BREAST CANCER FACTS

- Most common cancer in women.
- Second most common cause of cancer-related mortality.
- There are over 3.1 million breast cancer survivors in the US today.
# NEW BREAST CANCER CASES

<table>
<thead>
<tr>
<th>Year</th>
<th>Male</th>
<th>Female</th>
</tr>
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<tbody>
<tr>
<td>2012</td>
<td>2,190</td>
<td>226,870</td>
</tr>
<tr>
<td>2013</td>
<td>2,240</td>
<td>232,340</td>
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<tr>
<td>2014</td>
<td>2,360</td>
<td>235,030</td>
</tr>
<tr>
<td>2015</td>
<td>2,350</td>
<td>231,840</td>
</tr>
<tr>
<td>2016</td>
<td>2,600</td>
<td>249,260</td>
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BREAST CANCER IN 2016

- Decreased mortality
  - Death rates from breast cancer have steadily decreased since 1990 due to earlier detection and improved treatment.
  - Age-adjusted mortality rates have declined approximately 2% per year from 2002-2011.

- Decreased surgical morbidity
  - Less disfiguring breast surgery
  - Less extensive axillary surgery
EARLY DETECTION: SCREENING RECOMMENDATIONS

- Regular breast physical examinations by a health care professional
  - Every three years for women 20-40
  - Every year for women over 40
- Breast self-examination is an option
- Mammography
  - For average risk women, annually from age 45-54 and every other year thereafter
<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative risk</th>
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<tbody>
<tr>
<td>BRCA 1-2 mutation</td>
<td>10.0-32.0</td>
</tr>
<tr>
<td>Chest wall irradiation at &lt;30 yrs of age</td>
<td>7.0-17.0</td>
</tr>
<tr>
<td>Family history (no known mutation)</td>
<td>1.5-4.0</td>
</tr>
<tr>
<td>Breast density (very dense vs. fatty)</td>
<td>5.0</td>
</tr>
<tr>
<td>Atypical hyperplasia/LCIS on prior biopsy</td>
<td>4.0</td>
</tr>
<tr>
<td>Hormonal factors</td>
<td>1.2-1.7</td>
</tr>
<tr>
<td>Postmenopausal obesity</td>
<td>1.2-1.9</td>
</tr>
<tr>
<td>Alcohol consumption (2/day vs. none)</td>
<td>1.2</td>
</tr>
<tr>
<td>Sedentary lifestyle</td>
<td>1.1-1.8</td>
</tr>
</tbody>
</table>
FACTORS THAT REDUCE BREAST CANCER RISK

- Regular moderate to vigorous physical activity
- Maintaining a healthy body weight
- Limit alcohol intake
- Correct Vitamin D deficiencies
- Chemopreventive medications:
  - Tamoxifen
  - Raloxifene
  - Aromatase inhibitors
SCREENING HIGH RISK WOMEN

- **AGE TO BEGIN SCREENING:**
  - If risk based on positive family history, start screening ten years earlier than the age at diagnosis of affected relative.
  - If risk based on other factors (e.g. prior chest radiotherapy), start screening at age 30.
  - If BRCA-1 or 2 positive, start at age 25.

- **SCREENING MODALITIES:**
  - Yearly mammography and MRI scanning, alternating six months apart.
  - Clinical breast exam every six months.
BREAST CANCER DIAGNOSIS

- Diagnosis usually made by needle core biopsy
- Tissue sent for pathology, determination of hormone receptors and her2neu, proliferative rate
- Additional testing
  - MRI of both breasts
  - Staging studies to exclude areas of distant spread
- Additional biopsies, if needed
- Additional consultations, if needed
  - Medical or radiation oncology
  - Genetic testing
  - Plastic surgery
  - Oncofertility
BREAST CANCER STAGING:

