BREAST CANCER
BREAST CANCER

- Caused by the **malignant transformation of a breast cell** (hyperplasia → atypia → cancer) →
  - Infiltration of tissue ± spread through lymphatics & blood vessels to other organs = metastases

**Statistics:**
- 1 in 8 ♀ develop breast cancer during their lifetime →
  - #1 cause of ♀ cancer in the U.S., w/ a 35% mortality

**RISK FACTORS**

- ↑Age, w/ 90% of cases @ age > 50 years (<1% @ age < 30 years)
- **Gender:** ♀ 100X ♂
- **Skin color:** Whites > blacks
- ↑**Estrogen exposure**
  - Nulliparity
  - Early menarche (age < 12 years)
  - Late menopause (age > 50 years)
  - Late first pregnancy (age > 35 years)
  - Absence of breast feeding
  - **Postmenopausal obesity**, being protective premenopausally
  - Chronic anovulation
  - **Hormone replacement therapy**–HRT
    - Estrogen @ ≥5 years use
    - Estrogen/ Progestin combination without the 5 year delay
  - **Oral contraceptives** →
    - ↑Risk of breast & ?cervical cancer
    - ↓Risk of endometrial & ovarian cancer

- **Genetic**
  - Personal history of:
    - Endometrial, ovarian, or breast cancer (in situ or infiltrating)
Breast atypical hyperplasia ± fibrocystic disease
Epitheliosis
Papillomatosis

Family history of breast cancer, especially
1st degree relative—15% of patients
Bilateral occurrence
Premenopausal diagnosis

Family history of ovarian cancer
Expression of the HER–2/ neu proto–oncogene—25%, encoding a human epidermal growth factor receptor

Breast cancer = BRCA 1 or BRCA 2 gene mutations—10% of patients
BRCA 1→≈50% lifetime ♀ breast cancer risk
→≈30% lifetime ovarian cancer risk
BRCA 2→≈70% lifetime ♀ breast cancer risk & 6% lifetime ♂ breast cancer risk
→≈15% lifetime ovarian cancer risk
→↑Pancreatic cancer risk

Note: 1 in 800 persons in the general population carry a BRCA 1 gene mutation (being unknown for BRCA 2). However, 1 in 40 of Ashkenazi Jewish (Eastern European) descent carry a mutation of BRCA 1 &/or 2

• Dietary
  Alcohol
  Fat

• Endocrine
  Diabetes mellitus

• Environment
  Socioeconomic status
  Urban residence

• Procedures
  Prior breast biopsy
  Thoracic radiation treatment

• Other
Tall habitus

NORMAL BREAST ANATOMY

• Puberty →
  • ↑Estrogen levels (in conjunction w/ the permissive influence of insulin, thyroid hormone, & cortisol) → breast growth via:
    – ↑Adipose tissue
    – ↑Connective tissue (collagen & elastin)
    – ↑Glandular tissue, being milk secreting epithelial cells forming lactiferous ducts, w/ 5-20 emerging at the nipple

CLASSIFICATION

• Cancer in situ, being Latin for ‘in position’
  • Breast cancer that has not infiltrated the surrounding breast tissue
    – Ductal cell cancer
      Outcomes:
      • Ipsilateral infiltrating breast cancer risk of 3%/ year
    – Lobular cell cancer
      Outcomes:
      • Infiltrating breast cancer risk (ipsilateral or contralateral) of 1%/ year

• Infiltrating cancer
  • Ductal cell cancer – 80%
    – Pagets cancer: Ductal cell cancer w/ infiltration of the nipple epidermis
  • Lobular cell cancer – 10%
  • Papillary cancer – 2%
  • Medullary cancer
  • Mucinous cancer
  • Tubular cancer
  … w/ Inflammatory cancer – 5% being of any histologic type w/ infiltration of dermal lymphatic vessels →
    • Overlying inflammation, indicative of very poor differentiation, being rapidly lethal
Diagnosis

