Breast Cancer 101
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Disclosures

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None

OBJECTIVES

1. Discuss the epidemiology of breast cancer
2. Identify risk factors for development of breast cancer including preventative strategies to help decrease modifiable risks
3. Articulate the diagnosis and multidisciplinary approaches to treatment for breast cancer.
EPIDEMIOLOGY

Epidemiology

Breast cancer Facts and Figures 2017-18

Cancer Stat Facts: Female Breast Cancer

At a Glance

- Estimated New Cases in 2017: 261,780
- % of All Cancer Cases: 20.3%

- Estimated Deaths in 2017: 41,170
- % of All Cancer Deaths: 7.2%
Epidemiology

- Incidence and mortality going down
- Better treatments
- Reduced use of HRT since early 2000s

SCREENING
USPSTF recommendation

- Women, Age 50-74 Years
  - The USPSTF recommends annual screening mammography for women 50-74 years.
  - The decision to start regular, annual screening mammography before the age of 50 years depends on individual risk and preferences, including the medical and psychological factors in the patient’s life.
  - The USPSTF concludes that the benefits of screening mammography in women 50 years and older are outweighed by the harms.

ACS recommendation

American Cancer Society Recommendations for the Early Detection of Breast Cancer

- Women aged 40-44
  - Women should be able to make an informed decision about their own mammography screening.

NCCN recommendation

- Similar recommendation by American College of Radiology (ACR) and Society of breast imaging (SBI)
Why the discrepancy?
- Depends on which trial you look at.
- Benefit in age 50-74 is seen across the board.
- Magnitude of benefit in age 40-50 is not uniform across trials.
- Depends on the type of mammogram (2D vs 3D) and radiologist.

Screening for high risk patients
- BRCA mutation: Start screening at age 25 (Mammogram/MRI).
- Prior h/o thoracic radiation between age 10-30: Start screening 10 years after radiation (Mammogram/MRI).

RISK FACTORS
Non-modifiable risk factors

- Radiation
- Genetic factors
- Family/personal history
- Age
- Menstrual/Reproductive history

All women are at risk

Chlebowski et al. JNCI 2005; 97: 439-448
Pharoah et al. Int J Cancer 1997; 71: 800-809

Modifiable risk factors

- Obesity
- HRT
- Nulliparity
- Lack of exercise
- Birth control pills
- No breastfeeding

All women are at risk

Chlebowski et al. JNCI 2005; 97: 439-448
Pharoah et al. Int J Cancer 1997; 71: 800-809

Benign breast lesions

- No risk
  - Fibrocystic change
  - Fibrosis
  - Simple cysts
  - Mild hyperplasia

- RR 1.5 - 2
  - Usual ductal hyperplasia (without atypia)
  - Fibroadenoma

- RR ~ 4
  - Atypical ductal hyperplasia
  - Atypical lobular hyperplasia (no surgery needed)
  - Benign breast lesions

Breast cancer Facts and Figures 2017-18
Hereditary risk factors

- 5-10% of all women with breast cancer have a hereditary form of breast cancer
- BRCA 1 and BRCA 2 (Ovarian, pancreatic, prostate, melanoma)
- p53 - Li-Fraumeni syndrome (Leukemia, Sarcoma, GBM)
- PTEN - Cowden syndrome (Thyroid cancers, hamartomas, macrocephaly)

References:
- Chlebowski et al. NCI J 2005; 97:439-448

BRCA 1 - cumulative risk

- Risk of breast cancer by age 70: 75-78%
- Risk of ovarian cancer by age 70: 40%
- Risk of contralateral breast cancer by age 70: Up to 60%

BRCA 2 - cumulative risk

- Risk of breast cancer by age 70: 45-70%
- Risk of ovarian cancer by age 70: 15%
- Risk of contralateral breast cancer by age 70: Up to 60%
Who should be tested?

- Any individual with a breast cancer diagnosis meeting any of the following criteria:
  - Breast cancer diagnosed age < 50 yrs
  - Triple negative (ER-, PR-, HER2-), breast cancer diagnosed age < 60 yrs
  - 2 breast cancer primaries
  - Breast cancer at any age, and:
    - 1 close blood relative with:
      - Breast cancer diagnosed age < 50 yrs, or
      - Invasive ovarian cancer, or
      - Male breast cancer, or
      - Pancreatic cancer, or
      - High grade (Gleason score > 7) or metastatic prostate cancer
    - 2 close blood relatives with breast cancer at any age

Who should be tested?

