TRIPLE NEGATIVE BREAST CANCER

Finding the Positives in Triple-Negative Breast Cancer: A Three-Part Live CME Webcast Series

Seminar I: Wednesday, March 3, 2010, 8:00 PM - 9:00 PM EST

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Disclosures for Moderator Neil Love, MD

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Agenda

Module 1 — Dr Hudis

- Breast cancer demographics based on ER, PR and HER2 phenotype
- Presenting stage and prognosis of triple-negative breast cancer (TNBC)
- Sites of metastatic disease
- Potential heterogeneity of TNBC: Example — Targeting the androgen receptor-positive subset

Case Presentation from Dr Hudis

Panel Discussion

Response to Audience Questions/Cases

Agenda

Module 2 — Dr Carey

- Intrinsic subtypes of breast cancer
  - Challenges in classification
  - Overlap of TNBC and basal subtype
  - Clinical and research implications of BC subtypes
- BRCA mutations and "BRCAness"
- Claudin-low subtype

Case Presentation from Dr Carey

Panel Discussion

Response to Audience Questions/Cases

Submit a Challenging Case or Question

- Use the text box at the bottom-left of the screen to type in a case or question. You may also submit a case or question by phone at (866) 447-3623.
- You may include your full name, city and state of practice or you may choose to remain anonymous.
- Select entries will be discussed and reviewed by our esteemed faculty during the hour-long segment.

Seminar Overview

- This is the first of three unique online, integrated educational courses. Additional seminars will take place on March 11 and March 16, from 8:00 PM — 9:00 PM EST.
- An archive of these webcasts will also be available on **www.ResearchToPractice.com** within three days of the broadcast.
- Please remember to complete your CME evaluation. A link will be provided at the conclusion of each seminar.

54-yo presented with an abnormal mammogram showing a nodular density at 12:00. Core bx: invasive mammary duct carcinoma, Grade I/II, focus of LVI, ER/PR/HER2-negative. Mastectomy (patient preference): 1.2-cm, Grade II/III invasive duct cancer, 2/2 negative SLN, ER/PR/HER2-negative.

Should such patients be considered for BRCA1/2 testing even in the absence of other risk factors for a genetic predisposition?

— Patricia DeFusco, MD
Hartford, CT

Is there a difference between BRCA1 triple-negative breast cancer and those that are BRCA-negative?

— William Harwin, MD
Fort Myers, FL

TNBC | TRIPLE NEGATIVE BREAST CANCER

Triple-Negative Breast Cancer

Clifford Hudis, MD
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New York, New York

Disclosures for Clifford Hudis, MD

Advisory Committee	Amgen Inc, Boehringer Ingelheim Pharmaceuticals Inc, Genentech BioOncology, Roche Laboratories Inc
Paid Research	AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation

N/A = Not Applicable

Epidemiology

- Breast cancer is one of the most common life-threatening cancers in American women
  - Estimated 192,000 new cases will be diagnosed in 2009
  - Approximately 40,000 women will die from breast cancer in 2009
  - Lifetime risk: Approximately 1:8 will develop breast cancer

American Cancer Society. *Detailed Guide: Breast Cancer: What are the Key Statistics for Breast Cancer?* Available at: http://www.cancer.org. Accessed Sept. 14, 2009.

Epidemiology

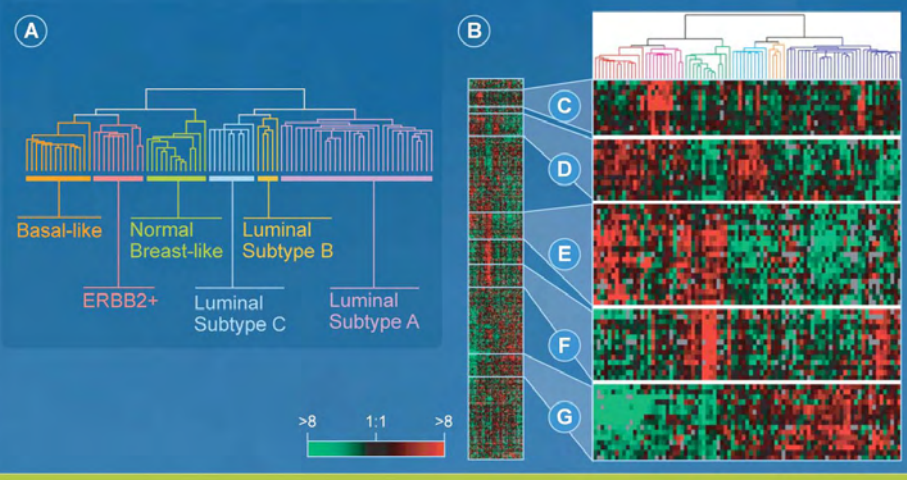
2009*	Cases (713,220 new cases)	Deaths (269,800 deaths)
Breast	27%	15%
Lung & bronchus	14%	26%
Colon & rectum	10%	9%
Uterine corpus	6%	3%
NHL	4%	4%
Melanoma of skin	4%	1%
Thyroid	4%	< 1%
Kidney/renal pelvis	3%	2%
Ovary	3%	5%
Pancreas	3%	6%