Tumor

- **T**0 – No evidence of tumor
- **Tis** = Carcinoma in situ
- **T**1 = Tumor ≤ 2 cm
  - **T1mi** = Tumor ≤ 1 mm
  - **T1a** = Tumor > 1 mm but ≤ 5 mm
  - **T1b** = Tumor > 5 mm but ≤ 1 cm
  - **T1c** = Tumor >1 cm but ≤ 2 cm
- **T**2 = Tumor >2 cm but ≤ 5 cm
- **T**3 = Tumor > 5 cm
- **T**4:
  - **T4a** = extension to chest wall, not including only adherence or invasion of pectoral muscle
  - **T4b** = Ulceration &/or ipsilateral satellite nodules ; Skin edema not meeting criteria for inflammatory carcinoma
  - **T4c** = Both T4a and T4b
  - **T4d** = Inflammatory carcinoma
BREAST CANCER STAGING: Nodes - Clinical

- **NX** = Nodes cannot be assessed
- **N0** = No regional node involvement
- **N1** = Metastases to movable ipsilateral axillary level I-II nodes
- **N2a** = Metastases to fixed ipsilateral axillary nodes
- **N2b** = Metastases in clinically detected ipsilateral IM nodes w/o axillary nodes
- **N3a** = Metastases in ipsilateral level III axillary nodes
- **N3b** = Metastases in ipsilateral IM and axillary nodes
- **N3c** = Metastases in ipsilateral supraclavicular nodes
BREAST CANCER STAGING: Nodes - Pathologic

- **pNX** = Nodes cannot be assessed
- **pNo(i-)** = No regional node involvement
- **pNo(i+)** = Malignant cells in regional node(s) no greater than 0.2 mm
- **pNo(mol-)** = No regional node involvement, RT-PCR negative
- **pNo(mol+)** = Positive molecular findings by RT-PCR, but negative by histology or IHC
- **pN1mi** = Micrometastases (> 0.2 mm - < 2.0mm)
- **pN1a** = Micrometastases or metastases in 1-3 axillary nodes
- **pN1b** = Metastases in IM nodes detected by SLN bx (not clinically)
- **pN1c** = Metastases in 1-3 axillary nodes and IM nodes detected by SLN bx
- **pN2a** = Metastases in 4-9 axillary nodes
- **pN2b** = Metastases in clinically detected IM nodes w/o axillary node involvement
- **pN3a** = Metastases in ≥ 10 axillary nodes or metastases to Level III nodes
- **pN3b** = Metastases in clinically detected IM nodes in the presence of one or more positive axillary nodes, or > 3 axillary nodes and IM nodes detected by SLN bx
- **pN3c** = Metastases in ipsilateral supraclavicular nodes
BREAST CANCER STAGING: Metastases

- Mo = No clinical or radiographic evidence of metastases
- cMo(i+) = No clinical or radiographic evidence of metastases, but molecularly or microscopically detected deposits of tumor cells in blood, bone marrow, or non-nodal deposits <0.2 mm in asymptomatic patient
- M1 = Clinically or radiographically demonstrated metastases > 0.2 mm
BREAST CANCER STAGING

- **Stage 0**: Tis
- **Stage IA**: T1 N0 M0
- **Stage IB**: T0-1 N1mi M0
- **Stage IIA**: T0-1 N1 M0; T2 N0 M0
- **Stage IIB**: T2 N1 M0; T3 N0 M0
- **Stage IIIA**: T0-3 N2 M0; T3 N1 M0
- **Stage IIIB**: T4 N0-2 M0
- **Stage IIIC**: Any T N3 M0
- **Stage IV**: Any T Any N M1
SPECIAL ISSUES IN STAGING

- **Multicentric disease** – stage according to the size of the largest tumor focus
- **Inflammatory cancer**
  - Term restricted to cases with typical skin changes involving a third or more of the breast skin.
  - Clinical diagnosis – Histologic proof of dermal lymphatic invasion not required
  - Dermal lymphatic invasion seen on pathology without the clinical findings does not constitute inflammatory cancer
- **Paget’s Disease**
  - Without underlying noninvasive or invasive cancer should be classified as Tis(Paget’s)
  - With an underlying noninvasive or invasive cancer should be classified according to the underlying cancer
Breast Cancer Treatment

