

Understanding Aggressive Breast Cancer in Women of African Descent

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The Plan

- A brief introduction of the status of breast cancer diversity among African Americans
- An overview of the morphology and the biology of triple-negative breast cancer compared to the other molecular subtypes
- A suggestion of the need for the development of strategies for improving breast cancer outcomes in African Americans



Why the Emphasis on Breast Cancer?

Facts about Breast Cancer

- The most common cancer among women across the globe accounting for 22% of 4.7 million new cancer cases per year
- The second leading cause of cancer death among women
- Women who die from breast cancer lose an average of 20 years of life

Facts about Breast Cancer

- A major public health problem across the globe
- A physical and psychosocial threat to women's lives

Advances in Breast Cancer

- Enhanced public awareness/screening
- Improvement in breast imaging
- Introduction of minimally invasive diagnostic and therapeutic procedures
- Renewed interest in breast cancer risk reduction and prevention
- Discovery of breast cancer genes and new molecular pathways
- Introduction of molecular targeted therapy

Progress in Breast Cancer

- Mortality from breast cancer has decreased 1-2% per year since the 1990's in resource-rich countries
- Mortality from breast cancer continues to increase in medically underserved populations and countries of limited resources

Closing the Gap

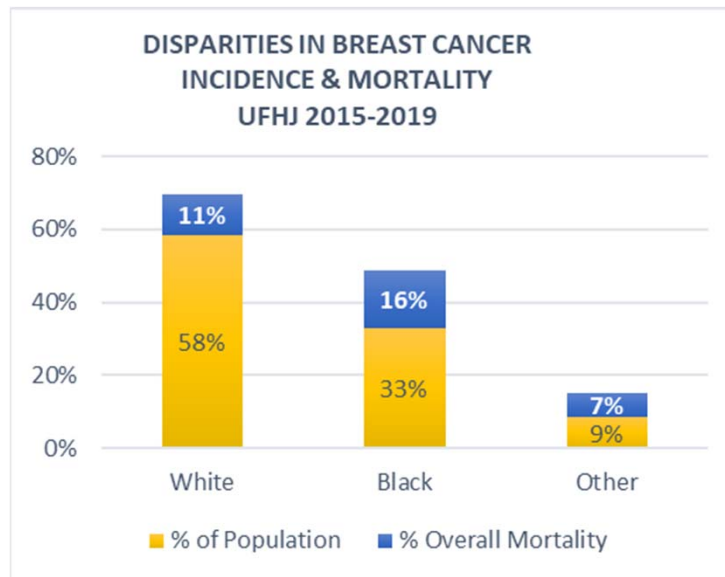
- Examples of neglected breast cancer patients referred to UF Health Jacksonville emergency room, similar to those seen in countries with limited resources



Masood S. Breast cancer in resource-limited countries. *Womens Health (Lond)*. 2006;2(6):797-800. doi:10.2217/17455057.2.6.797

Mortality Rate among African American Patients

- One of the highest incidences treated at UF Health Jacksonville (UFHJ)



