# Breast Cancer Care Update 2011

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Provincial Chair, Alberta Breast Cancer Program  
Palliative Care Conference – October 24, 2011

## Themes

### The Perversity of Cancer Diversity
- Heterogeneity (Breast Cancer + Patient)

### Forgone Lexicon
- Out with the old, in with the “new” language of Breast Ga

### Treat to beat or treat to retreat?
- What is the treatment intent? What is the target
- Moving towards individualized therapy

## Breast Cancer

### Who Gets it? + Why?

### Breast Cancer Risk Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative risk</th>
<th>High risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>2.5-3.0</td>
<td>General population</td>
</tr>
<tr>
<td>Geographic location</td>
<td>3.0-5.0</td>
<td>Developed countries</td>
</tr>
<tr>
<td>Age spectrum</td>
<td>2.5</td>
<td>70-79 yrs.</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>2.5</td>
<td>50-59 yrs.</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>2.5</td>
<td>60-69 yrs.</td>
</tr>
<tr>
<td>Family history</td>
<td>2.5</td>
<td>History of breast or ovarian cancer</td>
</tr>
<tr>
<td>Ethnic Background</td>
<td>2.5</td>
<td>African American</td>
</tr>
<tr>
<td>Previous breast cancer</td>
<td>2.5</td>
<td>History of breast or ovarian cancer</td>
</tr>
<tr>
<td>Presence of breast cancer in relatives</td>
<td>2.5</td>
<td>History of breast or ovarian cancer</td>
</tr>
<tr>
<td>Family history</td>
<td>2.5</td>
<td>History of breast or ovarian cancer</td>
</tr>
<tr>
<td>Genetic predisposition</td>
<td>2.5</td>
<td>BRCA1, BRCA2</td>
</tr>
<tr>
<td>Smoking History</td>
<td>2.5</td>
<td>History of breast or ovarian cancer</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>2.5</td>
<td>History of breast or ovarian cancer</td>
</tr>
<tr>
<td>Hormone replacement</td>
<td>2.5</td>
<td>History of breast or ovarian cancer</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>2.5</td>
<td>History of breast or ovarian cancer</td>
</tr>
</tbody>
</table>

FHx = 15-20%

## Genetic ~ 5-6% of all

<table>
<thead>
<tr>
<th>Genes</th>
<th>Associated syndromes</th>
<th>Chromosome site</th>
<th>Gene frequency</th>
<th>Gene predisposition for breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCAl</td>
<td>MSCI</td>
<td>17q21-22</td>
<td>1 in 100</td>
<td>Very high</td>
</tr>
<tr>
<td>BRC2</td>
<td>MSCI</td>
<td>13q11-13</td>
<td>1 in 100</td>
<td>Very high</td>
</tr>
<tr>
<td>LBD</td>
<td>Li-Fraumeni</td>
<td>13q12-q13</td>
<td>1 in 100</td>
<td>Very high</td>
</tr>
<tr>
<td>PTEN</td>
<td>Cowden</td>
<td>10q22-23</td>
<td>1 in 100</td>
<td>Very high</td>
</tr>
<tr>
<td>ATM</td>
<td>Li-Fraumeni</td>
<td>11q22-23</td>
<td>1 in 100</td>
<td>Very high</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Noonan</td>
<td>3p14.3</td>
<td>1 in 100</td>
<td>Very high</td>
</tr>
</tbody>
</table>

**++ Many Others**
- Lesser genetic mutations
- Polymorphisms
- SNP Variants
- Vast Majority Unknown...
**Why is Cancer, Cancer?**

- Growth - Self Signalling
- Evades Normal Cell Death “Suicide”
- Ignores anti-growth signals
- Promotes Blood Vessel Growth for Self
- Unlimited Replication
- Ability to Invade + Spread


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**Clinical Behavior of Breast Cancer**

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**The Spectrum of Disease**

- Rapid disease progression
- Extensive organ involvement
- Resistance to Treatment
- Death within weeks of diagnosis
- Long, slow disease course
- High sensitivity to treatment
- Long Term Survival

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**There is more than one type of “Breast Cancer”**

- HER2+
- ER-
- Luminal A
- ER+/Her2-
- Basal-like
- ER- / HER2 -
- Luminal B
- ER+

Sorlie T et al. PNAS 2001

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**The Law of the Instrument**

Maslow’s hammer

“It is tempting, if the only tool you have is a hammer, to treat everything as if it were a nail.”


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**Therapy needs to be tailored accordingly...**
Chemotherapy Drug Level Variability Among Patients Based on Genetic Polymorphisms

Uridine Glucuronosyltransferase 2B7 Pharmacogenetics Predicts Epirubicin Clearance and Myelosuppression (ASCO 2009, Abstract #2504)

M.B Sawyer, S. Damaraju, E. Phuskin, V. Damaraju, A.G. Scarfe, R.B. Bies, J. Hanson, M.J. Clemons, M. Kuzma, J.R. Mackey

Goals of Therapy

Treat to Beat? Or Treat to Retreat?

