Genetics and Genomics in Studying Breast Cancer Disparities Related to African Ancestry: Oncologic Anthropology

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Komen Scholar
I have no disclosures
Socioeconomic Disparities

- **Proportion Living Below Poverty Level**: 11.60% (White Americans) vs. 25.80% (African Americans)
- **Proportion Uninsured**: 8.20% (White Americans) vs. 11.90% (African Americans)
- **Proportion Unemployed, Age >19 Years**: 3.30% (White Americans) vs. 6.50% (African Americans)

*Sources: U.S. Census Bureau 2013, National Center for Health Statistics/DHHS 2015, US Department of Labor Statistics 2017*
Breast Cancer Burden of African Americans

- Higher mortality
- Advanced stage distribution
  - Younger age distribution
  - Increased risk of adverse tumor features
  - Higher incidence of male breast cancer

- Socioeconomic Disparities
  - Tumor biology
  - Genetics
  - Lifestyle & Reproductive Experiences
  - Environmental exposures
  - Diet/Nutrition
AA Mortality Risk: 1.28 (95% CI 1.18-1.38)

Newman et al, JCO 2006
Breast Cancer Burden of African Americans Compared to White Americans

• Higher mortality
• Advanced stage distribution
• Younger age distribution
  30-40% AA <50; 20% WA <50
• Higher risk of adverse tumor features
  Two-fold higher rates TNBC in AA vs WA
• Higher incidence Inflammatory Breast Cancer
• Higher incidence male breast cancer

• Socioeconomic Disparities
• Delivery of Care
• Tumor biology
• Genetics
• Lifestyle & Reproductive Experiences
• Environmental exposures
• Diet/Nutrition
Pooled analysis of SWOG adjuvant therapy trials for various cancers

- Equal treatments delivered through clinical trials resulted in equal outcomes (regardless of race/ethnicity)
- *Exception:* African Americans with hormonally-driven cancers (e.g. breast & prostate cancers)

<table>
<thead>
<tr>
<th></th>
<th>Recurrence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal</td>
<td>1.39 (1.12-1.73)</td>
<td>1.41 (1.10-1.82)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>1.45 (1.27-1.66)</td>
<td>1.49 (1.28-1.73)</td>
</tr>
</tbody>
</table>
“Why Racial Profiling Persists in Medical Research”

“Parsing the Etiology of Breast Cancer Disparities”
Newman, JCO 2016
Disparities in Breast Tumor Biology: ER-Negative Breast Cancer in the U.S.

Li et al; SEER Data, 1992-98
Arch Int Med 2003
Breast Cancer Subtypes

Sorlie T PNAS 2003;100:8418
Heterogeneity of Intrinsic Subtypes

Prat & Perou Mol Oncol 2011;5

Li et al, 2017
SEER Program
Increased Prevalence of TNBC Among AA Patients Regardless of Age or Stage at Diagnosis

TNBC more common in young women, and in AA women in all age categories

TNBC more common with more advanced stages, and in AA women at all stages of disease
“Breast cancer statistics, 2015: Convergence of incidence rates between black and white women”

Δ = 42%

TNBC in AA

CA: A Cancer Journal for Clinicians
29 OCT 2015
Racial Differences in Intrinsic Subtype

<table>
<thead>
<tr>
<th></th>
<th>Black, &lt;50</th>
<th>Black, 50+</th>
<th>White, &lt;50</th>
<th>White, 50+</th>
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</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Luminal B</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>HER2-E</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal-like</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Normal-like</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Percent

Black women: More Basal-like and HER2-Enriched Fewer Luminal subtypes. = Contribution to poorer outcomes.