**Local Therapy**
- Mastectomy and axillary lymph node assessment
  or
- Breast-conservation therapy and axillary lymph node assessment

**Systemic Therapy**
- Chemotherapy
- Hormonal Therapy
- Other targeted Therapy
ASSESSMENT OF NODAL STATUS IN BREAST CANCER
LYMPHATIC DRAINAGE OF THE BREAST

- Axillary nodes
  - Level I
  - Level II
  - Level III (infraclavicular)
- Internal mammary nodes
- Supraclavicular nodes
FACTS ABOUT NODAL INVOLVEMENT

- Overall nodal positivity rate in breast cancer is 40%.
- Nodal status is significant predictor of overall survival.
- Nodal involvement reduces 5-year survival by 28-40%.
- The risk of nodal involvement is related to tumor size.
- Clinical exam is inaccurate in determining nodal involvement.
- No accurate radiographic studies to determine nodal involvement.
SURGICAL TECHNIQUES FOR EVALUATION OF NODAL STATUS

- **Axillary node dissection**
  - Removes Levels I-II
  - No survival benefit to removing nodes (NSABP B-04)
  - Lymphedema risk 10-15%
  - Other associated morbidities: numbness, arm stiffness

- **Sentinel node biopsy**
  - Removal of main draining node(s) which represents status of axilla
  - Lymphedema risk = 3-5%
  - Fewer morbidities
Sentinel Node Biopsy: Patient selection

- Clinically node-negative invasive breast cancer
  - Not recommended for inflammatory cancer
- Accurate in:
  - Multicentric disease
  - Patients with prior breast surgeries
  - Reoperative sentinel node biopsy
  - Post-neoadjuvant chemotherapy
- Intraductal cancer (DCIS)
  - Intraductal cancer (DCIS) with microinvasion
  - DCIS undergoing mastectomy
INTRAOPERATIVE PATHOLOGIC ASSESSMENT OF SENTINEL NODE(S)

- Frozen section better at determining macroscopic metastatic disease than microscopic.
- Frozen section on nodes if mastectomy is being performed. If nodes are positive, perform Level I-II axillary dissection.
- Frozen section on nodes if post-neoadjuvant chemotherapy.
- No frozen section on nodes if breast conservation therapy with whole breast radiotherapy is planned.
ACOSOG Z0011

- Randomized trial of ALND or no further axillary-specific treatment in women with Clinical T1-2 No Mo breast cancer and a positive sentinel node.
- Trial activated 4-30-99. Data presented at ASCO June 2010
- 165 investigators in 177 institutions
- Target accrual = 1900 patients (closed early)
- Primary endpoint = Overall survival (OS)
Z0011 Study Design Schema

Breast Cancer Clinical T1 or T2, N0, M0 → BCT, SLND with Positive SN → Randomize → Arm 1: ALND → Breast Radiation Therapy → Systemic Adjuvant Therapy → Follow

Arm 2: No further surgery
<table>
<thead>
<tr>
<th>ELIGIBILITY</th>
<th>INELIGIBILITY</th>
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<tbody>
<tr>
<td>Clinical T1-2 No Mo breast cancer</td>
<td>Third field of XRT for nodal irradiation or APBI</td>
</tr>
<tr>
<td>H&amp;E detected metastases in SLN</td>
<td>IHC detected SLN metastases</td>
</tr>
<tr>
<td>Lumpectomy with whole breast XRT</td>
<td>Matted nodes</td>
</tr>
<tr>
<td>Adjuvant systemic tx – by choice</td>
<td>≥3 involved SLN’s</td>
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ACOSOG Z-11: RESULTS and CONCLUSIONS

- Results showed no difference in overall survival, disease-free survival, local recurrence.
- Radiation therapy treats any residual low tumor burden in the axilla.
- Fewer complications.
- Axillary dissection can safely be omitted in patients with early stage disease and minimal nodal disease burden undergoing whole breast radiation.
- These results do not apply to patients undergoing mastectomy or partial breast radiation.
LOCAL THERAPY

Breast Conservation Therapy

- Consists of wide local excision of the breast tumor followed by radiation.
- Appropriate option for women with Stage 0-II breast cancer with clear surgical margins.
- Prognosis equivalent to mastectomy
Local Recurrence

- **Definition:** The reappearance of cancer in the treated breast after breast conservation therapy, or on the chest wall after mastectomy.