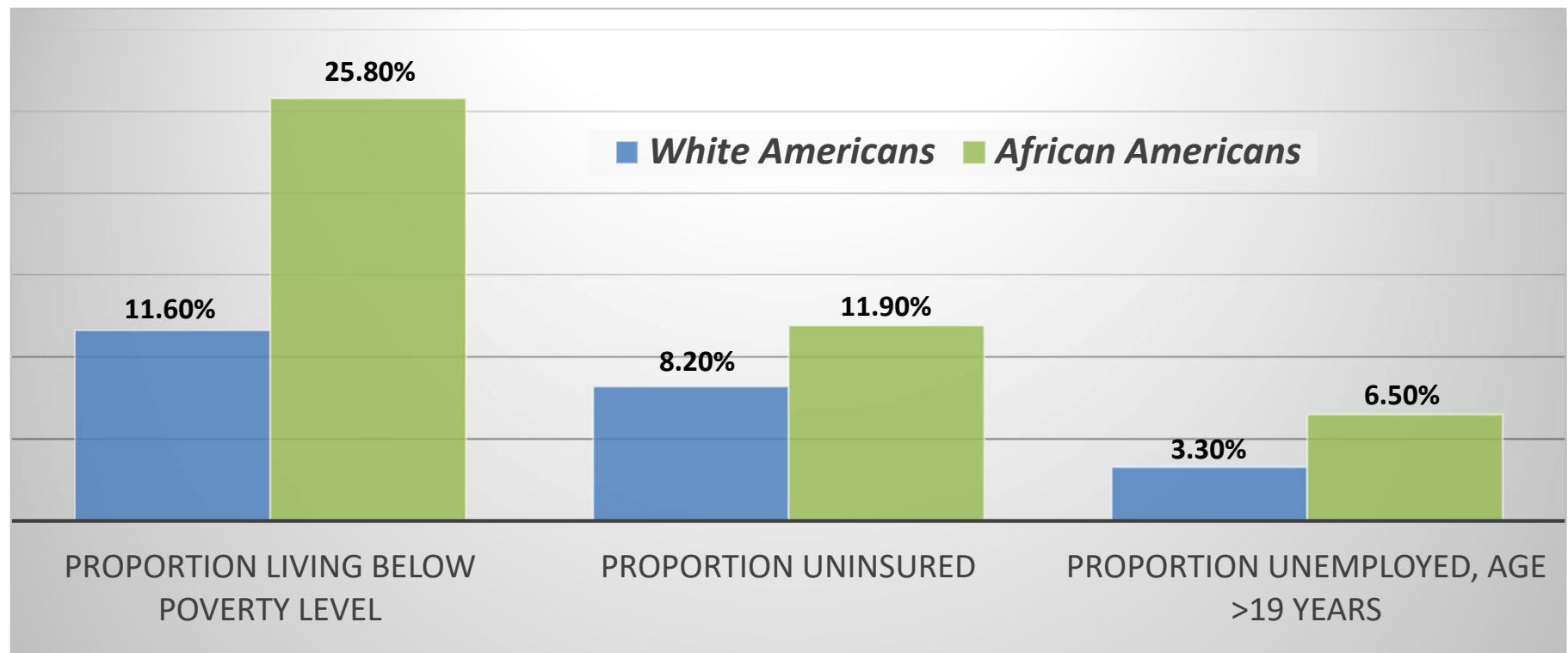
Reducing Breast Cancer Mortality

- Improvement in breast cancer survival is achievable when appropriate resources are available
- It is possible to favorably impact the breast cancer mortality rate by applying incremental changes in cancer care within a population

Barriers to Reduce Breast Cancer Mortality

- Diversity in patient population with different genetic backgrounds, social values, religious beliefs, lifestyles and cultures
- Differences in economic status and health care priorities

Socioeconomic Disparities



Sources: U.S. Census Bureau 2013
National Center for Health Statistics/DHHS 2015
US Department of Labor Statistics 2017

Race and/or Ethnicity-Associated Disparities

- Women with African ancestry in Western, Sub-Saharan Africa and United States represent a population with increased risk of being diagnosed with biologically aggressive breast cancer
- These tumors are commonly referred to as triple-negative breast cancer

Jiagge E, Jibril AS, Chitale D, et al. Comparative Analysis of Breast Cancer Phenotypes in African American, White American, and West Versus East African patients: Correlation Between African Ancestry and Triple-Negative Breast Cancer. *Ann Surg Oncol*. 2016;23(12):3843-3849. doi:10.1245/s10434-016-5420-z

