Non-Cancerous Breast Pathology

a. **Supernumerary** niples along embryonic ridge
b. **Inversion** of the nipple
c. **Engorgement**: occurs in 1st wk postpartum mother that does not breastfeed to relieve milk buildup resulting in bilateral pain, Tx: tight bra, ice packs, NSAIDs (NB do NOT stimulate production b/c will never go away even though logically you think that you are relieving the pressure in fact you are just keeping the stimulus for production)
d. **Obstructed Galactocele**: cystic dilation of an obstructed duct filled w/ milk, seen in lactating women, Tx: warm compresses, manual decompression
e. **Mastitis**: occurs in 2nd-3rd wk postpartum mother who is breastfeeding and thus introduces *Staph. aureus* from baby's mouth into nipple resulting in unilateral pain, Tx: 2wks of dicloxacillin + continue to pump (but obviously don't breast feed) to pull all the bacteria back out but if an abscess develops than I&D is necessary
f. **Mammary Duct Ectasia aka Plasma Cell Mastitis**: around menopause some women can have inspissation of duct w/ cellular debris resulting in nonbacterial mastitis w/ duct dilation/rupture confined to one area of the breast (NB important b/c it leads to induration of breast, retraction of skin/nipple, thick multicolored/sticky/bilateral discharge, noncyclic breast pain esp nipple TTP thus mimicking cancer) Tx: local excision of inflamed area or I&D
g. **Fat Necrosis**: 50% trauma/radiation vs 50% idiopathic necrosis of a part of a breast resulting in formation of a mass and retraction of skin thus mimicking cancer (NB Specific Histology: fat laden macrophages and foreign body giant cells), Tx: local excision
h. **Mondor's Disease aka Superficial Thrombophlebitis:** 2/2 trauma, surgery, infection, repetitive movements resulting in palpable/visible, tender cord running along upper quadrant resulting in mastodynia often confused for cancer, Tx: self-limiting w/in 2-6mo, NSAIDs, warm compresses, limit motion
i. **Fibrocystic Change**
    i. Seen in 50% of women with highest incidence in young women (~36yo) rarely in postmenopause
    ii. Reflects an exaggerated stromal response to hormones resulting (1) cysts, (2) fibrosis, (3) ductal epithelial hyperplasia, and (4) sclerosing adenosis
    iii. S/S: lumpy feeling (not a distinct 3D mass as in cancer), breast swelling, tenderness that is multifocal, bilateral, and size/pain increases b/f menses during estrogen stimulated proliferative phase, serous d/c
    iv. Tx: d/c nicotine/caffeine/chocolates/tea/coffee b/c they contain methylxanthines, administer Vit E and Primrose Oil, prescribe Progestins and if severe/refractory then prescribe Danzol or Tamoxifen, NSAIDs, very supportive bra, FNA for drainage
    v. NB fibrocystic changes confers no increased r/o breast cancer, rather it is epithelial hyperplasia that increases risk therefore true fibrocystic change is of no concern

Cancerous Breast Pathology

(1) **Intraductal Papilloma (100% B)**
    a. S/S: premenopausal women, tumor of epithelial tissue but not carcinoma resulting not in a mass but nipple retraction and discharge (50% bloody vs 50% serous)
    b. Dx: radially compress breast to determine which lactiferous duct expresses fluid and then perform a ductogram
    c. Tx: problem is that it is hard to distinguish it from invasive carcinoma therefore send discharge off for cytology and excise involved ducts
(2) **Fibroadenoma (100% B)**
    a. S/S: <30yo women, tumor of stromal tissue, enlarges during HRT/pregnancy but no change w/ menstrual cycle and often involutes after menopause
    b. Dx: small (<5cm), solitary, rubbery, nontender, well circumscribed, mobile, 25% bilateral, non fixed, easily "scooped"out, slow growing
    c. Tx: FNA if <30yo and <3cm and asymp then follow but if not for any of the three then excise (NB recurrences are common)
(3) **Cystosarcoma Phyllodes (90% B vs 10% M)**
    a. S/S: premenopausal women, tumor of stromal tissue basically a large fibroadenoma, rare
    b. Dx: large (>5cm), solitary, rubbery, nontender, well circumscribed, mobile, ?% bilateral, overlying skin is warm/erythematous/shiny/engorged, rapidly growing
    c. Tx: usually benign but 10% can become malignant therefore always do wide local excision with 1cm margin for small benign tumors or mastectomy for large malignant tumors (NB sarcoma there is hematogenous spread NOT lymphatic spread hence radiation not helpful)
(4) **Lymphoma (100% M)**
    a. always consider in a pt w/ a breast mass
(5) **Mets to Breast (100% M)**
    a. rare usually originating from contralateral breast, lung, skin, kidney, ovary, stomach, carcinoid
    b. pts almost never present with mets to breast w/o knowing about the primary tumor
    c. multiple foci in breast
(6) **Carcinoma (100% M)** below