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

Available at: http://www.cancer.org. Accessed Sept. 3, 2009

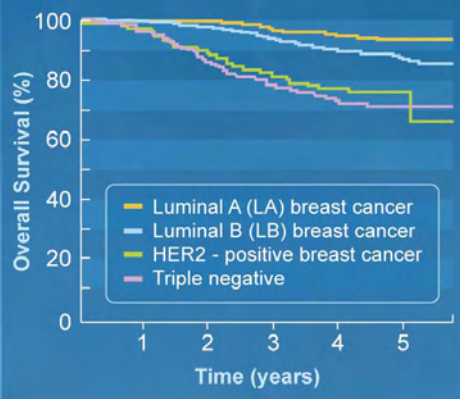
American Cancer Society. *Cancer Facts & Figures 2009*.

Breast Cancer Is Not One Disease: Intrinsic Subtypes



Sorlie et al, 2001

Breast Cancer Is Not One Disease: Survival by Subtypes in BCIRG 001



Number of patients at risk						
	Years					
	0	1	2	3	4	5
LA breast cancer	211	209	209	201	183	47
LB breast cancer	810	800	784	751	636	162
HER2 - positive breast cancer	113	107	98	89	73	20
Triple negative	192	183	163	148	119	30

Hugh J, et al. *J Clin Oncol* 2009;27:1168-1176

Pathologic and Molecular Features of TNBC

- High proliferative rate, pushing border of invasion, and central necrosis
- Associated with high expression of:
  - Ki-67
  - p16
  - p53
  - EGFR
  - BRCA1 mutations

Proposed Risk Factors

- Further research is needed to establish individual risk factors for TNBC
- Possible risk factors for TNBC:
  - BRCA mutation / Family Hx
  - Young and premenopausal women
  - African-American women
  - Younger age at first birth
  - High parity

NOTE: Watch for confounding effect of lower socioeconomic status

Schneider BP, et al. *Clin Cancer Res* 2008;14: 8010-8018;
Winkeljohn DL. *Clin J Oncol Nurs* 2008;12: 861-863

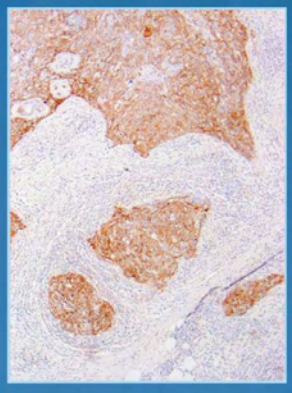
Characteristics and Features of TNBC Phenotype

- Often present with interval cancers
- Weak relationship between tumor size and nodal status
- Peak risk of recurrence at 1 to 3 years
- Increased mortality rate first 5 years
- Majority of deaths occur within first 5 years
- Rapid progression from distant recurrence to death

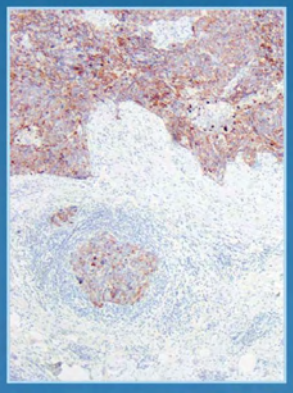
Is Triple-Negative Breast Cancer Really One Disease?

