– Breast Cancer Care Update 2011 –

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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 Ca**

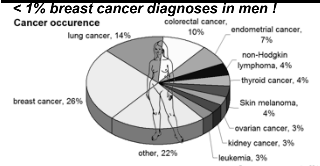
Treat to beat or treat to retreat?
- **What is the treatment intent ? What is the target**
- **Moving towards individualized therapy**

Breast Cancer

Who Gets it ?
+
Why ?

Women's Cancer
#1 Incidence #2 Mortality

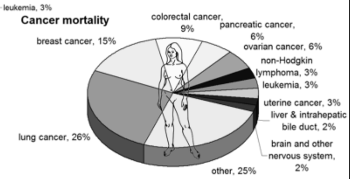
< 1% breast cancer diagnoses in men !



~ 1 in 9 women

- ***29 000 new cases / yr in Canada***

> 2000 new case / yr in AB



> 5400 deaths / yr Canada

Report on Cancer Statistics in Alberta – Nov 2009
Canadian Cancer Statistics 2009

Breast Cancer Risk Factors

Factor	Relative risk	High risk group
Age	> 10	Elderly
Geographical location	5	Developed country
Age at menarche	3	Menarche before age 11
Age at menopause	2	Menopause after age 54
Age at first full pregnancy	3	First child in early 40s
Family history	≥2	Breast cancer in first degree relative when young
Previous benign disease	4-5	Atypical hyperplasia
Cancer in other breast	>4	
Socioeconomic group	2	Groups I and II
Diet	1.5	High intake of saturated fat
Body weight:		
Premenopausal	0.7	Body mass index >35
Postmenopausal	2	Body mass index >35
Alcohol consumption	1.3	Excessive intake
Exposure to ionising radiation	3	Abnormal exposure in young females after age 10
Taking exogenous hormones:		
Oral contraceptives	1.24	Current use
Hormone replacement therapy	1.35	Use for ≥10 years
Diethylstilbestrol	2	Use during pregnancy

FHx + 15-20%

http://www.utoronto.ca/ois/SIA/2007/Breast%20Cancer/Risk%20Factors.jpg

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Genetic ~ 5-6% of all

Major breast cancer susceptibility genes

Gene	Associated syndrome	Chromosome site	Gene frequency	Gene penetrance for breast cancer
BRCA1	HBOC	17q21	Rare	Very high
BRCA2	HBOC	13q12-13	Rare	High
p53	Li-Fraumeni	17p13.1	Very rare	High
PTEN	Cowden	10q22-23	Very rare	High
ATM	Ataxia-telangiectasia (heterozygotes)	11q22-23	Common	Low to moderate
STK11	Peutz-Jeghers	19p13.3	Very rare	High

Uptodate 2010

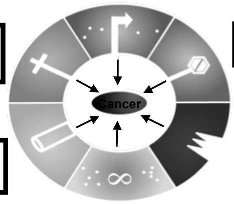
++ Many Others
- ***Lesser genetic mutations***
- ***Polymorphisms***
- ***SNP Variants***
- ***Vast Majority Unknown…***

Why is Cancer, Cancer ?

Growth - Self Signalling

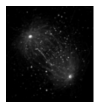
Evades Normal Cell Death "Suicide"

Ignores anti-growth signals



Promotes Blood Vessel Growth for Self

Ability to Invade + Spread



Unlimited Replication

Modified from - Hanahan D, et al. Cell. 2000;100:57-70.

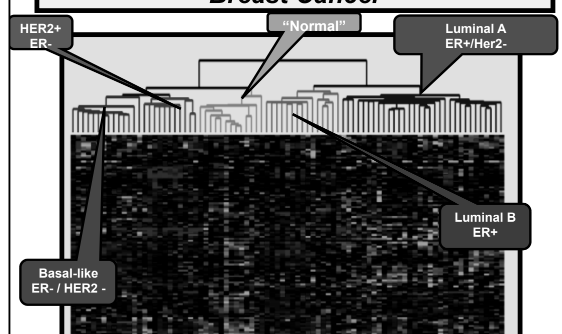
Clinical Behavior of Breast Cancer

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

There is more than one type of "Breast Cancer"



Sorlie T et al, PNAS 2001

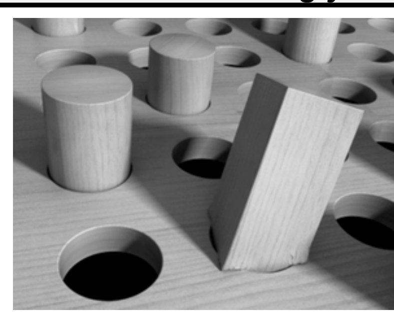
The Law of the Instrument

Maslow's hammer

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

Abraham H. Maslow (1966). The Psychology of Science. p. 15

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)