Important anatomy (refer to Netters)

- axillary tail of Spence

- UOQ supplied by lateral thoracic artery vs. all other Qs supplied by int mammary artery
- 97% breast drained by axillary LNs vs. 3% (very medial breast tissue), breast drained by internal mammary LNs, once these drain then you drain to the clavicular LNs
- Lobule (+ progesterone = growth / + prolactin = mild production) + Duct (+estrogen = growth / + oxytocin = mild let down) + Cooper's Suspensory Ligaments connected to fat lobules

Benign	Malignant

• Mass: soft, mobile, well circumscribed, changes size during menses
• Pain: increased tenderness during menses (Tx: same as fibrocystic change)
• Skin Changes: none except in Phylloedes
• LNs: <1cm, regular shaped, single, soft, mobile
• Discharge: various types of discharge regardless bilateral and multiple ducts involved
  ○ Galactorrhea (pregnancy, pituitary adenoma, acromegaly, hypothyroidism, stress, OCPs, anti-HTNs, psychotropics)
  ○ Serous (nl menses, OCPs, fibrocystic change, early pregnancy)
  ○ Straw-Tinged (fibrocystic change or galactocele)
  ○ Green Sticky (duct ectasia)
  ○ Purulent (abscess)
  ○ Bloody (intraductal papilloma)
• Mammogram
  (1) None or Macrocalcifications
  (2) No Mass
  (3) Normal Architecture
	• Mass: firm, fixed to overlying skin and underlying muscle, poorly circumscribed, constant size during menses but overall slowly enlarging (50% ULQ, 20% Middle, 15% UMQ, 10% LMQ, 5% LLQ, R>L, 3% bilateral)
	• Pain: rare but if so constant
	• Skin Changes: adherence to overlying skin with resulting retraction/inversion of nipple, dimpling of skin 2/2 shortening of Cooper's Ligaments (usually first sign of cancer!!!), ulceration, "peau d' orange" (occurs when the lymphatics are involved resulting in lymphadema that is characterized by thickening of the skin around skin follicles thus looking like an orange peel)
	  ○ *Paget's Disease of Nipple*: DCIS extends within duct to skin surrounding nipple disrupting epidermis resulting in flow of extracellular fluid to surface and "crusting" of nipple and pruritus
	• LNs: >1cm, irregular shaped, multiple, firm, fixed (NB 2% of pts present w/ axillary LAD but no palpable cancer, always check infra/supraclavicular LNs)
	• Discharge: rare but if so than bloody unilateral, only a few ducts involved
	  ○ *Comedo*: most aggressive histological type ("tooth-paste")
	• Mammogram
	  (1) Clustered Microcalcifications
	  (2) Irregular Stellate Mass
	  (3) Distorted Architecture

Age	SBE (Self Breast Exam)	CBE (Clinical Breast Exam)	Mammogram
20-40yo	Q1mo	Q3yrs	None
>40yo		Q1yr	Q1yr
	• 1wk after menses when least engorged and tender • No proven mortality benefit • USPSTF recommends against	• No proven mortality benefit • USPSTF is inconclusive on recommending for or against	• or 5-10yrs younger than onset of breast cancer in first degree relative • **USPSTF is now saying to screen b/t 50-75yo Q1-2yrs and <40yo based on individual patient b/c NNT is very high and NNH is very low w/ 30% False + requiring unnecessary Bx, screening before and after is very controversial** • less sensitive in women with dense fibrocystic breast tissue (aka young African American) b/c as you get older fat replaces fibrous tissue • 25% decrease in mortality • 10% of palpable masses are not picked up by mammography (MRI has higher sensitivity nearly 100% but lower specificity b/t 37-97%) • 30% of mammographic cancer are not palpable masses

- If mass on Mammogram or on PEx (SBE then CBE) then check US to determine if cystic or solid, if solid/complex cyst then Bx, if simple cystic then aspirate and if bloody or recurs then Bx
- NB MRI (to detect contralateral cancer which is seen in 3% of women w/ recently dx cancer, also used for screening high risk pts or those w/ breast implants, evaluate response to Tx)
- Types of Bx
  - FNA: rapid, painless, inexpensive but cannot distinguish CIS vs invasive carcinoma b/c all you see are cells no histology also there is high rate of false negatives 4-10%, those cysts that do not resolve or have blood in cyst should be further investigated
  - Large Needle Core Bx: just like FNA but you can see histology but there is a high rate of false negatives, with US or stereotactic guidance

