Battling Breast Cancer
Making Headway or Not?

Elyssa Del Valle, MD
January 25, 2016
Some Questions to Answer

• What are the current recommendations on screening?

• Have recurrence rates improved with treatments driven by the newer prognosticators?

• Does endocrine therapy (Tamoxifen, Arimidex) improve survival?

• Has there been any advances on morbidity?

• Has there been improvement in survival for metastatic disease?
Agenda

• Epidemiology
• Risk Factors
• Strategies on Screening: Who, When and For How Long
• Diagnostic Tests
• Staging: What’s New in Staging
• Prognosticators: Current and Future, including Genomics
• Morbidity
• Mortality
• Answer the question…. Has there been headway or not???
• Case Studies
Epidemiology

• Incidence
  o Most common malignancy diagnosed in women accounting for 30% of all female cancers and second most common cause of cancer death in US - (most common cause of cancer death worldwide)
  o In 2015, an estimated 232,000 new cases of invasive BC in women and 2,300 men are expected along with 60,000 new cases of DCIS
  o Observed incidence from 1975 to 2010 rose on average by 1.5% per year among all races per SEER
  o Observed incidence from 1992-2010 rose by 0.1%/year among all races per SEER

• Prevalence: affects 12% of women in US and less than 1% of men
• US. Deaths per year in 2015 estimates 40,700 women and 440 men
• Leading cause of death in women age 40-55
# Leading Sites of New Cancer Cases and Deaths – 2015 Estimates

<table>
<thead>
<tr>
<th>Estimated New Cases*</th>
<th>Estimated Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td><strong>Female</strong></td>
</tr>
<tr>
<td>Prostate</td>
<td>Breast</td>
</tr>
<tr>
<td>220,800 (26%)</td>
<td>231,840 (29%)</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>115,610 (14%)</td>
<td>105,590 (13%)</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td>69,090 (8%)</td>
<td>63,610 (8%)</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Uterine corpus</td>
</tr>
<tr>
<td>56,320 (7%)</td>
<td>54,870 (7%)</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>Thyroid</td>
</tr>
<tr>
<td>42,670 (5%)</td>
<td>47,230 (6%)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>39,850 (5%)</td>
<td>32,000 (4%)</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>Melanoma of the skin</td>
</tr>
<tr>
<td>38,270 (5%)</td>
<td>31,200 (4%)</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>Pancreas</td>
</tr>
<tr>
<td>32,670 (4%)</td>
<td>24,120 (3%)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Leukemia</td>
</tr>
<tr>
<td>30,900 (4%)</td>
<td>23,370 (3%)</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>Kidney &amp; renal pelvis</td>
</tr>
<tr>
<td>25,510 (3%)</td>
<td>23,290 (3%)</td>
</tr>
<tr>
<td>All sites</td>
<td>All sites</td>
</tr>
<tr>
<td>848,200 (100%)</td>
<td>810,170 (100%)</td>
</tr>
</tbody>
</table>

| **Male**             | **Female**       |
| Lung & bronchus      | Lung & bronchus  |
| 86,380 (28%)         | 71,660 (26%)    |
| Prostate             | Breast           |
| 27,540 (9%)          | 40,290 (15%)    |
| Colon & rectum       | Colon & rectum   |
| 26,100 (8%)          | 23,600 (9%)      |
| Pancreas             | Pancreas         |
| 20,710 (7%)          | 19,850 (7%)      |
| Liver & intrahepatic bile duct | Liver & intrahepatic bile duct |
| 17,030 (5%)          | 14,180 (5%)      |
| Leukemia             | Leukemia         |
| 14,210 (5%)          | 10,240 (4%)      |
| Esophagus            | Uterine corpus   |
| 12,600 (4%)          | 10,170 (4%)      |
| Urinary bladder      | Non-Hodgkin lymphoma |
| 11,510 (4%)          | 8,310 (3%)       |
| Non-Hodgkin lymphoma| Non-Hodgkin lymphoma |
| 11,480 (4%)          | 8,310 (3%)       |
| Kidney & renal pelvis| Kidney & renal pelvis |
| 9,070 (3%)           | 7,520 (3%)       |
| All sites            | All sites        |
| 312,150 (100%)       | 277,280 (100%)   |