Cutaneous/ subcutaneous

- **Breast examination** via a systematic examination of the breast, axillary, & supraclavicular tissue in both the upright & supine positions, w/ the ipsilateral hand placed behind the head →
  - Visualization of:
    - Breast asymmetry
    - Overlying skin tethering
    - Nipple eczema, being indicative of Paget’s cancer
    - Skin inflammation, being indicative of inflammatory cancer
    - Lymphatic obstruction → breast edema, described as **peau d’orange**, being 575 cadem for ‘orange peel’
  - Palpation of a **breast lump** being:
    - Hard
    - Irregular
    - Immobile
    - Usually painless, except w/ inflammatory cancer, w/ pain typically being focal, persistent, & noncyclic
    - Unchanged via the menstrual cycle

... w/ nipple pressure also performed for possible **discharge**, w/ ↑ risk features being:
  - Associated mass
  - Hemorrhage
  - Limited to 1 duct
  - Unilateral

- Palpation of **axillary &/or supraclavicular lymphadenopathy**, typically being
  - Immobile
  - Painless
  - ... & having a hard-matted texture, w/ lymphatic obstruction →
    - Hand/ arm edema

Occurrence of breast cancer via visible quadrants:
Hematologic
• Neoplastic cytokines, which may be used to monitor for treatment response & possible recurrence, if elevated @ initial diagnosis
  • CA 15–3 secretion
  • Carcinoembryonic antigen–CEA secretion (> 2.5ng/ mL)

IMAGING
• Breast ultrasound
  Indications:
  • To differentiate a cystic vs. solid lesion
Diagnostic course:
  • If cystic, perform a fine needle aspiration–FNA, w/ fluid sent for cytology
  • If solid, perform a diagnostic mammography, w/ a fine needle aspiration–FNA of the lesion

INVASIVE PROCEDURES
• Fine needle aspiration–FNA
  Indications:
  • All breast lesions
  • The value of a fine needle aspiration–FNA, is that a positive result may lead to the recommendation for mastectomy without the intermediate step of an excisional biopsy
Diagnostic course:
• If negative for cancer, perform an excisional biopsy, as fine needle aspiration—FNA cannot rule out cancer
• If positive for cancer, perform lymph node biopsy

• Lymph node(s) biopsy
  • Lymph node involvement occurs in 40% of patients
  Biopsy types:
  • Sentinel lymph node(s) biopsy, being preferred due to ↓complication risk relative to axillary lymph node biopsy
    Procedure:
    • Injection of either a dye or radiolabeled substance into the biopsy cavity &/or around the breast tumor→
      • Substance traveling via lymphatics to the closest draining = sentinel lymph node(s), allowing for biopsy of less lymph nodes for staging
  • Axillary lymph nodes biopsy
    Procedure:
    • Removal of ≥6 axillary lymph nodes
  Complications:
  • Nerve lesions→
    • Cutaneous numbness
    • Limitations in shoulder mobility
  • Axillary lymph nodes removal→
    • Hand/ arm lymphedema – 30% (7% w/ sentinel lymph node biopsy), which may develop any time after surgery, usually within 4 years→
      • ↓Microbial defense
      • Stiffness, heaviness, weakness, numbness, &/or aching discomfort
    Note: Avoid blood draws or intravenous lines in the arm, irrespective of lymphedema, due to increased infection risk, as well as possible exacerbation/ initiation of lymphedema
  Diagnostic course:
  • If positive for cancer, assume metastatic disease
• If negative for cancer, assume micrometastatic disease if the patient has ≥1 of the following high risk factors:
  ◦ Imaging
    – Breast cancer diameter > 4cm
  ◦ Microscopic
    – Markers of ↑cell proliferation (↑S phase = dividing fraction, Ki67)
    – Poorly differentiated
  ◦ Immunologic
    – Estrogen or progesterone receptor negative
    – Expression of certain cell surface proteins (cathepsin D, EGFR, HER–2/ neu, p53)

**METASTATIC SEARCH**

• Cells usually metastasize to the regional lymph nodes, as well as the bones, central nervous system, liver, & lungs