Troester et al, JNCI 2017
Population-Based Incidence Rates of TNBC, by Race/Ethnicity and Age: Implications for Screening Recommendations

Delayed mammography screening may worsen breast CA outcome disparities between AA and WA women (Amrikia and Newman, CANCER, 2011)
Clinical Relevance of Triple Negative Breast Cancer

- Inherently more aggressive pattern of breast cancer
- Fewer systemic therapy options for TNBC: no targeted therapies
- More common in African American women and in families with BRCA1 hereditary cancer susceptibility

- 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
## Early Stage TNBC: Detection and Outcomes

### Memorial Sloan Kettering
- Ho et al, *Cancer* 2012
- 194 T1a/b N0 TNBC; 1999-2006
- 69% screen-detected

<table>
<thead>
<tr>
<th></th>
<th>T1a/b N0</th>
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<tbody>
<tr>
<td></td>
<td>CTX</td>
</tr>
<tr>
<td><strong>5-Yr Locoregional Recurrence-Free Survival</strong></td>
<td>96.2%</td>
</tr>
<tr>
<td><strong>5-Yr Distant Mets-Free Survival</strong></td>
<td>95.9%</td>
</tr>
</tbody>
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### National Comprehensive Cancer Network
- Vaz-Luis et al, *JCO* 2014
- 363 T1a/b N0 TNBC; 2000-09
- 75% screen-detected

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<thead>
<tr>
<th></th>
<th>T1a N0</th>
<th>T1b N0</th>
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<tbody>
<tr>
<td></td>
<td>CTX</td>
<td>No CTX</td>
</tr>
<tr>
<td><strong>5-Yr Overall Survival</strong></td>
<td>100%</td>
<td>94%</td>
</tr>
<tr>
<td><strong>5-Yr Distant Mets-Free Survival</strong></td>
<td>100%</td>
<td>93%</td>
</tr>
</tbody>
</table>

- CTX: Chemotherapy
- No CTX: No Chemotherapy
“Breast cancer precursors revisited: molecular features & progression pathways”

Reis-Filho J et al; Histopathology 2010
Henry Ford Health System (HFHS) Benign Breast Disease Cohort

- Henry Ford Health System, Metropolitan Detroit
  - Approximately 30% African American patients
- Benign Breast Disease Cohort, 1994-2005
  - 2,588 African Americans
  - 3,566 White Americans
  - Follow-up (>10 years) and overall subsequent breast cancer detection rates (4%) as well as stage distribution similar for AA and WA pts

Newman et al, JAMA Onc 2016
HFHS Benign Breast Disease Cohort: TNBC Probability Estimates

Newman et al JAMA ONC, Dec 2016
ER-Negative and Triple Negative Breast Cancer and African Ancestry Population Subsets: England, Switzerland and Brazil

- Bowen et al, British J of Cancer 2008: London
  - 22% among Blacks vs 15% among Whites (overall)
  - 25% among Blacks vs 12% among Whites (<60yrs)
- Copson et al, British J of Cancer 2014: UK POSH Study
  - 26% among Blacks vs 18% among Whites, all ≤40 yo
- Carvalho et al, BMC Women’s Health 2014: Brazil
  - Highest TNBC frequency in regions with increased African ancestry
- Rapiti et al, Cancer Medicine 2016: Switzerland

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<tbody>
<tr>
<td>Swiss</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>European</td>
<td>1.22</td>
</tr>
<tr>
<td><strong>African</strong></td>
<td>2.52</td>
</tr>
<tr>
<td>North American</td>
<td>2.18</td>
</tr>
<tr>
<td>Central/South American</td>
<td>2.15</td>
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</tbody>
</table>
• Parallels between hereditary breast cancer and breast cancer in women with African ancestry
  – younger age distribution
  – increased prevalence of ER-neg, aneuploid tumors
  – higher risk of male breast cancer

• Is African ancestry associated with a heritable marker for high-risk breast cancer subtypes?