*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

©2015, American Cancer Society, Inc., Surveillance Research
Risk Factors

- **BRCA-1 or BRCA-2 mutations** (2.9% Caucasians, 10% of Ashkenazi, 3.5% Hispanic, 0.5% Asian Americans for BRCA1)
- Family history of breast or ovarian cancer
- Personal history of prior breast, endometrial or ovarian cancer
- **Increasing age**
- Nulliparity or late age at first pregnancy (age over 30)
- Absence of breast feeding
- Early menarche
- Late Menopause
- Hormone replacement therapy
- **Hyperplasia, multiple papillomatosis, sclerosing adenosis, fibroadenomas with proliferative change and atypical hyperplasia**
- Radiation to breast area
- No added risk for fibrocystic breast disease, simple fibroadenomas without proliferative change, duct ectasia and solitary papillomas
Newest Strategies On Screening

- Parameters that affect screening decisions are based upon evidence for screening for breast cancer, and weighing benefits and harms of screening.
- Benefits and harms depend upon an individuals’ risk for developing breast cancer and how good the screening test is.
- Discoveries in Genetic mutations have prompted more specific screening strategies.
- Evidence supports screening by risk stratification.
- Reduces overscreening and overdiagnosis.
Overdiagnoses From Screening

- If screening leads to early detection of cancers that are destined to become lethal, (when they can be curable at early stage) then we should have seen a corresponding drop in late stage cancer

- Well, have we?

- And so what if there is overdiagnosis. Is there any harm?
Recommendations on Screening

• American Cancer Society 10/15 revised their guidelines from age 40 to recommend routine screening at age 45 annually until age 55 then every 2 years and as long as life expectancy is 10 yrs or longer

• American College of Ob/GYN continue to recommend starting age 40 annually

• American College of Radiology continue to recommend routine screening age 40

• US Preventive Task Force, Canadian Task Force and American College of Physicians recommend beginning age 50 every 2 yrs through age 74

• American College of Radiology recommend until life expectancy is 5-7 more years

continued
Recommendations on Screening-continued

For Lifetime Risk 20-25% or more

• Should be referred for genetic counseling such as BRCA1 and 2 mutation

• Intensified surveillance with annual mammogram and MRI as well as clinical breast exam every 3-6 months

• Start screening mammogram at age 25
Diagnostic Testing: Current and Future

- 60% of biopsies clinically thought to have cancer were benign
- 30% of clinically benign clinical appearance were malignant
- Biopsy is critical to make diagnosis

The primary move this decade is toward minimally invasive techniques
Diagnostic Tests: SLN Dissection

• Has become the standard over last 15 years, replacing the Axillary Lymph Node dissection.... Here is Why:

• More accurate, and can pick up micrometasasis... which ultimately causes upstaging

• ASOSOG 2011 trial compared ALND to SLND in 900 patients: Results: comparable results and thus no clinical benefit of ALND in those patients with limited nodal disease- same 5 year disease free survival, 5 year local recurrence and 5 year overall survival

• Also, in large study (over 5000 women)comparing SLND followed by ALND versus SLND followed by ALND only if SLN was positive had no difference in regional control, overall survival or disease free survival at a median follow up of 8 years

• Less morbidity with SLN than ALND: ex. Lymphedema 2% with SLN as compared to 13% with ALND

• Conclusion from multiple large studies suggests SLND should be performed on all women less than 70 with clinically negative nodes.
Newer Staging Strategy

- TNM staging system
- Tumor size
- Regional Lymph Nodes
- Metastasis
- Micrometastasis and Isolated Tumor Cells
Newer Staging Categories

