Genomic Landscape of Breast Cancer in Women of African Ancestry

Olufunmilayo I Olopade, MD, FACP, OON
Walter L. Palmer Distinguished Service Professor
ACS Clinical Research Professor
The University of Chicago
Outline

1. Introduction

2. Define the genomic basis for inherited breast cancer

3. Describe ongoing research integrating germline and somatic genomic research.

4. Discuss opportunities in Precision Medicine for All
This requires genetic information for the best risk assessment and the best therapies.
Breast cancer rates by race/ethnicity
U.S. 2008-2012, age-adjusted

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Incidence Rate, per 100,000</th>
<th>Mortality Rate, per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Races</td>
<td>124.8</td>
<td>21.9</td>
</tr>
<tr>
<td>White</td>
<td>127.9</td>
<td>21.3</td>
</tr>
<tr>
<td>Black</td>
<td>124.4</td>
<td>30.2</td>
</tr>
<tr>
<td>Asian / Pacific Islander</td>
<td>96.3</td>
<td>11.4</td>
</tr>
<tr>
<td>American Indian / Alaska Native</td>
<td>82.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Hispanic</td>
<td>92.1</td>
<td>14.5</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>130.1</td>
<td>22.6</td>
</tr>
</tbody>
</table>
Breast cancer stage distribution by race, 2005-2011

Source: Surveillance, Epidemiology, and End Results Program
Breast cancer distribution by receptor status and race, 2010

**Note:** Based on data from the Surveillance, Epidemiology, and End Results database.

**Source:** J Natl Cancer Inst. 2014 May;106(5):dju055
Gene Expression Profiles in Hereditary Breast Cancer

Hedenfalk et al., NEJM, 344:539-548, 2001
BRCA1 Tumors Have a Distinct Phenotype

- Medullary and atypical medullary
- High mitotic rate
- Aneuploid
- High proliferation fraction – high KI67
- ER negative, PR negative
- No HER2 gene amplification
- Frequent Tp53 mutations
- BRCA1 – associated basal like breast cancers have the WORST outcomes
- African Americans have the worst overall breast cancer related outcomes

Breast Cancer Linkage Consortium
Crook T et al., Lancet, 1997
Subgroups of Breast Cancer

- Molecular subtypes
  - Estrogen receptor -- druggable target
  - Progesterone receptor
  - HER-2/neu -- druggable target
  - Gene expression profiling: 4 or more subtypes
  - Luminal A, luminal B, basal-like, her2-enriched
Breast Cancer Subtypes Across Populations
(N=482 in Nigeria & Senegal) (N=203, Ilorin, Nigeria)

- Luminal A
- Luminal B
- HER2+/ER–
- Basal-like
- Unclassified

Ilorin, Nigeria (mean age = 48 y)
Nigeria & Senegal (mean age = 45 y)
African American (premenopausal)
African American (postmenopausal)
White in US (premenopausal)
White in US (postmenopausal)
White in Poland (mean age = 56 y)
Japanese (median age = 54 y)

Huo et al. J Clin Onc 2009
## Estrogen Receptor Status by Regions

<table>
<thead>
<tr>
<th>Region</th>
<th>No. of studies</th>
<th>ER+ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North-eastern (Egypt, Sudan, and Libya)</td>
<td>30</td>
<td>0.63 (0.60-0.66)</td>
</tr>
<tr>
<td>North-western (Morocco, Algeria, and Tunisia)</td>
<td>24</td>
<td>0.54 (0.50-0.59)</td>
</tr>
<tr>
<td>Western (Ghana, Mali, Nigeria, and Senegal)</td>
<td>13</td>
<td>0.35 (0.23-0.46)</td>
</tr>
<tr>
<td>Eastern (Kenya, Uganda, Tanzania, and Madagascar)</td>
<td>7</td>
<td>0.41 (0.33-0.50)</td>
</tr>
<tr>
<td>Southern (South Africa)</td>
<td>6</td>
<td>0.60 (0.56-0.64)</td>
</tr>
<tr>
<td>US SEER, African Americans</td>
<td></td>
<td>0.64</td>
</tr>
<tr>
<td>US SEER, Caucasians</td>
<td></td>
<td>0.80</td>
</tr>
</tbody>
</table>

Heterogeneity across studies can also be explained by age at diagnosis, study design (prospective, retrospective)
64 yr old white woman with interval TNBC

Aggressive ER Negative Breast Cancer

Died 10/06
US Supreme Court -- Opening the Pandora’s Box
...or closing it?
45 year old diagnosed with TNBC after self palpating a mass 6 months after normal MMG.
Why not sequence everyone’s genome?

Adapted from Ian Foster, Computational Institute
Phenotypic Effect Size and Frequency of Occurrence of Cancer Susceptibility Genes

BROCA: African Americans in Chicago

• 289 African American patients with primary invasive breast cancer and with personal or family cancer history or tumor characteristics associated with high genetic risk.