Protypical Basal-Like Carcinoma

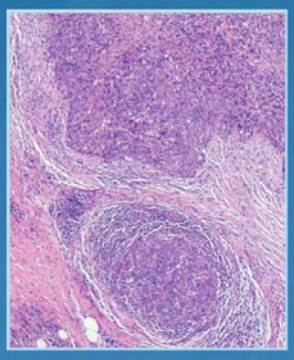
EGFR Positive



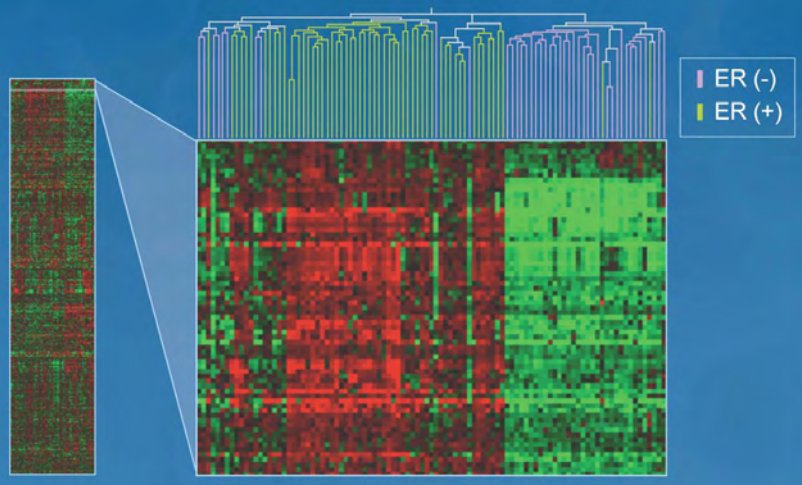
CK 5/6 Positive



Triple Negative

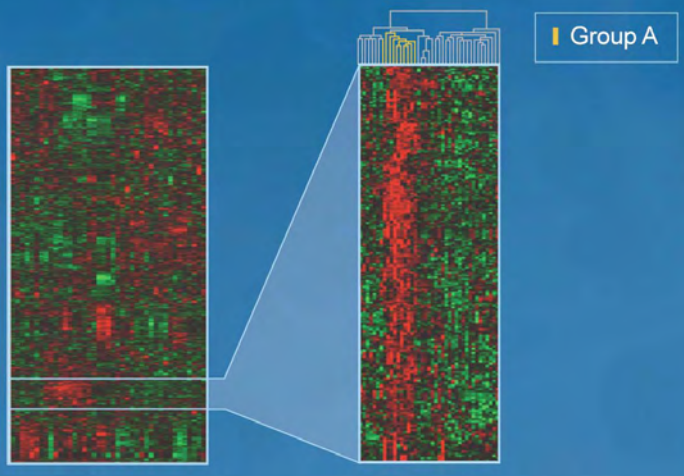


Unsupervised Cluster Analysis of 99 Primary Breast Carcinomas



Doane et al, *Oncogene* (2006) 25: 3994

Unsupervised Cluster Analysis of 41 ER(-) Tumors



Doane et al, *Oncogene* (2006) 25: 3994

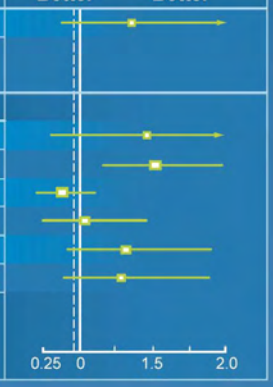
A Brief History of Platinums
(Bind & cause cross-linked DNA triggering programmed cell death)

1845	Peyrone described cis-PtCL2(NH3) "Peyrone's Salt" *(Ann Chemie Pharm* 1845, 51: 129)
1893	Werner deduced structure
1960s	Rosenberg and van Camp discover that electrolysis of a platinum electrode produces CDDP. This inhibits E. coli. (They grow very large but don't divide.) *(Nature* 1965, 205 (4972): 698–699)
1971	Clinical trials begin
1978	FDA approval: ovary and testes
1989	FDA approval: for CBDCA in ovary (similarly forms preferential cross-links with guanine in DNA, cross-resistant w/ CDDP)

"Class" now includes alkylating-like agents: Nedaplatin, Oxaliplatin, Triplatin tetranitrate, & Satraplatin

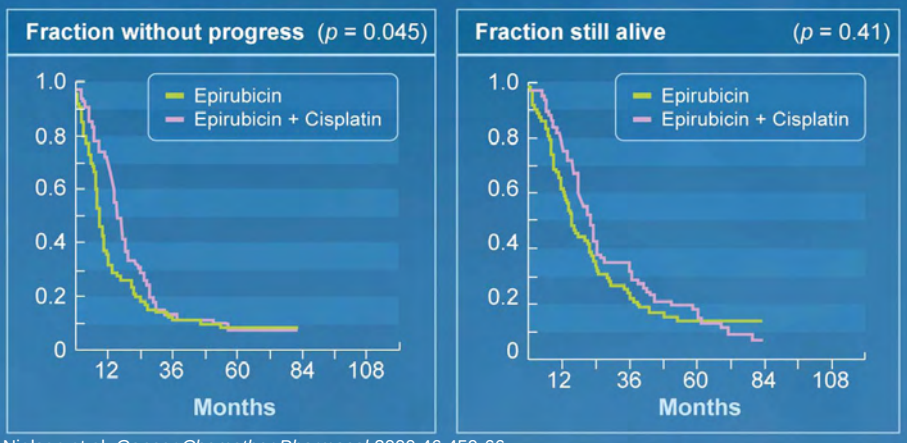
Chemotherapy Systemic Review

Study Name	Regimens: Poly (Anthra)	Regimens: Poly (No Anthra)
Poly (Anthra) vs Poly (No Anthra)		
1984 Creagan	CA + CDDP → CF + P	CF + P ± V
NOTE: Other studies from 1976-1996 are not shown		
Poly (Anthra) vs Poly (No Anthra) + P		
1981 Carmo - Pereira	VAC	CMF + P
1982 Tormey	AV	CMF + P
1983 Smalley	FAC	CMFV + P
1985 Cummings	FAC	CMF + P
1989 Rosner	AC	CMFV + P
1989 Rosner	AC	CF + P



Modified from Fossati et al *JCO* 1998, 16:3439-60

Epi vs Epi/CDDP
(n = 139)



Nielsen et al. *Cancer Chemother Pharmacol* 2000;46:459-66

Single Agent Pre-Op CDDP: DFCI 04-183

- 14/28 responded
  - (6/28 pCR)
    - 2 BRCA 1 mutants w/ pCR
    - 4 pCRs were NOT heterozygotes
- 4/26 (15%) with sporadic TNBC with pCR to single agent chemotherapy…
- Consider: (among responders to CVAP x 4)
  - CVAP 4 vs Docetaxel x 4, CR increased from 15% to 34% (19% higher w/ the taxane) Smith et al. *JCO* Mar 15 2002;1456-1466.

