Early Detection: How Molecular Pathology Can Change The Mortality Rates of Triple Negative Breast Cancer Patients

4th Annual Gayle Brinkenhoff Breast Cancer Symposium
I do not have anything to disclose.
How Common is Breast Cancer?

- Most Diagnosed Cancer In Women Each Year
- 230,000+ New Diagnoses
- 40,000+ BC-Related Deaths
- Lifetime Risk of Developing BC is 1 in 8

Breast Cancer Facts

- 5-10% of BCs have Inherited Genetic Mutations
- 85% of all BCs have No Family History

Risk Factors

- Non-modifiable
  - Gender, Age, Genetics
  - Family/Personal History, Breast Density
  - Early Menarche-Late Menopause
- Modifiable
  - Parity, Breast Feeding
  - Exposure to Hormones (Pill/IVF)
  - Alcohol, Obesity, Exercise
Triple-Negative Breast Cancer

This subtype of cancer lacks targeted therapies receptors, such as the estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor-2 (HER2).

Triple-negative Breast Cancer (TNBC)
- 15-20% of all BC diagnosed
- IHC receptor negative
  ER, PR and HER2 Gene Amplification
- 75% of BLBC are TNBC by gene expression
African American vs European American women

- Incidence rates
- Mortality rates

TNBC

- 42% increase in mortality rates AAW
- 22% of AAW cancers are TNBC
- 10% of EAM cancers are TNBC

Less than 20% of women with TNBC treated by chemotherapies have lasting results.
Breast Cancer Mortality Rates

White Women Are Diagnosed Earlier

Percent of breast cancer cases by stage at diagnosis

Source: American Association for Cancer Research

THE HUFFINGTON POST
Breast Cancer Survival Rates

African American Survival Rates
- 5 Year Survival: 81%
- Deaths: 19%

5 Year Survival Rates
- 0-1 Stage: 99%
- II Stage: 93%
- III Stage: 72%
- IV Stage: 22%

Mortality Rates in African Americans are 42% higher than European American
A 2007 study of more than 50,000 women with all stages of breast cancer found that 77 percent of women with TNBC survived at least 5 years. 99 percent of women with other forms of breast cancer were found to survive at least five years. 2007 found that after 5 years of their diagnosis, women with TNBC no longer had a higher risk of death. The five-year survival rate for women with TNBC was similar to the survival rates for women with other cancers of similar stages.
Survival Linked to Stage

5-year breast cancer survival rate

- Stage 0: Close to 100%
- Stage 1: 98%
- Stage 2: 93%
- Stage 3: 72%
- Stage 4: 22%
Do TNBC Mortality Rates Tell The True Story?

- Is there evidence that link the disparities found in the survival rates of African American women to the stage of detection?
- In general, how much do survival rates for TNBC depend on stage of diagnosis?
- Survival rates of all cancers
- Studies show survival rates of TNBCs and other breast cancers are comparable when stage of diagnosis is similar.

### 5-year breast cancer survival rate

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival Rate</th>
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<tbody>
<tr>
<td>0</td>
<td>Close to 100%</td>
</tr>
<tr>
<td>1</td>
<td>98%</td>
</tr>
<tr>
<td>2</td>
<td>93%</td>
</tr>
<tr>
<td>3</td>
<td>72%</td>
</tr>
<tr>
<td>4</td>
<td>22%</td>
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• STAGE V
The Stage TNBCs Are Diagnosed Play a Role in Survival

What are we doing differently that will enable the field to diagnosis TNBCs earlier?
Early Detection
Everything is up to the pathologist....
A Closer Look at the Gold Standard

- Pathologist confirmation
- Tissue biopsy
- Breast Cancer diagnosis made based on morphology and localization
What About Prognosis?

Elevated MED28 expression predicts poor outcome in women with breast cancer.
Yoon NK\(^1\), Maresh EL, Elshimali Y, Li A, Horvath S, Seligson DB, Chia D, Goodglick L.

Non-conventional role of haemoglobin beta in breast malignancy.

Styrene maleic acid-encapsulated RL71 micelles suppress tumor growth in a murine xenograft model of triple negative breast cancer.
Martey O, Nimick M, Taurin S, Sundararajan V, Greish K, Rosengren RJ.

Increase of GKLF Messenger RNA and Protein Expression during Progression of Breast Cancer
K. Wade Foster, Andra R. Frost, Peggy McKenzie-Bell, Chin-Yu Lin, Jeffrey A. Engler, William E. Grizzle and J. Michael Ruppert

Elevated expression of protein regulator of cytokinesis 1, involved in the growth of breast cancer cells.
Shimo A\(^1\), Nishidate T, Ohta T, Fukuda M, Nakamura Y, Katagiri T.