• Micrometastasis or Mi: 0.2 mm to 2.0 mm

• Isolated Tumor Cells or ITCs also called metastatic foci: <0.2 mm

• ITCs are found by special immunohistochemical staining (IHC)
Newer Stages

• **pN0(i+)** means isolated tumor cells no greater than 0.2 mm and are prognostically similar to node negative

• **pN1mi** refers to micrometastasis and would think worse prognosis, however this class has only slight increase in recurrence rate

• Data on SLN indicates that there was 0% additional positive nodes with ITC; 27% had additional positive node for Mi
Prognosticators

• Prognosticators are factors in someone already with history of breast cancer that aide in determining their chance of survival to 5 and 10 years and what their recurrence rate would be.

• Predictive factors indicate the likelihood of response to specific treatment.

• Of course, this would also mean that some predictive factors are also prognostic factors since treatment can alter prognosis (such as ER status).
Well Known Prognosticators

- Age
- Size
- Nodal Status
- Localized or Metastasized
- Histological grade
- Estrogen and progesterone receptor status
- HER status
- Mitotic Index
Prognosticators-ER/PR

- Immunohistochemical Staining for PR/ER
- Score on % of Cells that stain (>1% is deemed positive)
- Allred Score: points for both % cells and score for intensity of staining (0-2 points is negative and 3-8 points is positive)
- Respond better to hormone treatment (tamoxifen or aromatase inhibitors) than negative receptor status
- Better prognosis
- Higher rate of positive markers in age over 65
- This correlates with the better prognosis in older age women
Prognosticator: HER-2/neu

• Immunohistochemical Staining allows scoring:
  0 and 1+ is negative; 2+ is indeterminant; 3+ is positive
  • When indeterminant, FISH is performed (hybridization test)

• If HER-2 + BC is untreated: associated with shortened survival, shorter relapse time and worse prognosis

• HER-2 +, responds well to chemo (trastuzumab), so improves survival

• Triple negative (ER/PR neg and HER-2 neg) have limited therapeutic options and prognosis worsens
Newest Prognosticators - Genomics

- Microarray Studies
- Oncotype DX
- MammaPrint
- Genome Sequencing
Microarray Studies

• The Frontier into next prognosticators
• Additional research methods to look at breast cancer subtypes initially came from Microarray studies
• Signals on microchip that can be held in your palm, allow breast cancers to be molecularly divided into certain subtypes:
  o **Luminal A** best prognosis (ER/PR +)
  o **Luminal B** worse prognosis (ER/PR +)
  o **Basal**: correlates with triple negative phenotype
  o **HER2** enriched by microarray.. Comparable to HER2 from IHC
Genomics... Oncotype DX

- Currently in widespread use in USA to assess BC recurrence for ER/PR positive patients
- Requires breast cancer tissue to examine gene expression
- Oncotype DX looks at 21 genes
- Provides *recurrence score or RS*
- *Recurrence Score* is based on retrospective studies
- Women with stage I/II with negative nodes, fall into low to intermediate risk for 10 year recurrence. Oncotyping can select those at increased risk who can thereby elect more aggressive adjuvant treatments.
- Information from Oncotype DX can help with prognostication
- FDA has validated these scores
Genomics......Mammaprint

- Similar to Oncotype DX
- Currently more widespread use in Europe
- Tests for 70 genes
Cancer Genome Sequencing

- Introduced in 2009
- Compares DNA from Breast Cancer tissue to the woman’s own normal breast tissue
- Reveals areas of chromosomal rearrangement and mutations/deletions of individual genes
- Findings correlates to breast cancer subtypes: Luminal A, Luminal B, Basal and HER2
- Still in investigation
Prognostics of Future

- DNA/ploidy by flow cytometry
- P53
- Cathepsin D
- CEA
- Cyclin D
- CA 15-3
- CA 27.29
- Bone marrow micrometastases
- Circulating tumor cells
- Plasminogen activator inhibitor
- Urokinase plasminogen activator