Silver DP et al. *J Clin Oncol* 2010;[Epub ahead of print].

CALGB 40603: 2x2 Factorial Design

- Eligibility: Stage IIA-IIIA ER/PR-poor (<10),HER2 neg.
- Pretreatment evaluation: Tissue and blood samples
- Primary Objectives (overall & in basals defined by array):
  - Does Bev add to weekly paclitaxel (+/- CBDCA)?
  - Does q 3 wk CBDCA add to wkly paclitaxel (+/- Bev)?

N = 362	Bev	No Bev
Weekly P	90 - 91	90 - 91
Carbo Weekly P	90 - 91	90 - 91

Courtesy W Sikov

Other Rx Targets in TNBC

"There is currently no specific systemic regimen recommended for the treatment of triple-negative breast cancers, and little data on which to base treatment selection."

Treatment	Target	Rationale & Nature of Evidence	Accrued & Ongoing Studies
Cytotoxic chemotherapy with agents that cause interstrand breaks (eg, platinum-based drugs) and double-stranded breaks but not with agents that target mitotic-spindle apparatus (eg, vinca alkaloids and taxanes)	DNA	Abundant DNA aberrations suggest defective DNA repair Evidence of deficient BRCA1 In vitro evidence for selective chemosensitivity (in BRCA1 carriers) No clinical evidence	Study planned to assess activity of platinum-based drugs compared with taxanes (BRCA1 triple-negative cancersand sporadic triple-negative cancers)
PARP1 inhibition	PARP1	Evidence of deficient BRCA1; In vitro data showing activity (in BRCA1 carriers)	Phase I studies

Cleater S, Heller W, Coombes RC, *Lancet Oncology* 2007;8:235-44

Other Rx Targets in TNBC

Treatment	Target	Rationale & Nature of Evidence	Accrued & Ongoing Studies
Antibody treatment (eg, cetuximab); Small molecule inhibitors of receptor tyrosine kinase activity (eg, gefitinib)	EGFR	Overexpression of EGFR; No evidence of activity to date	Phase II studies
c-KIT tyrosine kinase inhibitor (eg, imatinib)	c-KIT	Overexpression of c-KIT; No evidence of activity to date	Phase II studies
Multikinase inhibitors (eg,lapatinib and pertuzumab)	EGFR/ERBB2	Overexpression of EGFR; No evidence of activity to date	Phase II studies
Second-messenger inhibition	Second messengers (eg, Ras farnesylation, Raf, MEK, MTOR, Src, HSP90)	High proliferative rate No evidence of activity to date	Phase I and II studies

Cleater S, Heller W, Coombes RC, *Lancet Oncology* 2007;8:235-44

Summary

- TNBC is not one disease
- Standard treatment consists of chemotherapy (+/- Bev…)
- Need to further develop targets and therapies
- Need to rationally develop combinations
- May inform treatment for other epithelial malignancies

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I have a subset of patients with "triple-negative" breast cancer who are older (70s and 80s) whose tumors have apocrine features and appear to behave very indolently. Some of them are androgen receptor-positive (test ordered by my local pathologist after noting apocrine features). This subset seems quite different clinically from the "BRCA-like" or basaloid group. How do these subtypes differ on a molecular level? Is there a role for antiandrogen therapy?

— Karen Tedesco, MD
Schenectady, NY

Case from Dr Clifford Hudis

- 45-yr-old woman presents with metastatic, biopsy-proven (liver) breast cancer, ER–, PR–, HER2 neg. After 7 months on docetaxel and bevacizumab, she has progression of disease.
- Her tumor is AR positive and she has mild symptoms.

Should one obtain BRCA 1 & 2 on all triple-negatives, regardless of age and lack of family history?

— Dr Raji McKenna
Willowbrook, IL

TRIPLE NEGATIVE BREAST CANCER

Intrinsic Subtypes and Triple Negative Disease

Lisa A Carey, MD
Medical Director, UNC Breast Center
University of North Carolina at Chapel Hill
Lineberger Comprehensive Cancer Center
Chapel Hill, North Carolina

Disclosures for Lisa A Carey, MD

Research Support/PI	N/A
Employee	N/A
Consultant	N/A
Major Stockholder	N/A
Speakers' Bureau	N/A
Scientific Advisory Board	N/A

N/A = Not Applicable

Unsupervised Gene Expression Array Analysis Gives Us Breast Cancer Intrinsic Subtypes

"**Unsupervised**" means analyzed without knowledge of clinical appearance or outcome

Intrinsic gene clusters that differentiate breast cancers into discrete groups:

- Hormone receptor-related genes
- HER2-related genes
- "Basal" genes
- Proliferation genes