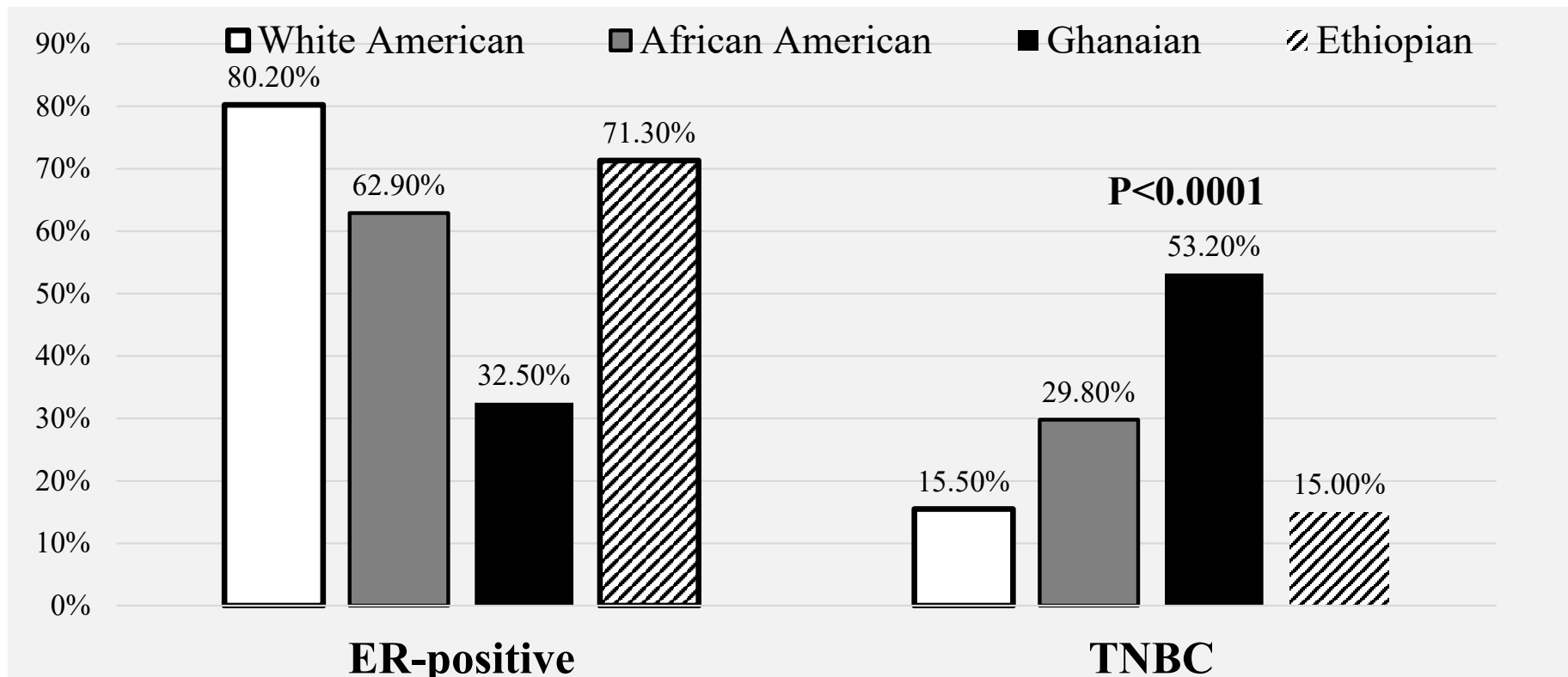
International Breast Cancer Research Collaborative

- Primary Goal: To evaluate the association between African ancestry & high-risk breast cancer subtypes

	WA N=321	AA N=272	Ghana N=234	PValue
Average Age	63	60	48.0	0.002
TNBC	16%	26%	53%	<0.001

Jiagge E, Jibril AS, Chitale D, et al. Comparative Analysis of Breast Cancer Phenotypes in African American, White American, and West Versus East African patients: Correlation Between African Ancestry and Triple-Negative Breast Cancer. *Ann Surg Oncol.* 2016;23(12):3843-3849. doi:10.1245/s10434-016-5420-z