• Possible metastases are assessed via:
  ◦ History & physical examination
  ◦ Hematologic studies
  ◦ Imaging
    – **Thoraco-abdomino–pelvic imaging via CT/ MRI** to look for a nodule, mass, infiltrate, lymphadenopathy, atelectasis, pleural effusion, pericardial effusion, &/or osteolytic lesions
      **Limitations:**
      • Does not reliably visualize the splenic, hepatic, para–aortic, or external iliac lymph nodes
    – **Positron emission tomographic–PET scanning**, as the computed tomographic–CT scan may remain abnormal long after treatment, a PET scan may help w/ both pre–treatment staging & monitoring treatment response
      **Mechanism:**
      • Intravenous radiolabeled glucose is utilized by malignant cells (as well as cells within an inflammatory focus) > normal cells, due to ↑metabolism→
Relative uptake
- Relative visualization

**Radionuclide whole body bone scanning**

Indications, being either:
- ↑Plasma alkaline phosphatase
- Hypercalcemia

Procedure:
- A radioactive agent, termed a tracer, is injected intravenously
  - Detection of ↑osteoblast activity, indicating new bone formation (as occurs w/ metastases to the bone)

Agents used:
- $^{99m}$Tc-technitium–Tc based agent ($^{99m}$Tc–sestamibi, $^{99m}$Tc–teboroxime, $^{99m}$Tc–tetrofosmin)

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**BREAST CANCER STAGING SYSTEM**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
<th>5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor ≤2cm in diameter, w/ no lymph node involvement</td>
<td>90%</td>
</tr>
<tr>
<td>2A</td>
<td>Tumor &lt;2cm in diameter, w/ metastases to mobile ipsilateral axillary node(s)</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>Tumor &gt;2cm, but ≤5cm in diameter, w/ no lymph node involvement</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Tumor &gt;2cm, but ≤5cm in diameter, w/ metastases to mobile ipsilateral axillary</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>node(s)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumor &gt;5cm in diameter, w/ no lymph node involvement</td>
<td></td>
</tr>
<tr>
<td>3A</td>
<td>Tumor ≤5cm in diameter, w/ metastases to immobile ipsilateral axillary node(s)</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Tumor &gt;5cm in greatest diameter w/ metastases to ipsilateral axillary node(s)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(mobile or fixed)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Tumor of any size, w/ direct extension to the skin or chest wall</td>
<td>45%</td>
</tr>
<tr>
<td></td>
<td>Inflammatory cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin edema, nodules, or ulcerations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>...w/ no known distant metastases</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Tumor of any size, w/ infraclavicular or supraclavicular lymph node involvement</td>
<td>40%</td>
</tr>
<tr>
<td>4</td>
<td>Distant metastases</td>
<td>15%</td>
</tr>
</tbody>
</table>

**TREATMENT**

**CURATIVE INTENT**

- Cancer in situ
  - Ductal cell cancer
    - **Lumpectomy vs. simple mastectomy**, being the removal of only the breast
    - Radiation therapy & hormonal prevention treatment
  - Lobular cell cancer
    - Close follow up & hormonal prevention treatment
–Consider prophylactic bilateral mastectomy

• Stages 1–3C
  ○ Cancer limited to the breast
    – Lumpectomy vs. simple mastectomy, being the removal of only the breast
  ○ Cancer metastasized to regional lymph nodes
    – Lumpectomy w/ axillary lymph node dissection, being equivalent to a modified radical mastectomy when combined w/ radiation therapy, except when a clear indication for a modified radical mastectomy exists (as follows)
    – Modified radical mastectomy, being the removal of the breast & axillary lymph nodes

Indications:
  • Cancer ≥ 5cm in diameter
  • Multiple breast cancers
  • Small breast
  • Contraindications to radiation therapy
    ◦ History of prior breast irradiation
    ◦ Pregnancy