- Excisional Bx: allows for complete histologic characterization, it may serve as the definitive lumpectomy w/ optimum margin of 1cm of normal breast tissue, but hard to do, painful, expensive and can lead to cosmetic changes

General

- 1/8 women regardless of RFs will get malignant breast cancer vs. 1/2 women get benign breast lesions
- Cancer: Breast (200k), Lung (80k), Colon (?), Endometrial (40k), Ovarian (20k), Cervical (10k)
  Cancer Death: Lung (50k), Breast (40k), Colon (?), Ovarian (15k), Endometrial (7k) Cervical (3k)
- when a women presents with lumps there can be a variety of causes
  - 3-5-9/10 in reproductive-perimenopausal-postmenopausal women are malignant
- **Risk Factors** (75% of women have no known RFs regardless they have a 5% chance of getting cancer)
  - RFs (~4x)
    - *Age* (uncommon under 30yo (only 2%), steadily increases up until menopause, and then plateaus such that 4/5 women w/ cancer are >50yo)
    - *Sex* (<1% of breast cancers are in males, with later onset ~60yo, dx is often delayed, worse prognosis b/c men often delay seeing a doctor and thus present w/ more advanced cancer, similar Tx to below, RFs: same + Klinefelters, all are ductal carcinoma)
    - *Personal History*
      - Atypical Hyperplasia
      - Breast Cancer
    - *Family History*
      - 20% have first degree relative
        - If relative has unilateral breast cancer then 2x increased risk
        - If relative has premenopausal unilateral breast cancer then 3x increased risk
        - If relative has bilateral breast cancer then 5x increased risk
        - If relative has premenopausal bilateral breast cancer then 8x increased risk
      - 5% have inherited mutations resulting in typically bilateral cancer b/f menopause and associated with other cancers (including breast cancer in males)
        - 50% BReast CAncer gene I aka BRCA I (AD Chr17, 60/30% r/o developing breast/ovarian cancer) vs BRCA II (AD Chr13, 60/15% breast/ovarian cancer and other cancers: pancreatic/fallopian tube/laryngeal/leukemia), these are tumor suppressor genes
        - 50% genes associated w/ Li Fraumeni, Cowden, Ataxia-Telangectasia, Peutz-Jegher, et al
  - RFs (~3x)
    - *Geographic*
      - 5x increased risk in America and Europe vs. 1x increased risk in Asia
      - environmental not genetic b/c if you move from high to low risk area your risk improves (vice versa)
    - *Unopposed E Exposure*
      - obesity, chronic anovulation, low to null parity, early menarche / late menopause , exogenous E w/o P, PCOD, E producing tumor like ovarian cancer, HRT (10% increased risk every 5yrs of use) however… OCP (questionable)
  - RFs (~2x)
    - *Single (not married)*
    - *High Socioeconomic Status*
    - *Urban Lifestyle*
    - *Caucasian*
    - *EtOH*
    - *Ionizing Radiation during breast development*
    - *Smoking*

Noninvasive (NO BM penetration)

- **Ductal Carcinoma in situ** (DCIS) (85%)
  - Premenopausal, unicentric, unilateral
  - mammography (clustered microcalcifications) & PEx (palpable mass)
  - 30% risk of turning to cancer per 10yrs at exact same spot
  - Met to bone, lung, liver, brain
- **Lobular Carcinoma in situ** (LCIS) (15%)
  - Postmenopausal, multicentric, bilateral
  - mammography (no findings) & PEx (no findings) therefore always found incidentally on Bx for another abnormality
  - 37% risk of turning to cancer per 10yrs anywhere in BOTH breasts
  - Met to axilla, serosa, meninges

Invasive (BM penetration)

- Favorable Prognosis
  - **Tubular Carcinoma** (type of tubular) (rare)

- **Mucinous Carcinoma** (type of tubular) (rare)
- **Medullary Carcinoma** (type of tubular) (rare)