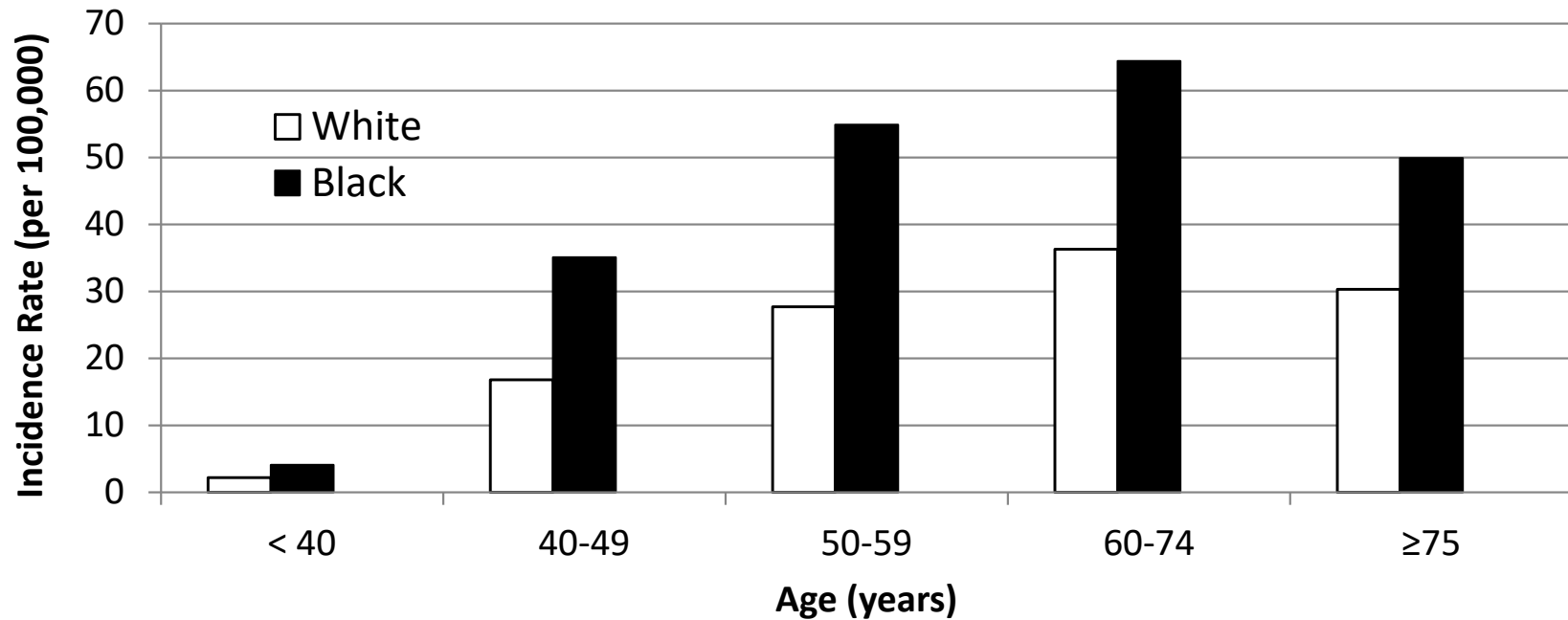
Breast Cancer Phenotypes



Jiagge E, Oppong JK, Bensenhaver J, et al. Breast Cancer and African Ancestry: Lessons Learned at the 10-Year Anniversary of the Ghana-Michigan Research Partnership and International Breast Registry. *J Glob Oncol.* 2016;2(5):302-310. Published 2016 Jul 27.

Triple-Negative Breast Cancer

- Population based incidence rates by age and race



Amirikia KC, Mills P, Bush J, Newman LA. Higher population-based incidence rates of triple-negative breast cancer among young African-American women : Implications for breast cancer screening recommendations. *Cancer*. 2011;117(12):2747-2753. doi:10.1002/cncr.25862

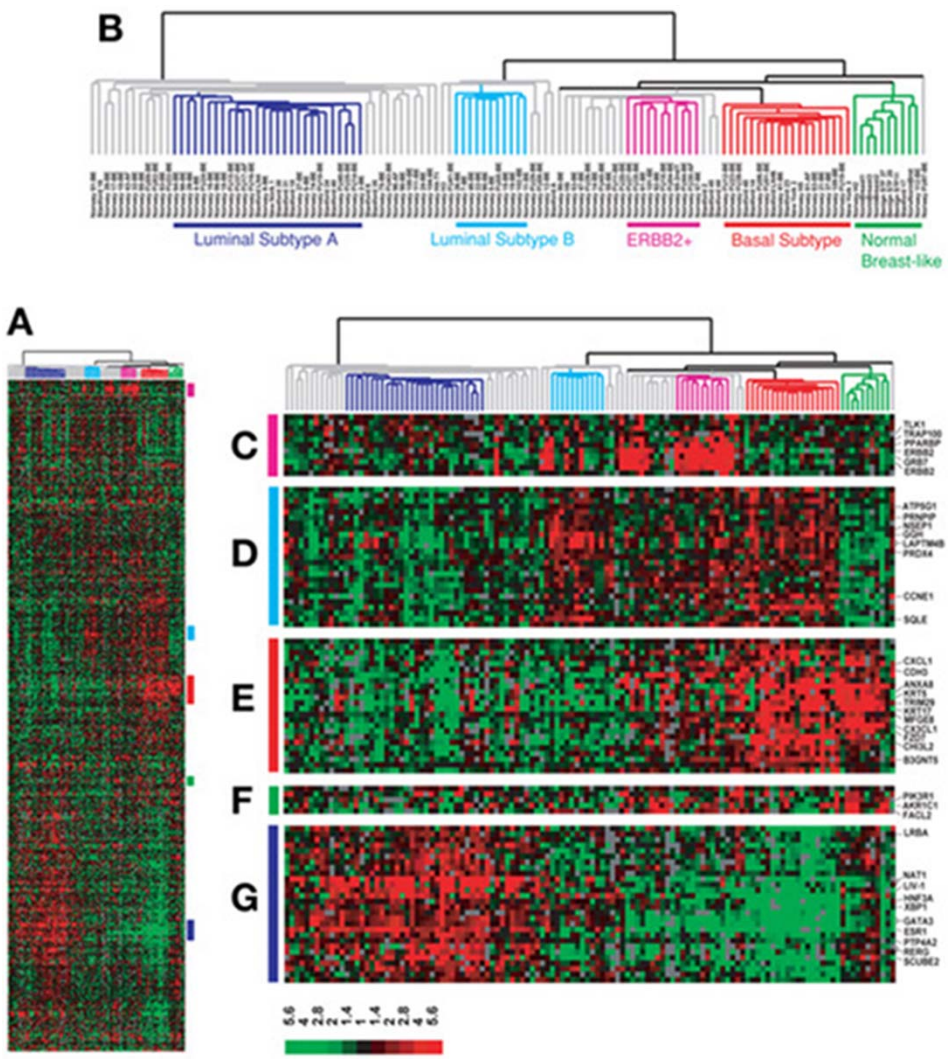
How to
identify the
most
aggressive
subtype of
breast
cancer
among
African
Ancestry?