- An individual who does not meet the above criteria but has a 1st or 2nd degree relative with any of the following:
  - Breast cancer diagnosed age < 45 yrs
  - Ovarian cancer
  - Male breast cancer
  - Pancreatic cancer
  - Metastatic prostate cancer
  - 2 breast primaries in a single individual
  - 2 individuals with breast cancer primaries on the same side of the family, 1 of which was diagnosed age < 50 yrs

Risk reduction

- Prophylactic bilateral mastectomy: Reduces risk by >90%
- Prophylactic bilateral salpingo-oophorectomy (by age 35-40):
  - Reduces risk of ovarian cancer by >90%
  - Reduces risk of breast cancer by 50% in premenopausal women
- Chemoprevention (Gail model score > 1.67, high risk breast lesions):
  - Tamoxifen: premenopausal women (NSABP-P1, STAR, 49% risk reduction)
  - Raloxifene: postmenopausal women (less risk of VTE, uterine cancer)
  - Exemestane, Anastrozole
DIAGNOSIS

Mammogram

- Microcalcifications, mass

Ultrasound

- Differentiates solid vs cystic lesion
MRI

- More sensitive but less specific
- Dense breasts
- Axillary nodal metastases with occult primary
- Women with high risk for contralateral breast cancer

Inflammatory breast cancer

- Often mistaken for an infection
- > 1/3rd of the breast is inflamed
- Clinical diagnosis
- Skin biopsy can confirm diagnosis
- Dermal lymphatic invasion is characteristic but not required for diagnosis
- Staging scans should be done
- Chemotherapy should be administered first, irrespective of biology

Biopsy

- Image guided core-needle biopsy
- FNA of axillary lymph nodes
- Clip placement at the time of biopsy
- Pathology assessment of malignant lesions (prognostic factors):
  - Histologic type
  - Grade
  - Ki-67 index
  - Receptor status (ER, PR, Her-2)
  - Lymphovascular invasion
SUBTYPES OF BREAST CANCER

Normal Breast

A. Breast Duct System
B. Lobules
C. Breast Duct System
D. Nipple
E. Fat
F. Chest Muscle
G. Ribs

A. Cells lining duct
B. Basement membrane
C. Open central duct

Non-invasive breast cancer

DCIS
LCIS
Invasive breast cancer

Histologic subtypes

Molecular subtypes
Breast cancer biomarkers

ER: Estrogen Receptor  
HER2: Human Epidermal Growth Factor Receptor 2  
IHC: Immunohistochemistry  
FISH: Fluorescence in situ Hybridization

Incidence of subtypes of breast cancer

STAGING OF BREAST CANCER
AJCC/TNM Staging

Breast cancer staging; AJCC 8th edition

Stage 1 and Stage 2: Routine staging scans not indicated
Stage 3: Consider staging scans

Stage is prognostic

Figure 9. Trends in Breast Cancer-specific Survival and Stage Distribution by Race/Ethnicity, 2007-2013, US

Breast cancer facts and figures 2017-18
MANAGEMENT OF BREAST CANCER

Lobular carcinoma in situ
- Risk factor for development of breast cancer
- Not part of breast cancer staging anymore
- 1% annual risk of transformation to breast cancer
- Almost 100% ER+, PR+
- Surgery not needed, if imaging is concordant
- Endocrine therapy for risk reduction
- No chemotherapy
- Can be bilateral

Ductal carcinoma in situ
- Pre-cancerous lesion
- Treated like stage 1 breast cancer - surgery (lumpectomy + Radiation or Mastectomy)
- 99% are ER+, PR+
- No role for checking Her-2
- No chemotherapy
- Endocrine therapy to reduce ipsilateral and contralateral breast recurrence
Management - Stage I-III Invasive Breast Cancer

- Loco-regional treatment
  - Breast conservation surgery (BCS)/Mastectomy
  - Axillary lymph node evaluation (Sentinel lymph node)
  - Radiation (with BCS, sometimes after mastectomy also)

Systemic treatment

- Chemotherapy (Adjuvant/Neoadjuvant)
- Endocrine therapy (ER+ positive)
- Anti-Her-2 targeted therapy (Her-2 + disease)
- Goal is to eliminate micrometastases
- Reduce the risk of distant metastases
- Downstage disease when used neoadjuvantly

Who needs chemotherapy?