- Moderate Prognosis
  - **Invasive Ductal Carcinoma** (80%)
  - **Invasive Lobular Carcinoma** (10%)
- Poor Prognosis
  - **Inflammatory Breast Carcinoma** (rare)
    - extremely aggressive cancer that diffusely spreads throughout the breast (therefore no mass) blocking lymphatics resulting in "peau d'orange" and classic signs of inflammation
    - very poor prognosis with metastasis 25% of time at time of diagnosis w/ survival of ~1yr
    - not a histologic type but a clinical reflection of tumor invasion of dermal lymphatics
    - get a Bx to rule out cellulitis or mastitis

Staging & Treatment					
Stage (the most important prognostic indicator but grade is also important)	**Size**	**LN**	**Met**	**10yr**	**Treatment** (20% of pts have bilateral cancer therefore always check other breast)
DCIS (believed to be a precursor for invasive ductal carcinoma at same spot, 30% at 10yrs)					• lumpectomy and if… • Low Risk for Recurrence (<1-2cm) then just post-op radiation • High Risk for Recurrence (>1-2cm) then proceed w/ simple mastectomy and post-op radiation • NASBP 24 Trial showed that tamoxifen reduced recurrence by 3.3% • NB no LN b/c CIS but if you suspect invasion then just go ahead and do ALND
LCIS (believed to be a marker (not a precursor) for both invasive lobular AND ductal carcinoma ANYWHERE in BOTH breasts, 10% at 10yrs)					• B/c just a marker you can't really just cut it out rather you have to aggressively search for cancer in the future with close surveillance or if young, +FHx, or high anxiety then just proceed w/ bilateral SM, the NSABP P1 prevention trial shows that Tamoxifen reduces risk by 56%
Stage I	T1 (<2cm)	N0	M0	90%	"Operable Locoregional" I-II REFER BELOW
Stage IIA	T1	N1 (**mobile LNs**)	M0	70%	
	T2 (**2-5cm**)	N0	M0		
Stage IIB	T2	N1	M0		
	T3 (>5cm)	N0	M0		
Stage IIIA	T1	N2 (**fixed LNs**)	M0	40%	"Locally Advanced" IIIA "Inoperable Locoregional" IIIB REFER BELOW
	T2	N2	M0		
	T3	N1	M0		
	T3	N2	M0		
Stage IIIB	T4*	N#	M0		
Stage IV	T#	N#	M1	20%	Just Systemic Chemo Pt should be entered into a clinical trial Bisphosphonates for bone mets
* cancer is inoperable regardless of size: **peau d'orange of inflammatory breast cancer, chest wall invasion, skin involvement, matted LNs**					

Stage **I/II** Treatment

- Breast Conserving Therapy (lumpectomy and radiation is equivalent to mastectomy for Stage I/II !!!)
  - **Lumpectomy** aka Partial/Segmental Mastectomy aka Wide Local Excision ± Axillary Lymph Node Dissection (ALND) (automatically remove Level I/II LNs however note that 5% of time the cancer skips to Level III nodes not affecting Level I/II LNs nevertheless III not taken out b/c little benefit for staging and increased r/o lymphedema) OR Sentinel Node Biopsy (technetium-labeled sulfur colloid and lymphazurin blue dye is injected into tumor and is used to identify the first LN that drains that part of the breast and then to examine that LN for metastasis, if it doesn't then very unlikely that more distal LNs contain metastasis, but if the sentinel LN shows metastasis then further LN investigation is performed) 40% of women have negative clinical evidence of LAD but are found to have + LNs at resection ± Skin removal if <1cm from skin or tethered, NB the definition of micrometastasis is very controversial but is based on + IHC but – H&E
    - NB studies indicate that simple mastectomy and breast conserving therapy are equivalent in survival for stage I/II but breast conserving therapy have improved cosmetic outcomes and safety, but if 1st/2nd trimester pregnant, previous radiation, pacemaker in radiation field, collagen vascular dz which would preclude radiation, very small breasts, lesions not seen on mammogram, or multifocal then proceed to non-conserving therapy below)
  - **Post-Op Radiation** (if you do BCT then do radiation if you do mastectomy radiation is not necessary, radiation reduces risk of recurrence by 50% but does not reduce survival)
- ± Systemic Therapy
  - **If <1cm/+LNs OR >1cm/–LNs then…**