Molecular Characterization of Breast Cancer

The Process

- Gene expression profiling provided an opportunity to classify tumors at a genomic level into subclasses of potential prognostic and predictive significance



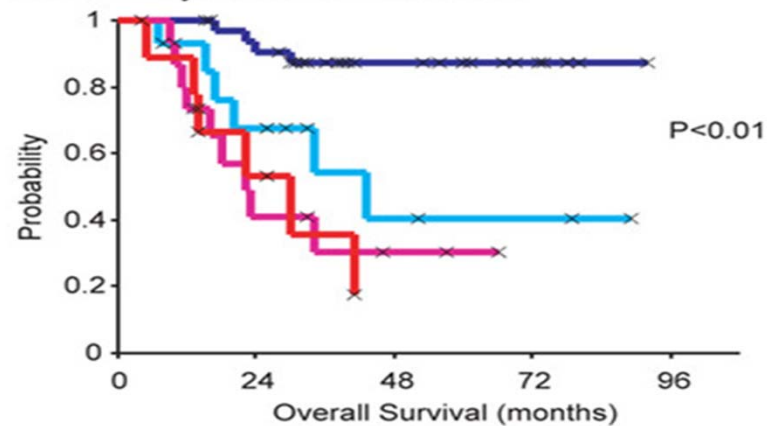
Sorlie T: Molecular Classification of Breast Tumors. *Methods in Molecular Biology* 2007;360:91-114

Kaplan-Meier analysis of disease outcome in two patient cohorts

A. Overall survival for 72 patients with locally advanced breast cancer in the Norway cohort. The normal-like tumor subgroups were omitted from both data sets in this analysis.

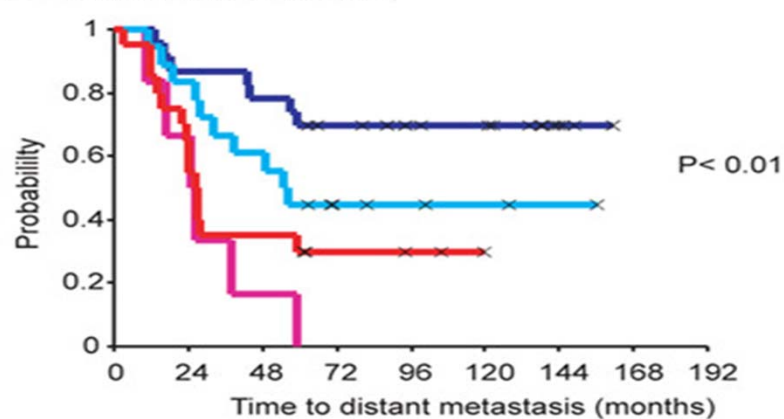
B. Time for development of distant metastasis in 97 sporadic cases.

A Norway/Stanford data set



× Censored, — Luminal A, — Luminal B, — Basal, — ERBB2+

B van't Veer data set



Sorlie T: Molecular Classification of Breast Tumors. *Methods in Molecular Biology* 2007;360:91-114