- **Local recurrence in the breast includes:**
  - **True recurrence**
    - Same histology
    - Same quadrant
    - Earlier time frame
  - **Second primary tumors**
    - Can be different histology
    - Different part of the breast
    - Occurs later after initial treatment
Over the past several decades, there has been a gradual, but substantial decrease in the risk of local recurrence following Breast Conservation therapy (10% in 1980’s to 2% currently) due to:

- Better mammographic imaging
- Better pathologic assessment of margins of resection
- Better adjuvant systemic therapy
MARGINS

- Positive margin = ink on invasive or noninvasive tumor
- Associated with $\geq 2$-fold increase in local recurrence
- Not nullified by radiation therapy, boost, systemic therapy, favorable biology
- Negative margin = no tumor on ink
- No difference in local recurrence between 1mm, 2mm or 5mm margins
BREAST RADIATION

- Purpose: To reduce local recurrence
- Types:
  - Whole breast – external beam
    - Six-week regimen
    - Three week (hypofractionated) regimen
  - Partial breast
    - External beam
    - Radiation catheter inserted into lumpectomy cavity
  - Intraoperative
- May be avoided in:
  - Low-grade noninvasive cancer with widely clear margins
  - Invasive cancer in women over 75 with receptor-positive disease
MASTECTOMY: DEFINITIONS

- Simple mastectomy = total mastectomy
  - Removal of breast tissue and nipple-areolar complex
  - No lymph nodes or muscles removed
- Modified radical mastectomy
  - Removal of breast tissue, nipple-areolar complex and axillary nodes
  - No muscles removed
- Radical mastectomy
  - Removal of breast tissue, axillary nodes, pectoralis major & minor muscles
- Subcutaneous mastectomy
  - Removes majority of breast tissue while preserving the entire skin envelope
  - Leaves 5-10% of breast tissue under nipple to preserve blood supply
- Skin-sparing mastectomy
  - Removes breast tissue and nipple-areolar complex, but spares the rest of the skin
- Nipple-sparing (or total skin-sparing) mastectomy
  - Removal of breast tissue while preserving the entire skin envelope
INDICATIONS FOR MASTECTOMY

- Multiple tumors in different quadrants of the same breast (multicentric disease).
- Diffuse malignant microcalcifications
- Persistently positive margins post-lumpectomy
- Tumors greater than 5 cm. in size
- Inflammatory cancer
- Contraindications to radiotherapy
  - Pregnancy
  - Prior therapeutic radiation to breast region
  - Scleroderma (collagen vascular disease)
RELATIVE INDICATIONS FOR MASTECTOMY

- Cosmetically unacceptable tumor/breast ratio for breast conservation
- Gene mutations
FACTORS RELATED TO NIPPLE-AREOLAR INVOLVEMENT

- Tumor proximity to nipple
- Tumor size
- Axillary nodal involvement
- Histologic subtype
- Presence of extensive intraductal component
NIPPLE-SPARING MASTECTOMY IN WOMEN WITH BREAST CANCER: SELECTION CRITERIA

- Tumors $\leq 3.0$ cm. in size
- Tumors located more than one cm. from nipple
- No gross involvement of nipple-areolar complex
c- No cancerous nipple discharge or Paget’s disease
- No inflammatory cancer
- Clinically negative axilla
NIPPLE-SPARING MASTECTOMY:

- Cosmetic issues in selection of suitable patients
  - Breast size
  - Breast ptosis
- Benefits
  - Preservation of breast shape and protrusion
  - Better sensation
  - Better sense of wholeness following mastectomy
RECONSTRUCTION

- Restoration of breast mound
  - Expander/implant
  - Myocutaneous flap (TRAM, Latissimus)
  - Free flap (DIEP)
- Reconstruction of nipple-areolar complex
POST-MASTECTOMY RADIATION: INDICATIONS