Early Stage Disease:

Treatment Goal = Cure

Visible Disease

Microscopic Residual Disease

\[ \text{Number of Cancer Cells} = 10^9 \]

\[ \text{Time} \]

“Cure” = 0 cancer cells

People are more willing to undergo toxic therapy if it means a chance at cure

Widespread “Incurable” Breast Cancer Treatment intent is Palliative

Treatment Goal = Disease Control

- Control cancer related symptoms
- Minimize treatment related toxicity
- Minimize interference in patient’s life
- Extend survival

Who Do We Treat? What Do We Treat With?

Prognostic Factor
- How bad is the cancer?
- Goal – to treat those @ highest risk (avoid Rx in low risk)

Predictive Factor
- What is the best treatment for the cancer
- Goal - Treat with most effective Rx (avoid giving ineffective Rx)
Estimating Benefit

- Clinical presentation
- Meta-analyses / Overview data
- Online calculators
  - Adjuvant!
    - based on SEER database / BC database
    - www.adjuvantonline.com
  - Numeracy
    - based on expert opinion
    - www.mayoclinic.com/calcs/adjuvant/index-bacals.cfm
- Gene Expression Analysis

Gene Expression Prognostic Signatures

- Molecular Classification
- Gene Expression Prognostic Signatures
  - Recurrence score
  - Hormone receptor status
  - Ki67
  - Grade

- Different Subtypes
  - Different Relapse/Mortality Risk
    - Constant Risk
      - Luminal HER2-negative subtypes
    - Variable Risk (Peak w/ 5 years of Dx then decline over time)
      - Non-luminal subtypes

Breast Cancer Stem Cell Hypothesis

Table 1: Commercially Available Genetic Assays for the Prediction of Clinical Outcome in Patients with Breast Cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Menzel-Aguilera</th>
<th>Clinical Health</th>
<th>Biometrics</th>
<th>Fluorescence</th>
<th>HER2 status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of assay</td>
<td>DGGE PCR</td>
<td>31-Gene recurrence score</td>
<td>2-Gene expression profile</td>
<td>1-2 copies of HER2</td>
<td>0-1 copies</td>
</tr>
<tr>
<td>Type of tissue sample</td>
<td>Formalin-fixed, paraffin-embedded</td>
<td>Formalin-fixed, paraffin-embedded</td>
<td>Formalin-fixed, paraffin-embedded</td>
<td>Fresh or frozen</td>
<td>Fresh or frozen</td>
</tr>
</tbody>
</table>

- Technique
  - DNA microarray
  - Q-RT-PCR
  - Q-RT-PCR
  - DNA microarray

- Sensitivity
  - 92.5%
  - 90.8%
  - 95.8%
  - 92.5%

- Specificity
  - 88.3%
  - 89.4%
  - 87.9%
  - 88.8%

- Positive predictive value
  - 90.7%
  - 91.6%
  - 90.5%
  - 91.4%

- Negative predictive value
  - 87.2%
  - 86.7%
  - 89.4%
  - 87.9%

- Additional information
  - All assays were performed on archival tissue
  - HER2 staining
  - 0-1 copies
  - 2 copies
  - 3 copies
  - 4 copies

- Risk factors
  - Age
  - Menstrual status
  - Family history
  - Menopausal status

- Outcome measures
  - Recurrence-free survival
  - Overall survival

- Conclusion
  - HER2 status is an important predictor of outcome
  - Genetic testing can help guide treatment decisions

Sotiriou S, NEJM Feb 19, 2009
Breast Cancer Potential Stem Cell Poisons

- Development of stable "stem cell" cultures
- Mass drug screening approach
- > 16,000 compounds
- 100x more potent than paclitaxel on breast cancer stem cells

Salinomycin (agricultural antibacterial compound)


Breast Cancer Treatment ER+ Disease

Goal = Stop / Halt / Kill ER+ Breast Cancer

Endocrine Therapy

Pre-menopausal
- GNRH Agonists
- Anti-estrogens
- SERMs
- Estrogen
- Aromatase Inhibitors
- Peripheral Aromatization

Postmenopausal
- LH, FSH
- Anti-estrogens
- SERMs
- Estrogen
- Antiesteremides
- Aromatase Inhibitors
- SERDs
- Peripheral Aromatization

Endocrine Therapy Resistance

New Treatment Strategies
Chemotherapy Regimens
Which one do we use and why?

We Need to Break Free from the Past
- Treatment Based on Gross Anatomical Features
  - LN(-) vs. LN(+)
- Treatment based on light microscopy alone
- Treat all people and all breast cancers “the same”

Take Home Messages
People + breast cancers are unique and therapy will need to be individualized
- Tumors
  - Need to sub-classify “breast cancer”
  - Need to better understand ‘at risk’ populations
  - Need to understand cancer resistance
  - Need to make sure we are hitting the right target
- Patient
  - Need to understand patient drug metabolism
  - Medication interaction, lifestyle factors