Molecular Characterization of Breast Cancer

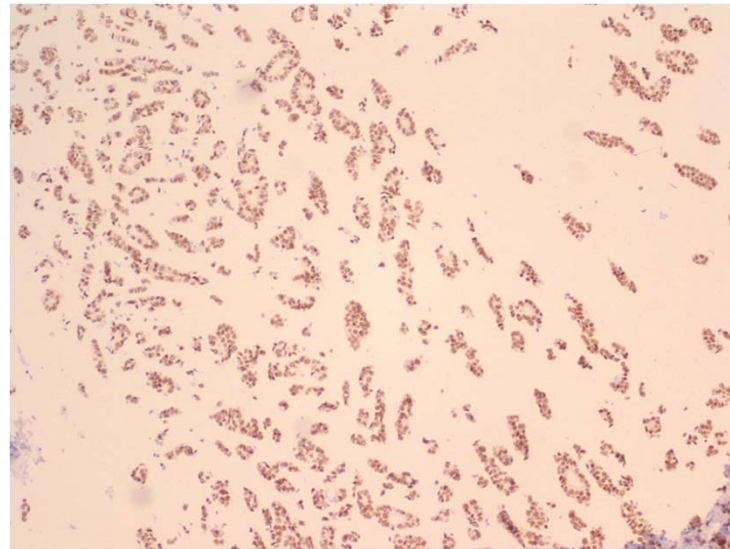
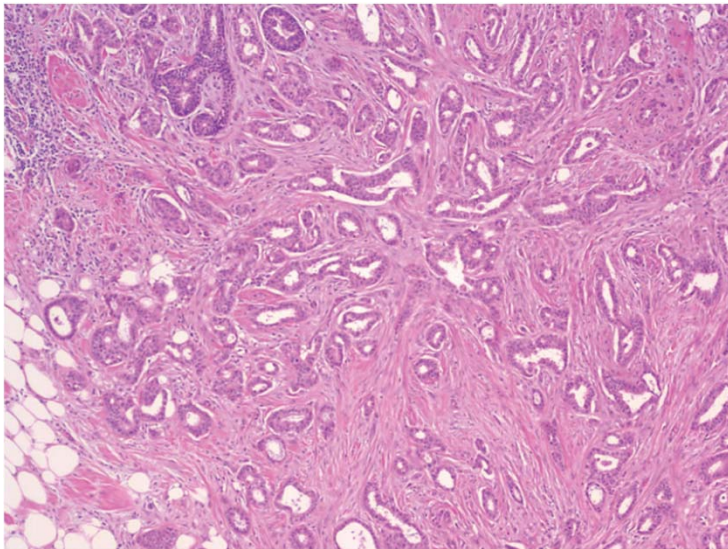
Breast Cancer is a Family of Diseases

- ER+ (Luminal A) (56%-61%)
- ER+ (Luminal B) (9%-16%)
- Her-2/neu + (8%-16%)
- Basal-like/Triple-negative (8%-20%)
- Unclassified/normal breast-like (6%-10%)

Molecular Characterization of Breast Cancer

Luminal Subtypes

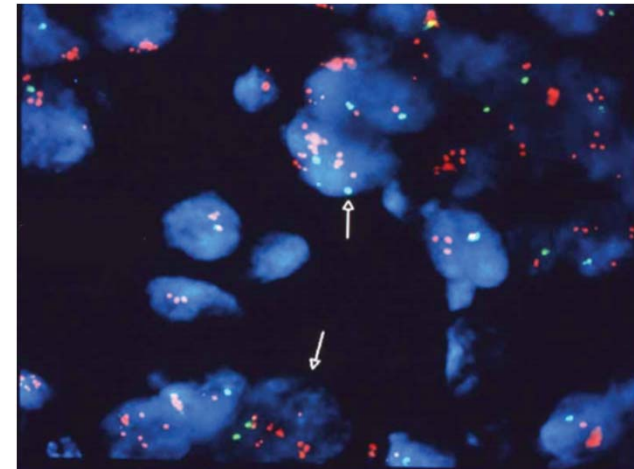
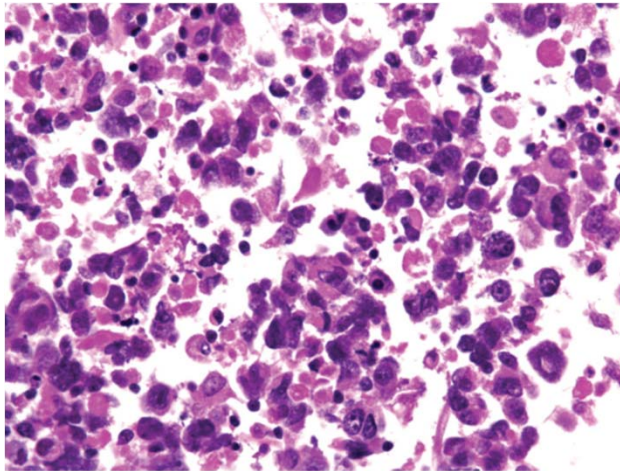
- **Luminal A/B** - generally carry a good prognosis and show a favorable response to endocrine therapy