        - x1 Cycle of 3-6mo of Adjuvant (after surgery) Chemo w/ the optimal regimen remaining controversial but usually containing an **anthracyclines** (eg. doxorubicin) + **antimicrotubule agents** (eg. paclitaxel) + **alkylating agents** (cyclophosphamide, methotrexate)
    - If **HER2/neu overexpression** (epidermal growth factor receptor aka EGFR w/ tyrosine kinase activity, overexpression is seen in 25% of pts and is associated w/ high grade, decreased responsiveness to chemo, shorter survival, early mets) then…
        - Humanized Monoclonal Ab Against Receptor: **trastuzumab** (**Herceptin**)
        - Tyrosine Kinase Inhibitor: lapatinib (Tykerb) if pt has failed Herceptin
        - NB if HER2/neu overexpression then an anthracycline chemo regimen is preferred
    - If either **ER+ or PR+** or unknown then (various combinations of below, studies are out to determine best strategy)…
        - If premenopausal then only SERMs: **tamoxifen** (**Saltamox**) or raloxifen (Evista) for 5yrs
        - If postmenopausal then various combinations of SERMs and Aromotase Inhibitors: **anastrozole** (**Arimidex**), letrozole (Femara), exemastane (Aromasin)
        - Other Options
            - LH Antagonists: goserilin (Zoladex)
            - Pure Estrogen Antagonists: fulvestrant (Faslodex)
            - Oopherectomy
    - NB genetic testing can now provide more refined prognosis

Stage **III** Treatment

- If Inflammatory Carcinoma or Stage ≥III then x4 Cycles of 3-6mo of **Neoadjuvant Chemo** (similar to above)
- NON Breast Conserving Therapy
    - **Simple Mastectomy** (SM): whole breast vs **Modified Radical Mastectomy** (MRM): whole breast + I/II LNs + skin ± muscle (Patey Procedure if remove pectoralis minor, if no muscle removed then called Auchincloss Procedure) vs Radical Mastectomy (RM): whole breast + I/II/III LNs + skin + minor/major muscle (rarely done anymore b/c not increase in survival just decreased recurrence rate)
        - complications: arm lymphadema, infection, nerve injury (long thoracic N. = anterior serratus M. = winging, thoracodorsal N. = latissimus dorsi M. = can't push from sitting position, pectoralis N. = pectoralis M. = can't bench, intercostobrachial N. = Inner Arm Skin = paresthesia, can be identified by stimulating them with forceps), skin flap necrosis, hematoma, seroma, phantom breast syndrome
        - will need reconstruction with TRAM, lat dorsi flap, or implant
- ± Systemic Therapy
    - ""
    - ""
    - ""

Prophylaxis

- only evidence is for tamoxifen therapy (20mg/d PO x5yrs) for pts w/ ≥1.7% absolute risk (www.bcra.nci.nih.gov) of developing cancer in the next 5yrs, decreases risk by 50% but increased r/o endometrial carcinoma and VTE events and increases ALL cause mortality (some recommend bilateral mastectomy and bilateral salpingo-oopherectomy in pts w/ LCIS or genetic mutations esp BRCA)

Determine if Metastasis has Occurred if Stage ≥III (only 5% of Stage ≤II cancers have mets)

- 1° LNs, Bone (Bone Scan, Ca, AlkPhos), Breast (Mammogram)
- 2° Lung (CT Chest), Liver (CT Ab, LFTs), Brain (CT Head), Adrenal (CT Ab), Skin, Pleura
- Some just do PET scan of the whole body

Follow Up

- Qmo SBE, Qyr Mammogram, and Q3-6mo x3yrs, Q6-12mo x2yrs, then Qyr H&P w/ CBE and Labs (Ca, AlkPhos, LFTs, CEA, CA15-3)
    - Recurrence usually at same quadrant, in first 2yrs has worse prognosis than in first 5 yrs
    - Always assess metastasis, other cancers associated with genetic breast cancer, and cancers 2/2 chemo (leukemias w/ alkylating agents, topoisomerase inhibitors, and anthracyclines) and radiation (sarcoma and lung cancer)
    - Data is insufficient to recommend routine bone scans, CXRs, CBCs, liver US, CTs, etc
    - Assess for endometrial cancer and VTE in pts who took tamoxifen
    - in the past it was recommended that post breast cancer pts not become pregnant or use OCPs or use SHORT TERM (<5yrs) HRTs b/c of the effects of estrogen on hidden cancer cells, however, studies indicate that pregnancy or OCPs or SHORT TERM (<5yrs) HRTs have NO effect of survival
    - Assess "Edema of Arm" seen in 10% of women who had axillary lymphadenectomy or mastectomy esp w/ radiation
        - avoid all minor trauma because any infection increases lymphatic obstruction by obliterating the remaining open channels with fibrosis in reaction to the bacteria hence even minor skin abrasions should be quickly treatment with antibiotics
        - if chronic treat with elastic sleeve or pneumatic compression device
        - complications: if >10yrs can develop lymphangiosarcoma