…as well as:
  • Radiation therapy
  • Systemic adjuvant ± neoadjuvant† therapy via:
    ◦ Combination chemotherapy. However, no survival benefit has been demonstrated from adjuvant chemotherapy in ♀ age > 70 years
    ◦ Hormone therapy if estrogen receptor positive, via a mixed estrogen receptor agonist/ antagonist &/or an aromatase inhibitor. Premenopausal ♀ being treated w/ an aromatase inhibitor, should concomitantly be treated w/ either a gonadotropin releasing hormone–GnRH analogue or bilateral oophorectomy
    ◦ Anti–HER–2 monoclonal antibody w/ over expression of the HER–2/ neu proto–oncogene
†Neoadjuvant therapy refers to the use of nonsurgical therapy (chemotherapy, radiation therapy, hormonal therapy, &/or monoclonal antibody treatment) as the initial treatment for cases in which surgery (lumpectomy or modified radical mastectomy) is a suboptimal initial approach, as w/ tumor:
• Affixed to underlying structures
• Involving breast skin (ex: Inflammatory breast cancer)
... in order to:
  • ↓Tumor size in order to allow for a complete surgical resection
  • Eradicate micrometastatic disease

LIFE PROLONGATION INTENT
• Stage 4
  ◦ Combination chemotherapy
    Indications:
    • Estrogen receptor negative
  ◦ Hormone therapy
    Indications:
    • Estrogen receptor positive
  ◦ Anti–HER–2 monoclonal antibody
    Indications:
    • Over expression of the HER–2/ neu proto–oncogene

PALLIATIVE INTENT
• Treatment failure
  ◦ Chemotherapy &/or radiation therapy
  ◦ Interstitial radiation treatment, termed brachytherapy
    Procedure:
    • Tissue placement of a radioactive substance
  ◦ Silastic tube vs. metal stent placement for obstructive lesions
  ◦ Consider surgical resection for painful &/or obstructive lesions
  ◦ Bisphosphonates→
  – ↓Pathologic fracture risk
  ◦ Surgery for pathologic fractures
  ◦ Drainage of pleural effusions, w/ subsequent pleurodesis via scler-
rosetting agents (sterile Bleomycin, Doxycycline, Mitoxantrone, Tetracycline, or talc slurry) to prevent reaccumulation

<table>
<thead>
<tr>
<th>MIXED ESTROGEN RECEPTOR AGONIST/ANTAGONIST</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic (Trade)</strong></td>
</tr>
<tr>
<td><strong>M/♀: Dose</strong></td>
</tr>
<tr>
<td><strong>Tamoxifen</strong></td>
</tr>
<tr>
<td>(Nolvadex, Tamone)</td>
</tr>
<tr>
<td>L/U: 20mg PO q12hours X 5 years, or 3 years if being followed by treatment w/ Exemestane (see below)</td>
</tr>
</tbody>
</table>

**Outcomes:**
- 30% respond if estrogen receptor positive
- 70% respond if estrogen & progesterone receptor positive

**Resistance screening:**
- **Hepatic cytochrome P450 2D6 enzyme genotyping**, as a variant, present in 10% of whites→
  - ↓Function (esp. in homozygotes)→
  - ↓Hepatic metabolism to the active form, Endoxifen

**Side effects in comparison to estrogen:**

<table>
<thead>
<tr>
<th>Positive effects</th>
<th>Estrogen</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer risk</td>
<td>↑↑↑</td>
<td>++</td>
</tr>
<tr>
<td>Favorable plasma lipid alteration</td>
<td>↓LDL &amp; total cholesterol</td>
<td>+++</td>
</tr>
<tr>
<td>↓Postmenopausal bone loss</td>
<td>+++</td>
<td>+†</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Negative effects</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular accident syndrome risk</td>
<td>↑</td>
</tr>
<tr>
<td>Thromboembolic syndrome risk</td>
<td>↑ (Deep venous thrombosis ± pulmonary embolism)</td>
</tr>
<tr>
<td>Endometrial cancer risk</td>
<td>✈ (1.5/1000)‡</td>
</tr>
<tr>
<td>Postmenopausal hot flashes</td>
<td>✈</td>
</tr>
<tr>
<td>Premenopausal hot flashes</td>
<td>✈</td>
</tr>
<tr>
<td>Uterine hemorrhage</td>
<td>✈</td>
</tr>
</tbody>
</table>