Elevated IL-1β expression induces invasiveness of triple negative breast cancer cells and is suppressed by zerumbone.
Jeon M, Han J, Nam SJ, Lee JE, Kim S.

HR+HER2- breast cancers with growth factor receptor-mediated EMT have a poor prognosis and lapatinib downregulates EMT in MCF-7 cells.

Tenascin C is a prognostic determinant and potential cancer-associated fibroblasts marker for breast ductal carcinoma.
Yang Z, Ni W, Cui C, Fang L, Xuan Y.

Brain-derived neurotrophic factor (BDNF)-TrkB signaling modulates cancer-endothelial cells interaction and affects the outcomes of triple negative breast cancer.
Tsai YF, Tseng LM, Hsu CY, Yang MH, Chiu JH, Shyr YM.

Myc mediates cancer stem-like cells and EMT changes in triple negative breast cancers.
Yin S\(^1\), Cheryan VT\(^2\), Xu L\(^1\), Rishi AK\(^3\,4\), Reddy KB\(^3\,4\).

Low levels of Stat5a protein in breast cancer are associated with tumor progression and unfavorable clinical outcomes
Amy R Peck

High-level JAG1 mRNA and protein predict poor outcome in breast cancer.
Dickson BC\(^1\), Mulligan AM, Zhang H, Lockwood G, O’Malley FP, Egan SE, Reedijk M.

Elevated expression of STK3 mRNA and protein is associated with poor outcome in invasive breast cancer

Non-conventional role of haemoglobin beta in breast malignancy

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Shimo A\(^1\), Nishidate T, Ohta T, Fukuda M, Nakamura Y, Katagiri T.

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The Stage is Set...Right?

Diagnosis

Prognosis

Anticancer Effects of Grape Seed Extract on Human Cancers: A Review
Dinicola S, Cucina A, Antonacci D, and Bizzarri M.
WHY?

If the biochemical status of a patient's tissue provides enough information to contribute to treatment regimen, why is it limited to just prognosis?

What about the biochemical status of breast cancer tissues at the different stages (0-4), can biochemical status predict morphological changes?

I WAS HERE FIRST!
Case Study: To determine if the biochemical phenotype of normal breast tissues from high risk women could predict breast cancer initiation.

Molecular Pathology Tissue Mapping Study

- Biomarker development
- Linking clinical risk to molecular signaling.
- Determine if the biochemical profiles could be used as an additional screening tool for the diagnosis of breast cancers.
Biomarkers.....

- Stem cell niche
- Polarity (initial changes in epithelial)
- Cell cycle regulation
- Cancer progression
- Epithelial Mesenchymal Transition (EMT)
- Oncogenes
- Tumor Suppressor genes
Prognosis Markers Predict TNBC

Early non-cancerous biopsies from patients who later developed TNBCs

- Wnt10b
- EZH2
- Aurora A
- Laminin 5
- GM130
- Vimentin
Case Study

GM130

- GM130 showed apical localization in normal epithelium
- Altered intracellular localization away from apical area in cancer
- Select normal ducts also display altered GM130 staining pattern similar to those seen in tumors. Suggesting GM130 has potential in detecting early polarity change

Laminin 5

- Laminin 5 stains along basement membrane of normal ducts and lobules
- Cytoplasmic staining seen in invasive cancer, including the majority of TNBC
- Cytoplasmic staining also seen in tissue with benign morphology change
- Staining patterns suggest laminin 5 has potential as indicator for early loss of basal polarity prior to development of TNBC
- **Aurora A**
  - Cell Cycle regulation
  - Increased levels in TNBC
- **Vimentin**
  - EMT, invasion, metastasis
- **Wnt10b**
  - Progenitor cell renewal
- **EZH2**
  - Genomic instability, decrease BRAC 1
Case Study Summary

- Protein signaling profiles of normal breast tissues from high risk patient display phenotypes similar to those of aggressive late stage breast cancers.
- Evidence that the onset of breast cancer may occur prior to any morphological changes.
- Adverse biochemical profiles of pathologically normal breast tissues may serve as an early indicator for aggressive disease.
- Findings suggest that morphological profiles used to diagnose breast cancer may need additional screening parameters.
Significance

- Promising results for prognosis markers (poor and favorable) usage as an additional diagnostic tool.
- Protein expression levels of non-cancerous breast tissues displayed a disease phenotype prior to any morphological changes.
- Protein expression levels accurately predicted cancer progression for TNBC patients.
Significance

Triple Negative Breast Cancers

- Less than 20% of women with TNBC treated by chemotherapies have lasting results.
- The mortality rates for African American Women are 42% greater than European American Women.
- 22% of AAW cancers are TNBC

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Source: American Association for Cancer Research
New Normal: Detection and Treatment of TNBC
Thanks To The Laboratories

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Thank You

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