- Tumors greater than 5 cm. in size or locally advanced cancer (T4)
- Multiple involved axillary nodes (4 or more)
- Lesser numbers of positive nodes with unfavorable tumor biology
- Tumor-involved surgical margin
BREAST CANCER: SYSTEMIC THERAPY

- Chemotherapy
- Hormonal Therapy
- Other Targeted Therapy
Factors to be Considered in Recommending Systemic Adjuvant Therapy

- **Patient Characteristics**
  - Age

- **Disease Characteristics**
  - Tumor size
  - Axillary node status
  - Tumor Grade
  - Angiolymphatic invasion

- **Biomarkers**
  - Her2neu
  - Hormone receptors
    - Estrogen receptor (ER)
    - Progesterone receptor (PR)

- **Oncotype**
ONCOTYPE DX ASSAY

- 21-gene panel
  - Expression of these genes is used to calculate recurrence score.
  - Useful in hormone receptor-positive, her2neu negative cancers to determine additional benefit of chemotherapy.
GENOMIC SUBTYPES OF BREAST CANCER

- **LUMINAL A**: ER/PR +, Her2Neu-, Ki67 low
- **LUMINAL B**: ER/PR +, Her2Neu -, Ki67 high
- **LUMINAL Her2Neu**: ER/PR +, Her2neu +
- **HER2NEU enriched**: ER/PR -, Her2neu +
- **TRIPLE-NEGATIVE**: ER/PR -, Her2neu -
RECEPTOR POSITIVE TUMORS: Available modalities

- SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMs)
  - Tamoxifen
- AROMATASE INHIBITORS
  - Anastrozole, letrozole, exemestane, faslodex
- SURGICAL ABLATION (OOPHORECTOMY)
- MEDICALLY-INDUCED MENOPAUSE
- CDK4, CDK6 Inhibitors
  - Palbociclib
- mTOR INHIBITORS
  - Everolimus
ENDOCRINE THERAPY

- Premenopausal patients:
  - Tamoxifen
    - Standard duration of therapy has been 5 years.
    - Recent data (ATLAS and aTTom trials) show survival benefit with 10 years of therapy
  - Ovarian suppression and aromatase inhibitor
    - SOFT and TEXT trials – slight advantage (improved 5-year disease free survival of just under 4%) to using this regimen over tamoxifen alone or ovarian suppression with tamoxifen.
    - Increased symptoms of menopause, depression, hypertension, diabetes and osteoporosis
- Post-menopausal patients:
  - Tamoxifen or Aromatase inhibitor
    - 5 years vs. longer duration of therapy
Her2neu positive tumors

- 25% of breast cancers overexpress Her2neu.
- More aggressive tumor subtype.
- Standard first-line adjuvant therapy: 
  Trastuzumab (Herceptin) combined with chemotherapy. Treatment with trastuzumab for one year.
- Other anti-Her2 neu drugs:
  - Pertuzumab (Perjeta) combined with trastuzumab in the neoadjuvant setting
  - TDM-1
TRIPLE-NEGATIVE BREAST CANCER

- More common in African-American women
- Seen in association with BRCA-1 mutations
- Current systemic treatment is chemotherapy.
- Area of intense research interest looking for targets in this subgroup.
NEoadjuvant Chemotherapy: Indications

- Patients with tumors >5 cm in size if breast conservation therapy is desired
- Inflammatory cancer
- Patients with her2 positive or triple negative disease and other extenuating factors (like surgical decisions dependent on results from genetic testing)
- Her2 positive tumors > 2 cm in size or smaller size with positive nodes
- Fixed and matted nodes
- Disease initially unresectable
Consider in locally advanced, receptor positive disease in selected cases

Response is usually gradual- over several months
Breast cancer patients are at risk for local recurrence, systemic recurrence, new primary tumor in ipsilateral or contralateral breast.

Follow-up consists of periodic careful history and physical exam, breast imaging.
QUESTIONS?