**Other side effects:**

**Gastrointestinal**
- Hepatitis
- ↑Hepatocellular cancer risk

**Genitourinary**
- Vaginal discharge

**Mucocutaneous**
- Alopecia

**Musculoskeletal**
- Bone pain

**Ophthalmologic**
- **Cataracts**
- Keratopathy – rare
- Optic neuritis – rare

**Hematologic**
- Hypercalcemia

**Interactions:**
- Selective serotonin reuptake inhibitors – SSRIs (esp. Fluoxetine & Paroxetine) & serotonin– norepinephrine reuptake inhibitors – SNRIs inhibit the hepatocyte cytochrome P450 2D6 enzyme →
  - ↓ Metabolism of Tamoxifen to its active form

↑ In premenopausal♀, Tamoxifen →
- ↓ Bone mass

‡ Especially in postmenopausal♀

**Monitoring:**
- Regular gynecologic & ophthalmologic screening examinations

**Contraindications:**
- History of thromboembolic disease

### AROMATASE INHIBITORS

**Indications:**
- Consider starting as adjunctive treatment to Tamoxifen:
  - Exemestane after 3 years of Tamoxifen
  - Anastrozole or Letrozole after 5 years of Tamoxifen
- For Stage 4 disease, upon failure of one medication, the others may be tried sequentially

<table>
<thead>
<tr>
<th>Generic (Trade)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anastrozole</strong> (Arimidex)</td>
<td>1mg PO q24hours</td>
</tr>
<tr>
<td><strong>Exemestane</strong> (Aromasin)</td>
<td>25mg PO q24hours</td>
</tr>
<tr>
<td><strong>Letrozole</strong> (Femara)</td>
<td>2.5mg PO q24hours</td>
</tr>
</tbody>
</table>

**Mechanism:**
- Inhibit the function of ovarian & peripheral tissue aromatase activity:
Anastrozole & Letrozole are non-steroidal medications →
- Reversible inhibition of aromatase
Exemestane, a derivative of androstenedione, is a steroid medication →
- Irreversible inhibition of aromatase

...→↓ Conversion of androgens (testosterone & androstenedione) secreted by the ovaries & adrenal cortices (being the main source of estrogen precursors in postmenopausal ♀) to estrogens:
  • Ovarian follicle conversion →
    ○ β-estradiol, estriol, & estrone
  • Peripheral tissue conversion →
    ○ β-estradiol & estrone

... β-estradiol being the most potent & main estrogen produced

Outcomes:
  • 30% respond if estrogen receptor positive
  • 70% respond if estrogen & progesterone receptor positive

Side effects:

General
  • Malaise
  • Weakness

Cardiovascular
  • ↑ Cerebrovascular accident syndrome risk↑
  • ↑ Thromboembolic syndrome risk↑
    ○ Deep venous thrombosis ± pulmonary embolism
  • Hot flashes↑

Gastrointestinal
  • Diarrhea
  • Nausea ± vomiting

Genitourinary
  • ↑ Endometrial cancer risk↑
  • Uterine hemorrhage↑
  • Vaginal discharge

Musculoskeletal
  • Osteopenia→
    ○ Osteoporosis

Neurologic
  • Headache
Exemastane specific:

**Mucocutaneous**

- Acne
- Hypertrichosis, being ↑↑hair growth

↑Being less common compared to Tamoxifen
GONADOTROPIN RELEASING HORMONE—GnRH ANALOGUES

Indications:
• Premenopausal ♀ being treated w/ an aromatase inhibitor, should concomitantly be treated w/ either a gonadotropin releasing hormone–GnRH analogue or bilateral oophorectomy

<table>
<thead>
<tr>
<th>Generic (Trade)</th>
<th>M Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goserelin (Zoladex)</td>
<td>L 3.6mg SC implant qmonth or 10.8mg SC implant q3months</td>
</tr>
<tr>
<td>Leuprolide (Lupron)</td>
<td>L 1mg SC q24hours 7.5mg IM qmonth or 22.5mg IM q3months or 30mg IM q4months</td>
</tr>
<tr>
<td></td>
<td>L Subcutaneous implant 65mg SC implant qyear</td>
</tr>
</tbody>
</table>