Most important will be derived from Genetic Sequencing
Treatment Advances

- Poly(ADP-ribose) Polymerase Inhibitors (PARP Inhibitors)
  - Family of enzymes involved in DNA repair and apoptosis
  - May make other treatments more effective
  - May kill cells with defective DNA repair genes (BRCA 1 and 2 and others)
- Nanotechnology (Dimensions < 100 nm)
  - Diagnostic potential
  - Therapeutic possibilities
    - Targeted drug delivery
- Surgery and radiation in selected instances
- HER2 targets (EGFR)
  - Monoclonal Abs (Trastuzumab), TKIs, (Lapatinib)
- Angiogenesis inhibitors, anti-VEGF
  - Bevacizumab, others in development
Morbidity

- Chemotherapy effects:
  - Neurotoxicity - peripheral neuropathy from certain chemo agents such as Cisplatinum
  - Plexopathy can be permanent
  - Cardiomyopathy from Trastuzumab
  - Cardiomyopathy from Adriamycin
  - In 2012 study of 12,500 women, 6-11% of older women had CHF and 20% had cardiomyopathy with Trastuzumab plus anthracylcine

- Surgical complications:
  - Chest wall and breast complications - seromas, fat necrosis, recurrent skin infection
  - Reduced arm mobility
  - Lymphedema 2% in SLN and 13% in axillary lymph node

Continued
Morbidity -continued

• Radiation therapy effects:
  o Premature CAD, especially left sided breast radiation
  o Secondary malignancies: increase risk for esophageal and lung cancer as well as sarcomas, leukemias, myelodysplastic syndrome
    - Occurs within 5-7 years post treatment in 1.5% of patients

• General or other related adverse effects:
  o Long term effects for primary therapy include cognitive dysfunction, fatigue, insomnia, pain and debilitating menopausal symptoms
  o Pulmonary – cough, dyspnea
  o Fatigue
  o Chemo brain-real or Memorex
Mortality

SEERS 13 US Cancer Mortality Data

• 1975-2010 declined by 0.4%/yr among all races
• 1992-2010 declined by 3%/yr among all races
• Estimated 40,700 women and 440 men died in US in 2015

Bottom line: With improved screening and treatment, there has been an overall 30% reduction in mortality over the last 2 decades.
Relative Survival By Year For Invasive BC

**SEER RELATIVE SURVIVAL (PERCENTAGE) BY YEAR FOR ALL RACES**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>94.4</td>
<td>96.8</td>
<td>97</td>
<td>97.5</td>
<td>97.8</td>
<td>97.8</td>
</tr>
<tr>
<td>5 years</td>
<td>74.6</td>
<td>84</td>
<td>86.8</td>
<td>90.2</td>
<td>90.5</td>
<td></td>
</tr>
<tr>
<td>10 years</td>
<td>62.4</td>
<td>77</td>
<td>80.6</td>
<td>84.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 years</td>
<td>56</td>
<td>71.8</td>
<td>75.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 years</td>
<td>51.7</td>
<td>67.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5 Year Survival by STAGE

5 year survival (percent) 2003-2009 (SEER Data)

<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>All Ages</th>
<th>Ages &lt;50</th>
<th>Ages 50+</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Stages</td>
<td>89.2</td>
<td>89.1</td>
<td>89.3</td>
</tr>
<tr>
<td>Localized</td>
<td>98.6</td>
<td>96.4</td>
<td>99.3</td>
</tr>
<tr>
<td>Regional</td>
<td>84.4</td>
<td>85.8</td>
<td>83.7</td>
</tr>
<tr>
<td>Distant</td>
<td>24.3</td>
<td>32.9</td>
<td>21.9</td>
</tr>
<tr>
<td>Unstaged</td>
<td>50.0</td>
<td>71.6</td>
<td>45.3</td>
</tr>
<tr>
<td>In Situ</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Back to Question: Any Headway or Not?