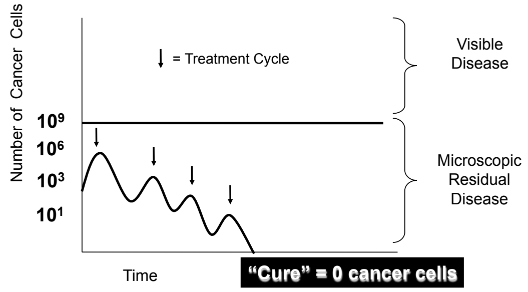
M.B Sawyer, S. Damaraju, E. Pituskin, V. Damaraju, A.G. Scarfe, R.B. Bies, J. Hanson, M.J. Clemons, M. Kuzma, J.R. Mackey

Goals of Therapy

Treat to Beat ?
Or
Treat to Retreat ?

Early Stage Disease:

Treatment Goal = Cure



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

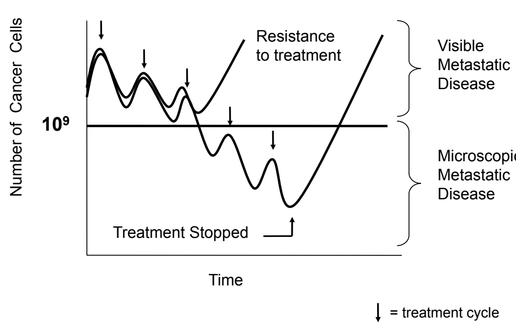
Widespread "Incurable" Breast Cancer Treatment intent is Palliative

Treatment Goal = Disease Control

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

Quality **O**f **L**ife

Metastatic Breast Cancer Rx



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)**

P**redictive Factor**
- What is the best treatment for the cancer
- **Goal - Treat with most effective Rx (avoid giving ineffective Rx)**

Estimating Benefit

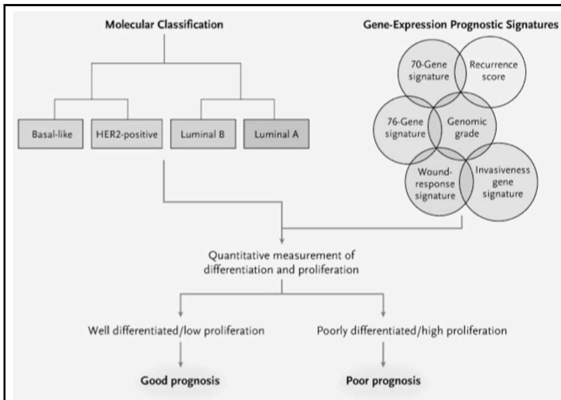
- Clinical presentation
- Meta-analyses / Overview data
- Online calculators
  - *Adjuvant!*
    - based on SEER database / BC database
    - www.adjuvantonline.com
  - *Numeracy*
    - based on expert opinion
    - www.mayoclinic.com/calcs/adjuvant/index-bcacalc.cfm
- Gene Expression Analysis

Table 1. **Commercially Available Genomic Assays for the Prediction of Clinical Outcome in Patients with Breast Cancer.***

Variable	MammaPrint	Oncotype DX	Theros	MapQuant Dx
Provider	Agendia	Genomic Health	Biotheranostics	Ipsogen
Type of assay	70-Gene assay	21-Gene recurrence score	2-Gene ratio of HOXB13 to IL17R (H/I) and molecular-grade index	Genomic grade
Type of tissue sample	Fresh or frozen	Formalin-fixed, paraffin-embedded	Formalin-fixed, paraffin-embedded	Fresh or frozen
Technique	DNA microarrays	Q-RT-PCR	Q-RT-PCR	DNA microarrays
Centrally certified laboratory†	Yes	Yes	Yes	Yes
Indication	To aid in prognostic prediction in patients <61 yr of age with stage I or II, node-negative disease with a tumor size of ≤5 cm	To predict the risk of recurrence in patients with ER-positive, node-negative disease treated with tamoxifen; to identify patients with a low risk of recurrence who may not need adjuvant chemotherapy	To stratify ER-positive patients into groups with a predicted low risk or high risk of recurrence and a predicted good or poor response to endocrine therapy	To restratify grade 2 tumors into low-risk grade 1 or high-risk grade 3 tumors, specifically for invasive, primary, ER-positive grade 2 tumors
Level of evidence (I–V)‡	III	II	III	III
FDA clearance	Yes	No	No	No
Availability	Europe and United States	Europe and United States	United States	Europe