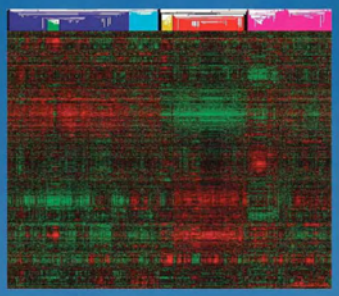


Image Courtesy C. Perou

Breast Cancer Subtypes and Prognosis

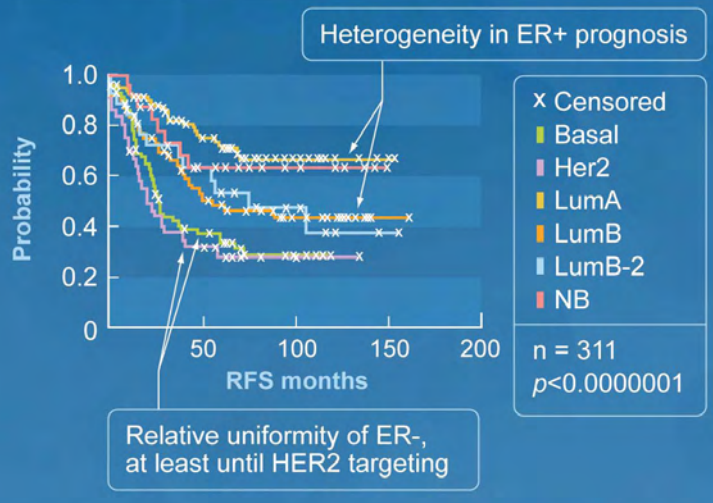
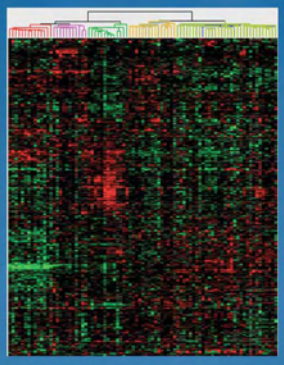


Image Courtesy C. Perou

Hormone Receptor-Driven: Luminal Subtypes

Majority of tumors:

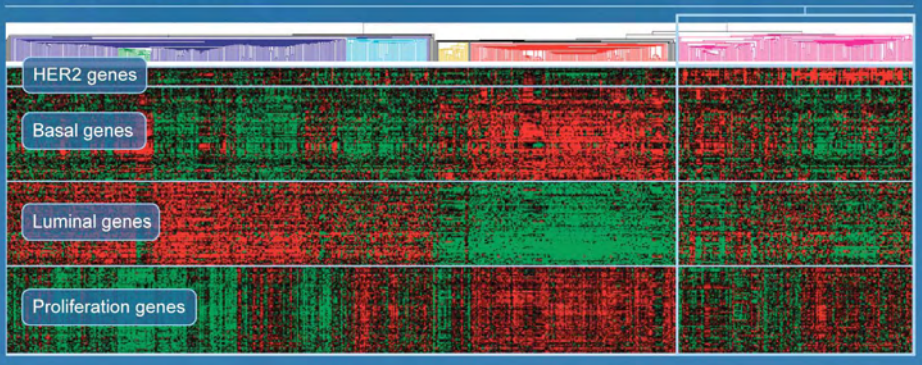
- High expression hormone receptor-related gene cluster.
- HER2 (+) or (-)
- Can be proliferative or not
- Most heterogeneous group



Sorlie T et al, *PNAS* 2001

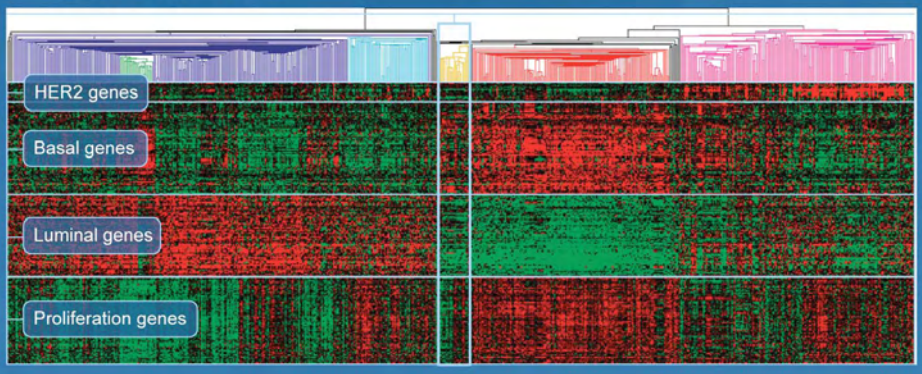
HER2-Enriched Subtype

- 15-20% of tumors
- High HER2 cluster expression
- Low ER (and related genes) cluster expression
- ER+ is a different subtype
- Very proliferative



Claudin-Low Subtype
(Recently described, still lots of questions)

- 5-10% of tumors
- Typically triple negative
- Low expression of cell-cell junction proteins
- Lymphocyte infiltrates
- Stem cell features