Molecular Characterization of Breast Cancer

Her-2/neu + Type

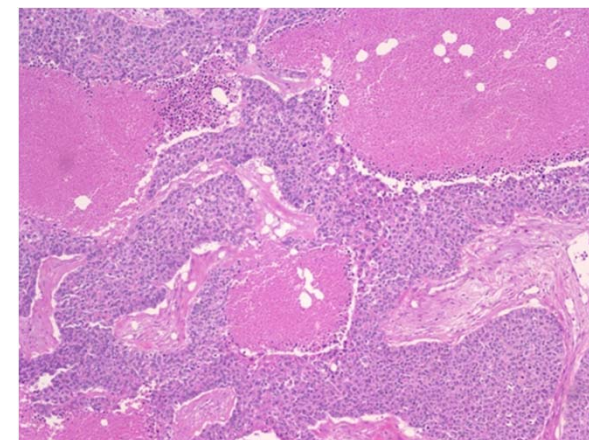
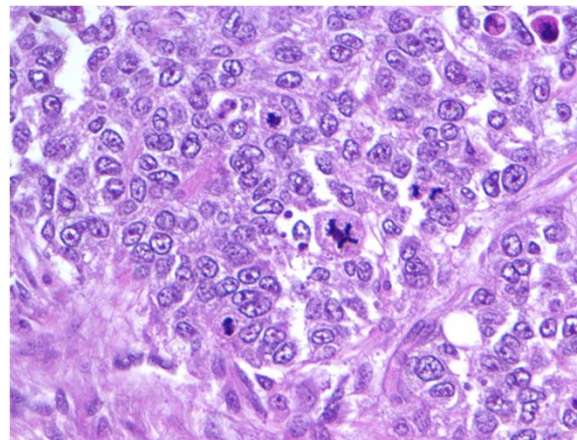
- Presents as two distinct forms
 - ER-
 - ER+
- Associated with poor prognosis



Basal-Like Breast Cancers

Morphologic Features

- Triple-negative phenotype (ER-, PR-, and HER2-/neu-)
- High mitotic rate
- Geographic, central necrosis with lymphoplasmacytic infiltrate



Triple-Negative Breast Cancer

- Triple-negative breast cancer is a surrogate for the aggressive basal breast cancer subtype in clinical practice
- This is a marker of hereditary breast cancer susceptibility
- Multiparity appears to increase the risk of triple-negative breast cancer
- African American identity is a risk factor for triple-negative breast cancer among women with benign breast disease

Newman LA, Stark A, Chitale D, et al. Association Between Benign Breast Disease in African American and White American Women and Subsequent Triple-Negative Breast Cancer. *JAMA Oncol.* 2017;3(8):1102-1106. doi:10.1001/jamaoncol.2016.5598

Newman LA. Disparities in breast cancer and African ancestry: a global perspective. *Breast J.* 2015;21(2):133-139. doi:10.1111/tbj.12369

Triple-Negative Breast Cancer

- Triple-negative tumors represent the majority of cancers within the basal-like subtype
- Not all triple-negative breast cancers display the basal-like phenotype and vice versa

Lehmann BD, Bauer JA, Chen X, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *J Clin Invest*. 2011;121(7):2750-2767. doi:10.1172/JCI45014

Burstein MD, Tsimelzon A, Poage GM, et al. Comprehensive genomic analysis identifies novel subtypes and targets of triple-negative breast cancer. *Clin Cancer Res*. 2015;21(7):1688-1698. doi:10.1158/1078-0432.CCR-14-0432

Triple-Negative Breast Cancer

- Other breast cancers with no basal-like phenotypes
 - Medullary, secretory, apocrine and adenoid cyst carcinomas
 - Have more favorable biologic behavior
 - Metaplastic carcinomas:
 - Biologically are more aggressive

Lehmann BD, Bauer JA, Chen X, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *J Clin Invest*. 2011;121(7):2750-2767. doi:10.1172/JCI45014

Burstein MD, Tsimelzon A, Poage GM, et al. Comprehensive genomic analysis identifies novel subtypes and targets of triple-negative breast cancer. *Clin Cancer Res*. 2015;21(7):1688-1698. doi:10.1158/1078-0432.CCR-14-0432

Triple-Negative Breast Cancer

- Account for 10%-20% of all breast cancer
- More frequently affects younger patients
- More prevalent in women of African descent
- More prevalent in those with germline BRCA-1 mutation carriers
- Are biologically more aggressive

Kohler BA, Sherman RL, Howlader N, et al. Annual Report to the Nation on the Status of Cancer, 1975-2011, Featuring Incidence of Breast Cancer Subtypes by Race/Ethnicity, Poverty, and State. *J Natl Cancer Inst.* 2015;107(6):djv048.