Mechanism:
• Gonadotropin releasing hormone–GnRH is secreted intermittently by the hypothalamus q1–3hours→anterio pituitary gonadotropin secretion, being Leuhenizing hormone–LH & Follicle stimulating hormone–FSH. When given intermittently, the GnRH analogues mimic physiologic release. However, steady dose administration→↓LH & FSH secretion→↓ovarian follicle secretion of both:
  ◦ Estrogens (β–estradiol, estriol, & estrone), w/ β–estradiol being the most potent & main estrogen produced
  ◦ Progestins, being progesterone (mainly) & 17–α–hydroxyprogesterone
  ◦ Androgens (testosterone & androstenedione)→↓conversion of androgens to estrogens:
    – Ovarian follicle conversion→β–estradiol, estriol, & estrone
    – Peripheral tissue conversion→β–estradiol & estrone

Side effects:
General
• Hot flashes
• ↓Libido
Musculoskeletal
• Osteopenia→
  ◦ Osteoporosis
Hematologic
Anemia

RECOMBINANT HUMANIZED ANTI–HER–2 MONOCLONAL ANTIBODY

Generic (Trade)

Trastuzumab (Herceptin)

Side effects:

Cardiovascular

- Cardiac toxicity, being synergistic when used in combination w/ Doxorubicin →
  - Dilated cardiomyopathy →
  - Heart failure ~2%

SCREENING

- Although often recommended, the following screening methods have NO MORTALITY BENEFIT
- Patient performed breast exams qmonth @ age > 18 years, performed 1 week after menstruation
- Physician performed breast exams qyear @ age > 18 years
- Screening mammography q2 years @ age ≥ 50 years

Findings:

- Calcifications
- Masses
- Tissue distortion
...necessitating diagnostic mammography w/ a fine needle aspiration–FNA

Outcomes:

- No proven overall mortality benefit
  - When aggregating data from trials in which randomization was appropriate, there was no reduction breast cancer specific mortality
  - When all trial data is aggregated, breast cancer mortality is reduced by 15%, w/ overall mortality still being unaffected... indicating that mammography is likely to be taking as many lives as it is saving. However... breast cancer mortality is not
as important as overall mortality, as individuals want to avoid death, rather than simply avoiding death from one possible cause. When analyzing these numbers... for every 2000 ♀ screened for 10 years:
–1 will live longer
–10 who would have otherwise not been diagnosed if there had not been screening, will be diagnosed w/ breast cancer & treated unnecessarily (surgery, radiation treatment, &/or chemotherapy), as the cancer would not have affected them
–200 will suffer psychological distress & undergo surgical procedures due to false positive results

SCREENING IN HIGH RISK PATIENTS
• Screening mammography q2years
  –Magnetic resonance imaging–MRI q2years if either:
    –Age < 40 years
    –Age ≥ 40 years w/ dense breast tissue on mammogram

Indications:
• Positive family history
  –Begin @ age 35 years, or 5 years prior to the age of youngest relatives’ first sign or symptom, whichever is earlier
• History of thoracic radiation
  –Begin 8 years afterwards
• BRCA 1 or 2 gene mutation carrier
  –Begin @ age 25 years

Indications for genetic testing:
• Significant family history of breast cancer

PREVENTION IN HIGH RISK ♀

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<td>Tamoxifen (Nolvadex, Tamone)</td>
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</tbody>
</table>

Outcomes:
•50% ↓ invasive cancer incidence

**Prophylactic bilateral oophorectomy**

**Indications:**
• Consider in BRCA 1 or 2 gene carriers

**Outcomes:**
• ↓ Breast & ovarian cancer incidence
  ○ ↓ Breast cancer by 50% in carriers of the BRCA 1 mutation

**Prophylactic bilateral mastectomy**, which may be skin, areola, & nipple sparing, termed subcutaneous mastectomy

**Indications:**
• Consider in BRCA 1 or 2 gene carriers
• Consider w/ lobular cell cancer in situ

**Outcomes:**
• 90% ↓ cancer incidence

**Side effects:**
• Chest wall anesthesia
• Psychological sequelae
• The need for multiple reconstructive operations