- Higher risk of recurrence in the next 5 years
- Triple negative breast cancer (ER-, PR-, Her-2-)
- Her-2 positive breast cancer
- ER+ Her-2- breast cancer with:
  - High risk based on genomic assay (Oncotype Dx, MammaPrint)
  - Multiple lymph nodes positive
  - Large primary tumor
- Biology is most important
- Chemotherapy can be administered before or after surgery depending on the clinical situation
Oncotype Dx

- No chemotherapy benefit for score 0-25
- ER+, Her-2-, LN- disease

*JCO, 26: 721-728, 2008*

MammaPrint

- Clinically high risk but MammaPrint low risk can skip chemotherapy
- Applicable to ER+, Her-2-, LN+/- disease


Benefit of chemotherapy

*Polychemotherapy vs. Not, by Entry Age: 15-year Probabilities of Recurrence and Breast Cancer Mortality (Age 50-69)*

*EBCTCG: Lancet 2005; 365: 1887–1891*
Benefit of chemotherapy - Age < 50

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>Mortality</th>
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<tbody>
<tr>
<td>Control</td>
<td>53.5%</td>
</tr>
<tr>
<td>Chemo</td>
<td>41.1%</td>
</tr>
<tr>
<td>Control</td>
<td>42.4%</td>
</tr>
<tr>
<td>Chemo</td>
<td>32.4%</td>
</tr>
</tbody>
</table>

15 year gain 12.3% (SE1.6)
Log rank 2 p<0.00001

15 year gain 10.0% (SE1.6)
Log rank 2 p<0.00001

Chemotherapy - common adverse effects
- Nausea, Vomiting
- Mucositis
- Myelosuppression
- Fatigue
- Infection
- Alopecia
- Cognitive dysfunction
- Premature ovarian failure

Chemotherapy drugs and adverse effects
- Doxorubicin (Adriamycin) (A) - Cardiotoxicity, secondary leukemia, MDS
- Cyclophosphamide (C) - Renal dysfunction, Secondary leukemia, MDS
- Paclitaxel (T) - Liver dysfunction, Peripheral neuropathy
- AC followed by T is the most commonly used regimen
- Docetaxel (Taxotere) (T) - Mucositis, Liver dysfunction, Peripheral neuropathy
- Eribulin (Metastatic disease) - Neuropathy
- Gemcitabine (Metastatic disease) - TTP
- Carboplatin (Neoadjuvant/Metastatic disease) - Peripheral neuropathy, Myelosuppression
- Capecitabine (Adjuvant/Metastatic disease) - Mucositis, diarrhea, Hand-foot syndrome

Chu et al. Physicians' Cancer Chemotherapy Drug Manual 2019
Tamoxifen
- Significant reduction of breast cancer deaths and recurrence with 5 years of tamoxifen, even after 15 years from study entry
- Benefit of at least 5 years of tamoxifen carries over for at least 10 more years (carry-over effect)
- Improvement in breast cancer mortality was seen across all age groups, irrespective of menopausal status
- Selective estrogen receptor modulator
- Cataracts
- DVTs
- Endometrial cancer
- Hot flashes (can consider duloxetine/venlafaxine), mood changes, vaginal discharge, depression
- Does NOT increase risk for osteoporosis
- Early and advanced stage disease
- Drug interactions - CYP2D6 inhibitors - SSRIs

Aromatase Inhibitors
- Prescribed for at least 5 years
- Prolonged DFS, TTR
- Reduced risk of distant metastases and contralateral breast recurrence
- Prevent peripheral conversion to estrogen
- Increased risk for osteoporosis
- Myalgias/Arthralgias (can consider duloxetine)
- Hot flashes, mood changes
- Hyperlipidemia
- Anastrozole = Letrozole = Exemestane
- Early and Advanced stage disease