* ER denotes estrogen receptor, FDA Food and Drug Administration, and Q-RT-PCR quantitative reverse-transcriptase–polymerase chain reaction.
† Laboratories were certified according to the criteria of the Clinical Laboratory Improvement Amendments or by the International Organization for Standardization.
‡ Levels of evidence are measured on a scale ranging from I (strongest) to V (weakest).[54]

Sotiriou S, NEJM Feb 19, 2009



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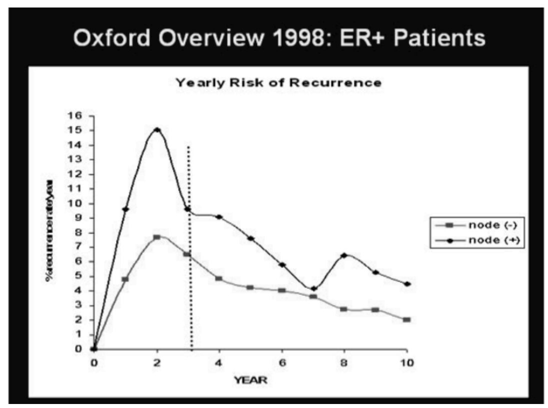
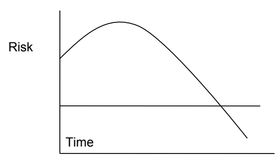


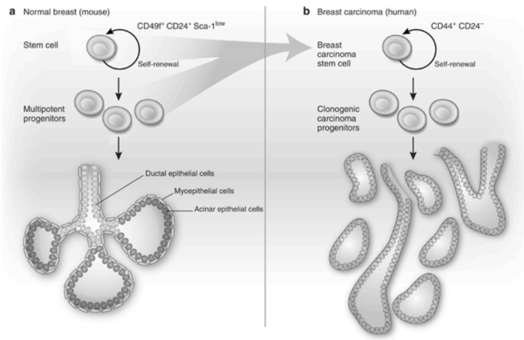
Different Subtypes
Different Relapse/Mortality Risk

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



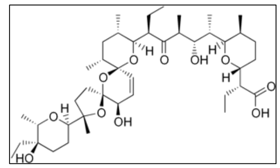
PLoS Med. 2010 May 25;7(5):e1000279.

Breast Cancer Stem Cell Hypothesis



Laboratory Investigation (2006) 86, 1203–1207. doi:10.1038/labinvest.3700488; published online 30 October 2006

Breast Cancer
Potential Stem Cell Poisons



Salinomycin
(agricultural antibacterial compound)

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

P. Gupta et al. Cell. August 2009

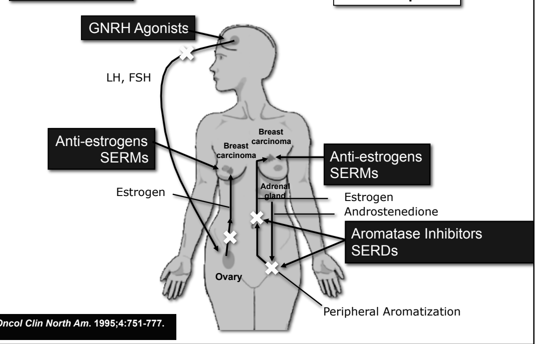
Breast Cancer Treatment
ER+ Disease

Goal = Stop / Halt / Kill
ER+ Breast Cancer

Endocrine Therapy

Pre-menopausal

Postmenopausal



***Surg Oncol Clin North Am.* 1995;4:751-777.**

Endocrine Therapy Resistance

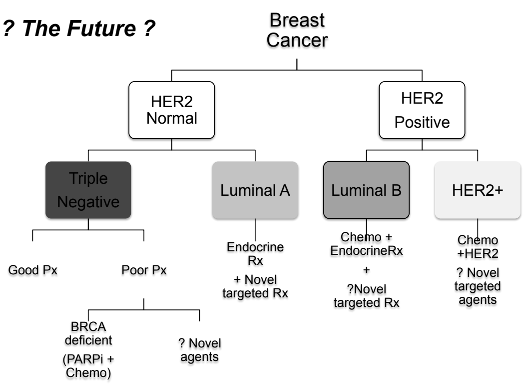
New Treatment Strategies

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"

? The Future ?



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