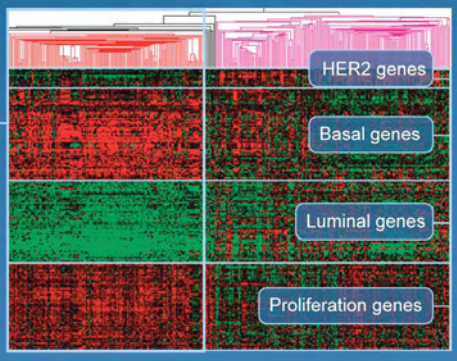


Basal-like (AKA "Triple Negative") Subtype

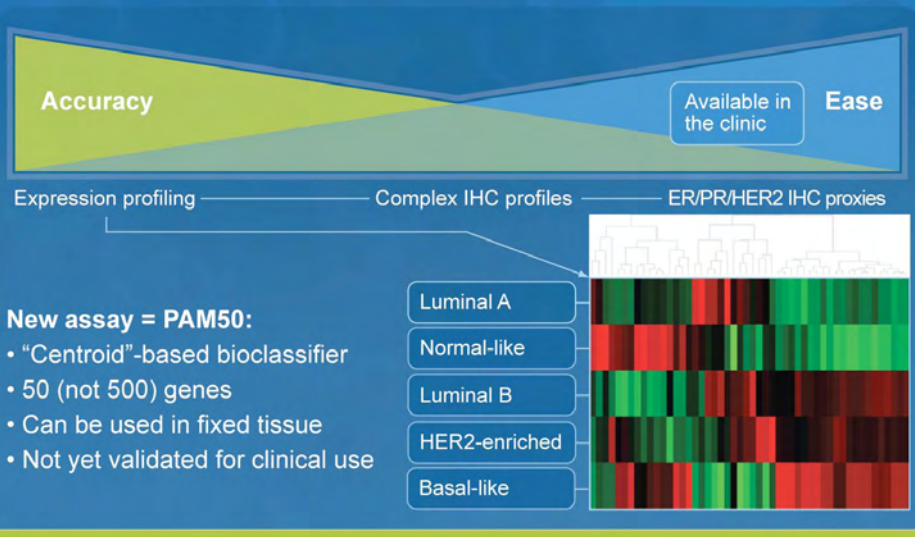
- About 15% of tumors
- Low expression of HER2 and ER-related genes
- High basal cluster (CK 5, 17, EGFR, αB crystallin, c-kit etc) expression
- Very proliferative

Abnormal DNA repair:

- Evidence of genomic instability
- Majority of tumors in BRCA1 mutation carriers
- Evidence of BRCA1 dysfunction even in sporadic tumors



Intrinsic Subtypes: How To Identify?



New assay = PAM50:

- "Centroid"-based bioclassifier
- 50 (not 500) genes
- Can be used in fixed tissue
- Not yet validated for clinical use

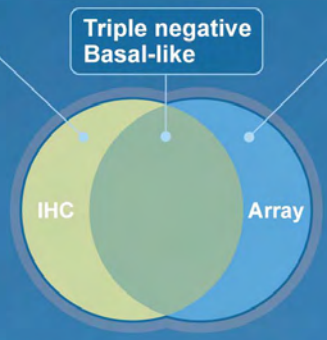
Overlap of Triple Negative and Basal-Like Breast Cancer

When we talk about "triple negative" breast cancer, we are mostly (but not entirely) talking about the basal-like molecular subtype

Triple negative Not basal-like

10-30%

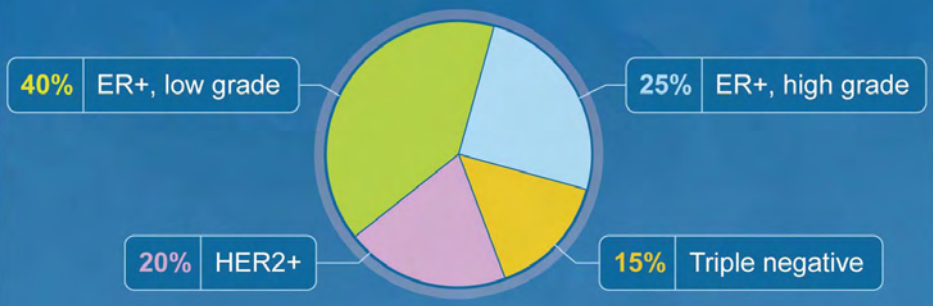
Can also include "claudin-low", a subtype notable for high expression of stem cell markers



Not triple negative Basal-like

15-40% are ER+, PR+, or HER2+

Triple Negative Breast Cancer is a Minority of Incident Breast Cancer



Only approximately 25,000-30,000 cases per year in U.S., but responsible for a disproportionate number of deaths

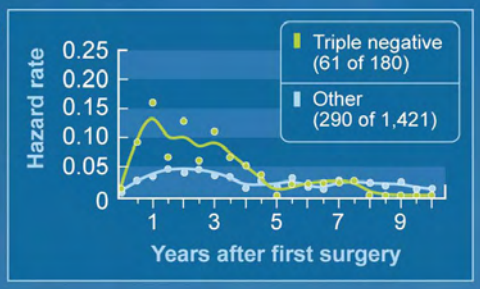
Triple Negative: Clinical Characteristics