Endocrine therapy – Mechanism of action
Anti-Her-2 drugs – Mechanism of action

Trastuzumab and Pertuzumab
- Adjuvant/Neoadjuvant treatment
- Also in advanced stage
- Overlap with chemotherapy - works better
- Trastuzumab is continued for 1 year when used in localized disease
- Improved overall and disease free survival and changed natural course of Her-2+ breast cancer
- Potentially Cardiotoxic (Echo every 3 months)
- Pertuzumab (used only with Trastuzumab) - can cause diarrhea

Neratinib
- Tyrosine kinase inhibitor
- Blocks Her-4 also
- Approved for extended anti-Her-2 therapy in localized Her-2 positive breast cancer
- After completion of one year of trastuzumab
- Potentially cardiotoxic
- Diarrhea is a common side effect (scheduled loperamide)
- Has shown impressive CNS penetration
Metastatic Disease - ER+

- Prefer endocrine therapy as first line with CDK 4/6 inhibitor
- Can use single agent Fulvestrant also
- Reserve chemotherapy (preferably single agent) for a visceral crisis or endocrine resistant disease
- Role of systemic therapy is palliative only
- Assess performance status
- Skeletal metastases should be treated with Bisphosphonates or Denosumab
- Palliative care, hospice and advanced directives

Fulvestrant

- Estrogen receptor antagonist
- Approved only in metastatic disease (first line or subsequent)
- Hot flashes
- Mood changes
- Injection site reactions

CDK 4/6 inhibitors

- Palbociclib, Ribociclib, Abemaciclib
- Palbociclib and Ribociclib only in advanced stage ER+, Her-2- breast cancer along with AIs or Fulvestrant
- Halt cell cycle in G1-S phase
- All of them cause cytopenias, especially neutropenia.
- QT prolongation with Ribociclib & diarrhes with Abemaciclib.
- Abemaciclib also approved in high risk adjuvant setting
**Everolimus**
- mTOR inhibitor (common mechanism of resistance to endocrine therapy)
- 2nd line treatment of metastatic ER+, Her-2- breast cancer
- In combination with exemestane
- Stomatitis (prophylactic oral steroid)
- Anemia
- Dyspnea
- Hyperglycemia
- Pneumonitis


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**Alpelisib - PIK3CA inhibitor**

Adverse effects:
- Hyperglycemia
- Diarrhea
- Nausea
- Rash

Metastatic HR+/Her-2+ Breast Cancer

1ST Line
- Ribociclib + ET
- Abemaciclib + ET
- Palbociclib + ET
- ET Alone

2ND Line
- ESR1 mut: Elacestrant
- PIK3CA Mut: Alpelisib + Fulvestrant
- gBRCA: Olaparib/Talazoparib
- No mutation: Everolimus with ET
- CDK Inhibitor switch

3RD Line and Beyond
- Her-2 Low: T-DxD
- ADC: Sacituzumab-Govitecan
- Various Chemotherapy
- Single Agent Abemaciclib
- MSI-H / High TMB Pembrolizumab

Metastatic Disease - Her-2+
- Trastuzumab, Pertuzumab and Docetaxel as first line
- T-DM1 in 2nd line and Lapatinib (with capecitabine) in 3rd line
- Potentially cardiotoxic - periodically check Echo
- Role of systemic therapy is palliative
- Assess performance status
- Skeletal metastases should be treated with Bisphosphonates or Denosumab.
- Palliative care, hospice and advanced directives

Trastuzumab Emtansine (T-DM1)
- Antibody drug conjugate
- Adjuvant therapy in some patients
- Advanced stage Her-2+ disease - 2nd line
- Potentially Cardiotoxic
- Hypomagnesemia
- Peripheral neuropathy
- Thrombocytopenia
Trastuzumab deruxtecan
- Approved in second and third line Her-2 positive metastatic disease
- Destiny Breast - 01 was a single arm study with excellent ORR
- Pneumonitis
- Nausea
- Fatigue

Tucatinib
- Approved in second and third line Her-2 positive metastatic disease
- Her-2 CLIMB was a randomized study comparing it with capecitabine and trastuzumab
- To be used with capecitabine and trastuzumab
- Active for intracranial metastases
- Rash
- Diarrhea