Newman LA, Reis-Filho JS, Morrow M, Carey LA, King TA. The 2014 Society of Surgical Oncology Susan G. Komen for the Cure Symposium: triple-negative breast cancer. *Ann Surg Oncol.* 2015;22(3):874-882. doi:10.1245/s10434-014-4279-0

Triple Negative Breast Cancer

- Fewer systemic therapy options for triple-negative breast cancer, no targeted therapies
- More challenging to detect on mammogram
 - more often mammographically-occult
 - may masquerade as benign lesion
- More likely to present as an interval cancer
- Higher mortality rate even when detected early

Kohler BA, Sherman RL, Howlader N, et al. Annual Report to the Nation on the Status of Cancer, 1975-2011, Featuring Incidence of Breast Cancer Subtypes by Race/Ethnicity, Poverty, and State. *J Natl Cancer Inst.* 2015;107(6):djv048.

Newman LA, Reis-Filho JS, Morrow M, Carey LA, King TA. The 2014 Society of Surgical Oncology Susan G. Komen for the Cure Symposium: triple-negative breast cancer. *Ann Surg Oncol.* 2015;22(3):874-882. doi:10.1245/s10434-014-4279-0

Genomic Disparity in Triple-Negative Breast Cancer

- Comparing the genomic landscape between breast cancer in African American vs. White Americans demonstrated that African Americans have a greater intratumor genetic heterogeneity and more basal gene expression
- This pattern suggests more aggressive tumor biology in African Americans and may contribute to racial disparity in breast cancer outcome

Keenan T, Moy B, Mroz EA, et al. Comparison of the Genomic Landscape Between Primary Breast Cancer in African American Versus White Women and the Association of Racial Differences With Tumor Recurrence. *J Clin Oncol*. 2015;33(31):3621-3627. doi:10.1200/JCO.2015.62.2126

Triple-Negative Breast Cancer

- The most frequent breast cancer somatic mutations identified as driver mutations in African Americans are:
 - TP53, PIK3CA, CDH1, GATA3, MLLT3, and MAP3K1 mutations
- African Americans are more likely to have PAM50 basal tumors and unlikely to have PAM50 luminal tumors

Quackenbush J. Microarray analysis and tumor classification. *N Engl J Med.* 2006;354(23):2463-2472. doi:10.1056/NEJMra042342

Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA.* 2006;295(21):2492-2502. doi:10.1001/jama.295.21.2492

Triple-Negative Breast Cancer

- There is critical need for comprehensive genomic analysis of triple-negative breast cancer among different ethnic groups
 - Germline genetic patterns
 - Somatic/tumor genetics
- The stem cell module in mammary tissue/breast cancer suggests the significance of identifying the subpopulation of tumor cells that are involved in metastatic virulence

Triple-Negative Breast Cancer

- Strategies to overcome the burden of breast cancer disparity among different ethnic groups
 - Acknowledgement of the fact that race factors into healthcare outcomes
 - Increasing public breast health education
 - Development of a coordinated plan for access to cancer prevention services including behavioral life style changes and screening
 - Access to early breast cancer diagnosis and optimal breast cancer care
 - Implementation of team-based approach and community empowerment for support and follow up measures

Masood S. Is it time to address the continuous dilemma of breast cancer disparities among African Americans? A call to action. *Breast J.* 2020;26(12):2339-2340. doi:10.1111/tbj.14124

Masood S. This is Not Only about the Biology: The Socioeconomic Disparities among African American Women with Breast Cancer Still Play a Significant Role. *Breast J.* 2021;27(7):571-572. doi:10.1111/tbj.14263

Triple-Negative Breast Cancer

- The issue of breast cancer disparity can only be resolved if the issue will be considered as a national healthcare priority
- It will be necessary for the healthcare leaders and state legislators to develop an appropriate action plan to reduce breast cancer disparity between African Americans and White Americans

Triple-Negative Breast Cancer

- Establishment of a region-wide population based active registry
- Implementing cancer control programs
- Enforcing participation of women of color in clinical trials
- Providing sufficient funding for breast cancer disparity research

Thomas AS, Kidwell KM, Oppong JK, et al. Breast Cancer in Ghana: Demonstrating the Need for Population-Based Cancer Registries in Low- and Middle-Income Countries. *J Glob Oncol*. 2017;3(6):765-772. doi:10.1200/JGO.2016.006098

“Of all the forms of inequality, injustice in healthcare is the most shocking and inhumane.”

- Rev. Dr. Martin Luther King Jr.