Risk factors:
- Young
- African-American
- BRCA1 carriers (80%)

No consistent association with nodal status or stage

Relapse pattern:
- Higher risk
- Early timing
- Sites differ from luminal:
  - CNS 46% over time (Lin et al, *Cancer* 2008)

(1)



(2)

	N	Bone	Soft Tissue	Viscera
TNBC	79	13%	13%	**74%**
ER+	123	39%	7%	54%
HER2+	78	7%	12%	81%

(1) Dent, *Clin Cancer Res* 07; (2) Liedtke, *JCO* 08

Intrinsic Subtypes Often Have Reproducible Prognostic Profiles

Subtype	N	Recurrence Score	70-gene	Wound healing
Basal-like	**53**	**100%**	**100%**	**94%**
HER2+/ER-	35	100%	91%	100%
Luminal B	55	91%	84%	93%
Luminal A	123	29%	29%	63%

Although some triple negative breast cancers do well, currently available prognostic profiles are not useful in identifying them.

Fan C et al. *NEJM* 2006

Response To Chemotherapy Differs by Subtype (Triple Negative is Sensitive to Conventional Agents)

- Triple Negative is sensitive to conventional Agents
- Suggests that if cancer stem cells are present, they are killed in pCR

NEOADJUVANT T/FAC		
Classification	**RD**	**pCR**
Basal-like	11 (41%)	16 (59%)
HER2-enriched	17 (59%)	12 (41%)
LumA	36 (100%)	0 (0%)
LumB	22 (82%)	5 (18%)
Normal-like	13 (93%)	1 (7%)
Triple Negative	13 (50%)	13 (50%)
Any Positive	82 (80%)	20 (20%)
Triple Negative/Basal	6 (35%)	11 (65%)
Triple Negative/Non-Basal	7 (78%)	2 (22%)
Non-Triple Negative/Basal	4 (50%)	4 (50%)
Non-Triple Negative/ Non-Basal	78 (83%)	16 (17%)

Parker et al. *J Clin Oncol* 2009

Risk Factors for Basal-like May Be Different, Potentially Modifiable

	Adjusted OR Cases vs Controls	
n = 1424 pop.-based	Luminal A (n = 796)	Basal-like (n = 225)
Menarche < 13	1.1 (0.9-1.3)	1.4 (1.1-1.9)
> 3 children	0.7 (0.5-0.9)	1.9 (1.1-3.3)
Waist:hip > 0.84	1.5 (1.1-1.9)	2.3 (1.4-3.6)
First birth < 26	0.7 (0.5-0.9)	1.9 (1.2-3.2)
Breastfeeding ≥ 4m	0.9 (0.7-1.1)	0.7 (0.4-0.9)
BMI ≥ 30	0.8 (0.6-1.0)	0.8 (0.6-1.2)

Varying **magnitude** of effect

Varying **direction** of effect

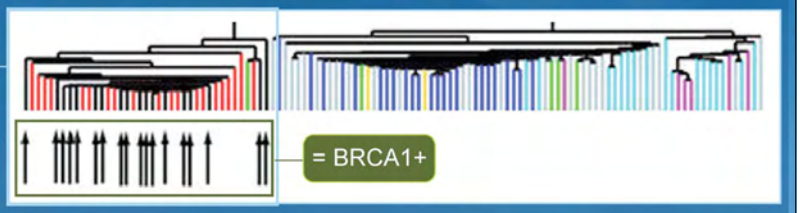
If confirmed 68% of basal-like breast cancer in young African-American women could be prevented through weight control and breast feeding!

Basal-like Breast Cancer and BRCA1

- Most BRCA1 carriers get basal-like breast cancers
- Shared characteristics with sporadic basal-like: *"BRCAness"*

(1)

Basal-like



(2)

High grade	DCIS less common
ER- and HER2-negative	Lymphocytic infiltrate
C-myc amplified	TP53 mutations
Medullary	Basal phenotype
Pushing margins	EGFR expression

(1) Sorlie T, *PNAS* 2003; (2) Modified from Turner N, *Nat Rev Cancer* 2004

Why Would It Matter if BRCA1 and Sporadic Basal-like Cancers are Similar?

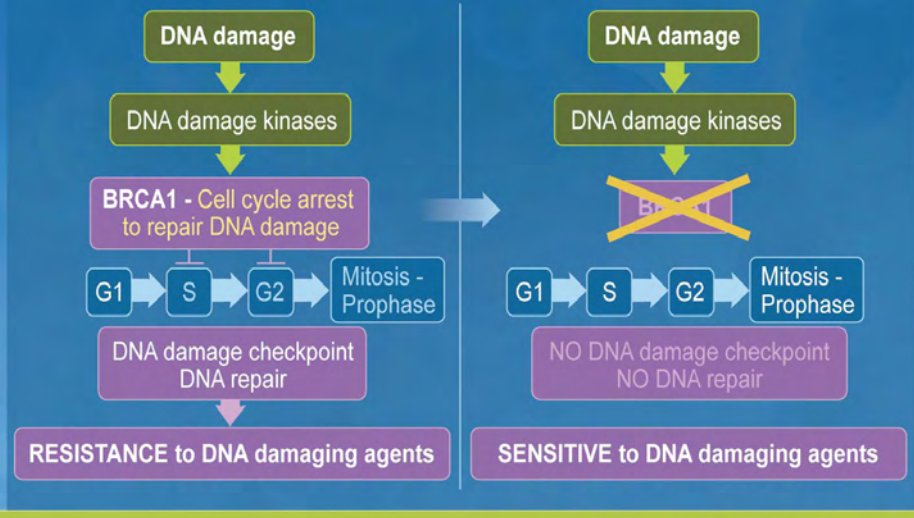
- BRCA1 is a key mediator of DNA damage repair:
  - Implications for chemosensitivity
  - Implications for targeted agents with PARP inhibition