• Unique opportunity to gain insights regarding etiology of breast cancer disparities and the pathogenesis of triple-negative breast cancer
Breast Cancer Phenotypes in WA, AA, Ghanaians and Ethiopians


ER-positive

- White American: 80.20%
- African American: 71.30%
- Ghanaian: 32.50%
- Ethiopian: 29.80%

TNBC

- White American: 15.00%
- African American: 15.00%
- Ghanaian: 53.20%
- Ethiopian: 71.30%

P<0.0001 for both ER-positive and TNBC categories.
Biologic Plausibility: “Oncologic Anthropology”
African Diaspora/Patterns of Forced Population Migration
Breast Cancer Phenotypes and East/West African Ancestry in USA

- Jemal A and Fedewa S,
- SEER Registry, 1996-2008
- Frequency of ER-negative breast cancer
  - 183,777 White American patients: 21%
  - 24,639 African American patients: 39%
  - 143 *West African-born* patients: 40%
  - 186 *East African-born* patients: 22%
Melissa Davis, PhD
Scientific Director,
International Center for the Study of Breast Cancer Subtypes

Expression and sub-cellular localization of an epigenetic regulator, co-activator arginine methyltransferase 1 (CARM1), is associated with specific breast cancer subtypes and ethnicity

African Americans with pancreatic ductal adenocarcinoma exhibit gender differences in Kaiso expression

Distinct Transcript Isoforms of the Atypical Chemokine Receptor 1 (ACKR1) / Duffy Antigen Receptor for Chemokines (DARC) Gene Are Expressed in Lymphoblasts and Altered Isoform Levels Are Associated with Genetic Ancestry and the Duffy-Null Allele
Duffy Antigen Receptor for Chemokines/Atypical Chemokine Receptor 1 significantly associated with race, molecular subtype, & survival

(Davis lab, in press, Cancer Epi Bio Prev 2019)
“Genetic ancestry and population differences in levels of inflammatory cytokines in women: Role for evolutionary selection and environmental factors”, Yao et al 2018

Duffy antigen receptor for chemokines/Atypical chemokine receptor 1; 1q23 rs2814778: Duffy-null allele
Biologic Plausibility: “Oncologic Anthropology” and Duffy as a Candidate Gene to Explain Breast Cancer Disparities Related to African Ancestry

Malaria; Selection pressure for Duffy-null; African Diaspora

Duffy-Null Frequency
African Americans: 60-70%
White Americans: <5%

Ghanaians: 100%
Ethiopians: 50-60%

Trans-Atlantic slave trade
Bantu Expansion
International Collaborations:

• Opportunities to study variations in high-risk patterns of disease
• Opportunities to improve the standard of health care in medically-underserved populations
• Opportunities to cultural and academic exchange
• Opportunities to forge powerful friendships

• ICS BCS Mission: To reduce the global breast cancer burden through advances in research and delivery of care to diverse populations worldwide
ICS BCS Collaborations: Academic Exchange

Establishment of Immunohistochemistry Program in Kumasi and Addis Ababa

Core Needle Biopsy Training Program (AnnSurgOnc 2010)

Weekly Telemedicine Tumor Board Mtgs and Annual ICS BCS “Breast Cancer in Africa” Symposia
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Dr. Michael Ohene-Yeboah
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Patients of the Komfo Anokye Teaching Hospital

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Dr. Abebe Engida
Dr. Bekele Mahteme
Dr. Abebe Zerihun
Patients of the St. Paul’s Millenium Teaching Hospital

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Dr. Jessica Bensenhaver
Dr. Erica Proctor
Dr. David Nathanson
Dr. Dhanitale Chitale
Barbara Salem
Dr. Azadeh Stark

Dr. Evelyn Jiagge
Dr. Max Wicha
Dr. Celina Kleer
Dr. Sofia Merajver
Kathy Toy
Dr. Mark Hoenerhoff
SURVIVAL RATES

- 60%
- 43%
- 20%
<table>
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<tr>
<th>Passenger Status</th>
<th>Survival Rate</th>
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<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Class</td>
<td>60%</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Class</td>
<td>43%</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Class</td>
<td>20%</td>
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Outcome is dependent on access to care

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

*Rev. Dr. Martin Luther King, Jr.*
Thank You!!!!!