Lapatinib
- Tyrosine kinase inhibitor
- Able to bind and inhibit p185 Her-2
- Approved only for metastatic Her-2+ breast cancer
- 2nd line and beyond for Her-2+ positive breast cancer
- Diarrhea
- Skin rash
- Potentially cardiotoxic

Her-2+ Metastatic Breast Cancer

- Single agent chemotherapy
- Consider PARP inhibitors (Olaparib, Talazoparib) in patients with BRCA mutations
- Immunotherapy (Pembrolizumab + Chemotherapy) in patients with PD-L1 CPS >10%
- Role of systemic therapy is palliative
- Assess performance status
- Skeletal metastases should be treated with Bisphosphonates or Denosumab.
- Palliative care, hospice and advanced directives

PARP inhibition - Olaparib, Talazoparib

Adverse effects:
- Anemia
- Nausea
Sacituzumab govitecan

- Approved in third line for triple negative metastatic disease
- IMMU-132-01 and then ASCENT trials
- Impressive ORR and improvement in PFS and OS
- First ADC approved in this space
- Diarrhea
- Nausea
- Cytopenia

Metastatic TNBC

- Check for PD-L1 expression by the 22C3 test and if the CPS is at least 10, consider pembrolizumab with either nab-paclitaxel or paclitaxel or carboplatin + gemcitabine (KEYNOTE 355)
- Check for germline BRCA mutation: If positive, can use talazoparib (EMBRAACA, Litton et al, NEJM 2018) or olaparib (olympiAD, Robson et al, Annals of Oncology 2019)
- Check for MSI: If high, Pembrolizumab in 2nd line and beyond
- Check for tumor mutational burden: If high, can consider Pembrolizumab in 2nd line and beyond
- If no target, single agent chemotherapy preferred: Paclitaxel, Docetaxel, Eribulin (2nd line and beyond), Capcitabine, Doxorubicin, Cyclophosphamide, Carboplatin, Gemcitabine, Irinotecan (microtubule stabilizer, effective in taxane resistant cells, used as monotherapy or in combination with capcitabine)
- Sacituzumab Govitecan: FDA approved for advanced stage triple negative breast cancer, that has progressed on at least 2 prior lines of chemotherapy, with at least one of them in the metastatic setting (IMMU-132-01, ASCENT)

ER-, Her-2 low (1- by IHC or 2+ by IHC and non-amplified FISH) metastatic breast cancer

- Trastuzumab-dleucovorin after progression on at least 1 line of chemotherapy - improved PFS and OS
Management of Bone metastases
- Bisphosphonates (IV zoledronic acid, every 3 months)
- Denosumab (subcutaneous, every month)
- Delayed skeletal related events
- Reduced rate of distant recurrence
- Reduced breast cancer mortality
- Hypocalcemia, Renal dysfunction


SURVEILLANCE/SURVIVORSHIP
- Follow up
  - Every 3-6 months for the first 2 years
  - Every 6-12 months for the next 3 years
- History and Physical Examination
  - Symptoms of local recurrence or metastatic disease
  - Update family history and genetic referral if needed
  - Examination of chest wall, breast and axilla
  - Adverse effects from treatments
  - Gynecologic exam - annually for patients in tamoxifen
  - Lymphedema
- Imaging
  - Annual mammogram
  - DEXA every 2 years for patient on AI
- Education
  - Breast awareness
  - Adherence to medications

Take Home Points
- Breast cancer is a common but curable disease with multiple treatment options
- It is a heterogeneous group of cancers with varied biology and consequent prognosis
- Multiple risk factors need to be reviewed and strategies to reduce risk need to be incorporated accordingly
- Screening mammogram is an essential tool for early diagnosis
- Pathology and genomic assays provide important prognostic information that helps direct treatment
- Surgery, Chemotherapy, Radiation, endocrine therapy and anti Her-2 drugs have a definite role in localized disease based on biology
Take Home Points

- Sequence of surgery and chemotherapy does not matter in terms of overall outcome
- Metastatic disease also has numerous treatment options and improved outcomes
- Endocrine therapy, targeted agents (CDK 4/6 inhibitors, PIK3CA inhibitors, PARP inhibitors), anti-Her 2 drugs, immunotherapy and single agent chemotherapy drugs form the cornerstone of treatment for metastatic disease with the aim of palliation
- Survivorship referrals help improve quality of life

Thank you!