DNA Damage Repair

Damaging Agents	• X-rays • Oxygen radicals • Alkylators • Spontaneous reactions	• UV light • Polycyclic aromatic hydrocarbons	• X-rays • Chemotherapy (cis-Pt, MMC)	• Replication errors
Damage	• Uracil • Abasic site • B-oxoguanine • Single-strand break	• (6-4)PP Bulky adduct CPD	• Interstrand cross-link • Double-strand break	• A-G mismatch • T-C mismatch • Insertion • Deletion
Repair Process	• Base-excision repair (BER) **(PARP-dependent)**	• Nucleotide-excision repair (NER)	• Recombinational (Homologous, End Joining) **(BRCA1-dependent)**	• Mismatch Repair

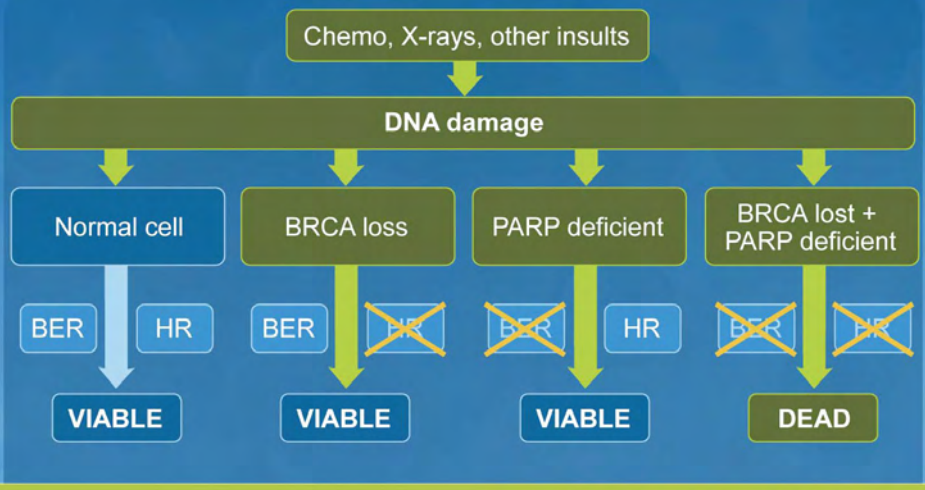
Modified from Hoeijmakers JH, *Nature* 2001

Specific Therapy Implications of BRCA1 Dysfunction (Theory, not Fact)



Modified from Kennedy, *JNCI* 2004

BRCA Loss and PARP Inhibition = Synthetic Lethality



Adapted from Comen and Robson, *Oncology* 2010

Summary

- The intrinsic subtypes reflect biologic differences among different classes of breast cancer.
- There really IS a fundamental difference between hormone receptor-positive and -negative disease.
- The most difficult therapeutic challenge is the basal-like subtype, which comprises the majority of “triple negative” breast cancer.
  - Unique risk factor profile raises questions about prevention!
  - Sensitive to modern chemotherapy, but relapses are early and common.
- Therapeutic implications of “BRCAness” of sporadic basal-like breast cancer.
  - Choice of DNA-damaging chemotherapy
  - PARP inhibition

Case from Dr Lisa A Carey

- 2008: 59-yr-old woman with Stage I, Grade 3 TNBC treated with BCT only per pt’s choice.
- 2009: Recurrent disease as inflammatory breast cancer, IMLN, subpectoral LN (Biopsy-confirmed TNBC).
  - AC x 3 with PD → Paclitaxel/bevacizumab x 12 weeks (complicated by perforated diverticulum).
- Mastectomy/AND with no mass, + dermal lymphatic invasion, + LVI, 26/26 positive LN.
  - Declined RT. Paclitaxel/bevacizumab (2 mos) with locoregional PD.
  - Gem/carbo x 2 weeks with cutaneous PD. BSI-201 added.
    - Tolerating well other than fatigue.
    - No restaging yet, but clinically stable.

TRIPLE NEGATIVE BREAST CANCER

Finding the Positives in Triple-Negative Breast Cancer: A Three-Part Live CME Webcast Series

Seminar I: Wednesday, March 3, 2010, 8:00 PM - 9:00 PM EST

TRIPLE NEGATIVE BREAST CANCER

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