, includes both benign and malignant stromal tumours without an epithelial component

Benign entities include: **Myofibroblastoma** (composed of myofibroblasts; the only breast tumour that is equally common in males), **Lipomas** (benign neoplasms of fat), **Fibromatosis** (clonal proliferation of fibroblasts and myofibroblasts; presents as an irregular infiltrating mass that can involve both skin and muscle. Locally aggressive but does not metastasize)

Malignant: **Angiosarcoma** (the only sarcoma that occurs with any frequency in the breast but still accounts for less than 0.05% of breast malignancies; can be sporadic or treatment-related secondary to radiation or lymphedema), **Rhabdomyosarcoma**, **Liposarcoma** etc.

Other malignant tumours of the breast

Rare, less than 5% of breast cancers. Includes metastasis from other sites (e.g. melanomas, ovarian ca), skin tumours, lymphomas