• What are the current recommendations on screening?

• Have recurrence rates improved with treatments driven by the newer prognosticators?

• Does endocrine therapy (Tamoxifen, Arimidex) improve survival?

• Has there been any advances on morbidity?

• Has there been improvement in survival for metastatic disease?
What are the current recommendations on Screening?

- Collected data over last several decades has allowed improved strategies on effective screening by stratifying those at different risk levels into guidelines on when to start screening as well as when to stop.

- Based on the risk/benefits of screening.

- Self-breast examination is currently under debate as to value.
Have recurrence rates improved with treatments driven by the newer prognosticators?

- Majority diagnosed at early stage (only 5% have evidence of metastasis at presentation)
- Treatment has delayed recurrence as it is more directed at tumor subtypes and improved stratification due to upgrading
- Adding Genomics provides risk assessment for recurrence allowing better decisions on whether or not to treat with chemo- especially for Stage I/II node negative
- What has been driving the improved mortality appears to be the advances in stratifying breast cancer subtypes and subsequently selecting better patient populations for targeted therapy
Does Endocrine Therapy improve survival?

- Study comparing 5 and 10 years of Tamoxifen:
  - Control study showed 25% mortality with 5 years of Tamoxifen as compared to control with 34% mortality
  - There was a 3% improved benefit with 10 years of Tamoxifen

This study concludes: 30% risk reduction with endocrine therapy

From Lancet 2005; 365
Has there been any advances on morbidity?

- Reduced morbidity with SLN with 2% lymphedema versus 13% with the old gold standard approach of ALND
- Still have numerous adverse effects from aggressive chemotherapy/RT
- Increase use of endocrine therapy which has low risk for adverse effects (some increase in DVT, PE with tamoxifen and some increase osteoporosis with AIs)
- Next 10 years to really tell as current treatment continues to have significant side effects
- More aggressive and early treatment has higher incidence of long term effects with continued morbidity concerns
- Overdiagnosis by overscreening has its own morbidity issues
Has there been improvement in survival for metastatic disease?

- SEER Data has clearly shown improvement

- No clear data to show benefit with early diagnosis of metastatic disease, however the survival is improving, but no difference whether diagnosed early or later

- 5 year survivals and relative mortality by age of diagnosis graphs have shown improvement over the decade

- Recurrence rates for triple negative are still grim

- HER 2 positive may have improved survival due to traz however they have high recurrence rate
Headway.....

• Due to better screening, majority diagnosed at early stage (only 5% have evidence of metastatic disease)

• Treatment has delayed recurrence as it is more directed at tumor subtypes and improved stratification due to upstaging

• Less morbidity with SLN

• Genomics allowing better stratification of recurrence rates to make better decisions on whether to treat with chemo or not

• Next generation Genome Sequencing will drive the new advances over this decade

• Good prognosis for ER+,PR+, HER 2 neg/pos receptor status
Headway.... OR NOT

• Morbidities with treatment

• Still no cure for metastatic disease

• Poorer prognosis still for triple negative BC as they are aggressive and metastasize earlier

• 25-30% with invasive BC die and there is increased mortality risk for at least 20 years after initial diagnosis and treatment

• Breast cancer that recurs will do so within 3 years in 60-80% of cases.

• Thus 20-40% of recurrences will be after 3 years
What to Watch For This Decade

• Next generation Breast Cancer Genome Sequencing

• Will drive the new therapies and we will likely see further reduction in mortality for BC as well as for other cancers

• Biologics will soon trump Staging
Breast Cancer Case Studies
Case 1:

52 year old female dentist applying for $500,000 of term life insurance

- Mother with breast cancer at 50, she is still alive. BRCA testing (-).
- Because of this family history, she started screening mammography at age 40 and in August, 2005 suspicious calcifications were noted prompting a biopsy that showed infiltrating ductal breast cancer.
- She had a lumpectomy & sentinel node bx:
  - final path: 1.6 cm high grade infiltrating ductal breast cancer, clear margins, ER(-), PR(-), Her 2/neu ab (+); nodes (-). Dx: T1c,N0,M0.
- She was treated at MD Andersen receiving 6 months of chemotherapy completing treatment in April, 2006.
- She is followed yearly with mammograms which have been normal.

How would you assess this risk?
Case 1

Risk Issue: Early stage breast cancer in young female 10 yrs ago s/p optimal treatment and without recurrence.

- **Favorable factors**
  - Young age
  - BRCA (-)
  - Early stage breast cancer
  - Her 2/neu ab +
  - Appropriate treatment & follow-up

- **Unfavorable factors**
  - Young age
  - High grade histology
  - Hormone receptors (-)

- **Risk assessment:** *Life – Standard*
Case 1:

52 year old female dentist applying for $500,000 of term life insurance

- Mother with breast cancer at 50, she is still alive. BRCA testing (-).
- Because of this family history, she started screening mammography at age 40 and in August, 2005 suspicious calcifications were noted prompting a biopsy that showed infiltrating ductal breast cancer.
- She had a lumpectomy & sentinel node bx:
  - final path: 1.6 cm high grade infiltrating ductal breast cancer, clear margins, ER(-), PR(-), Her 2/neu ab (+); nodes (-). Dx: T1c,N0,M0.
- She was treated at MD Andersen receiving 6 months of chemotherapy completing treatment in April, 2006.
- Her treatment was complicated by CHF d/t a drug-induced cardiomyopathy that has resolved. Most recent echo WNL.
- She is followed yearly with mammograms which have been normal.
Case 2

66 year old female radiologist applying for $5,000,000 WL.

– In 2008, she had an abnormal mammogram with suspicious calcifications noted in the left upper quadrant of her right breast; biopsy showed DCIS.

– She underwent a lumpectomy which confirmed a single, grade 2 12 mm DCIS with clear wide margins, ER (+), PR (+), HER2 (-). No comedonecrosis.

– She was then treated with 5 years of tamoxifen.

– She is followed closely with yearly mammograms; her most recent this year was BIRADS 2 (OK).

How would you assess this risk?
Case 2

Risk Issue: DCIS in older woman

• Favorable factors
  – Older age applicant
  – DCIS – small, single lesion & without comedonecrosis
  – Optimal treatment with surgery with wide clear margins
  – Good follow-up without recurrence

• +/- Prognostic factor
  – Hormone receptors (+)

• Unfavorable factors
  – Grade 2

• Risk assessment: Life - Standard, Preferred as qualifies
Case 3

61 year old female pediatrician applying for $2,000,000 term life insurance

– Family history of premenopausal breast cancer in her mother and sister; subsequently all tested (+) for BRCA 1.

– At age 46 (fifteen years ago), she was found to have an intermediate grade infiltrating ductal carcinoma of the breast.
  • Path: 2.4 cm lesion; 3/8 movable axillary nodes +, ER (+), PR (+). Her2/neu ab (-); Metastatic w/u was negative; Dx: Stage IIB: T2N1M0 infiltrating ductal breast cancer

– Treated with bilateral mastectomies & reconstruction and chemotherapy and subsequently received 5yrs of tamoxifen.

– Followed closely with physical exams and CA27.29, no mammograms; no recurrence.

How would you assess this risk?
Case 3

- Risk Issue: Node (+) breast cancer in young woman
- Favorable factors:
  - Young age
  - While she is node (+), they were movable and level 1
  - ER & PR (+)
  - Her 2/neu ab (-)
  - She received appropriate treatment & follow-up
  - She is now 15 years out and is without recurrence
- Unfavorable factors:
  - Young age
  - BRCA 1 (+)
  - Nodal involvement
  - Intermediate grade histology
- Risk assessment: **Life - Low substandard**;