• Sixty-eight damaging germline mutations were identified in 65 subjects (22%, 95% CI 18–28%).

Fig. 2 Eight genes with mutations in African American breast cancer patients. A total of 68 mutations were identified, 76 % in BRCA1 or BRCA2 and 24 % in other breast cancer genes.

## Fine-mapping of known susceptibility loci

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean ± SD</strong></td>
<td>48.0 ± 12.0</td>
<td>47.2 ± 17.2</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Age &lt; 50 yrs, n (%)</strong></td>
<td>878 (58.4%)</td>
<td>799 (57.9%)</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>% of African ancestry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nigerian</td>
<td>0.980 ± 0.012</td>
<td>0.981 ± 0.010</td>
<td>0.08</td>
</tr>
<tr>
<td>Barbadian</td>
<td>0.856 ± 0.104</td>
<td>0.857 ± 0.098</td>
<td>0.93</td>
</tr>
<tr>
<td>African American</td>
<td>0.776 ± 0.135</td>
<td>0.787 ± 0.120</td>
<td>0.10</td>
</tr>
<tr>
<td>Baltimore</td>
<td>0.807 ± 0.133</td>
<td>0.795 ± 0.122</td>
<td></td>
</tr>
<tr>
<td>Pennsylvania</td>
<td>0.780 ± 0.134</td>
<td>0.793 ± 0.112</td>
<td></td>
</tr>
<tr>
<td>Chicago</td>
<td>0.773 ± 0.141</td>
<td>0.796 ± 0.115</td>
<td></td>
</tr>
<tr>
<td>Northern California</td>
<td>0.758 ± 0.125</td>
<td>0.763 ± 0.131</td>
<td></td>
</tr>
</tbody>
</table>
GWAS consortia of breast cancer in women of African Ancestry

<table>
<thead>
<tr>
<th>Study consortium</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>AABC (discovery phase)</td>
<td>2120</td>
<td>1917</td>
</tr>
<tr>
<td>ROOT (discovery phase)</td>
<td>1657</td>
<td>2028</td>
</tr>
<tr>
<td>AMBER (validation phase)</td>
<td>2754</td>
<td>3698</td>
</tr>
<tr>
<td>Total</td>
<td>6522</td>
<td>7643</td>
</tr>
<tr>
<td>ER+</td>
<td>2933</td>
<td></td>
</tr>
<tr>
<td>ER-</td>
<td>1876</td>
<td></td>
</tr>
</tbody>
</table>
Somatic Signatures in whole exome data

ARTICLE

doi:10.1038/nature12477

Signatures of mutational processes in human cancer

A list of authors and their affiliations appears at the end of the paper

All cancers are caused by somatic mutations; however, understanding of the biological processes generating these mutations is limited. The catalogue of somatic mutations from a cancer genome bears the signatures of the mutational processes that have been operative. Here we analysed 4,938,362 mutations from 7,042 cancers and extracted more than 20 distinct mutational signatures. Some are present in many cancer types, notably a signature attributed to the APOBEC family of cytidine deaminases, whereas others are confined to a single cancer class. Certain signatures are associated with age of the patient at cancer diagnosis, known mutagenic exposures or defects in DNA maintenance, but many are of cryptic origin. In addition to these genome-wide mutational signatures, hypermutation localized to small genomic regions, ‘kataegis’, is found in many cancer types. The results reveal the diversity of mutational processes underlying the development of cancer, with potential implications for understanding of cancer aetiology, prevention and therapy.
Significantly mutated genes in breast cancer

*TCGA consortium, Nature 2012*
Angelina Jolie

- Not all women need risk reducing mastectomies
- BRCA1+ women need risk reducing oophorectomies
- BRCA-associated cancers benefit from Parp Inhibitors
  - Positive trials in ovarian cancer, prostate cancer and breast cancer etc
A Modified Definition of Precision Medicine

Interventions to prevent, diagnose, or treat a disease (e.g., cancer), based on a molecular and/or mechanistic understanding of the causes, pathogenesis, and/or pathology of the disease. Where the individual characteristics of the patient are sufficiently distinct, interventions can be concentrated on those who will benefit, sparing expense and side effects for those who will not.

Modified by D. Lowy, M.D. from: IOM’s Toward Precision Medicine, 2011
$700mm  Center for Care and Discovery

“Devoted to complex specialty care, with a focus on cancer and advanced surgical programs”

“Major advances will be driven by discoveries in genomics and personalized medicine”
The “Forefront” of Oncology

Achieving distinction in cancer genomics and personalized care requires:

1. Cutting Edge Research
   - Multidisciplinary Collaboration
   - Improved Biospecimen Collection and Repository System

2. Innovative Clinical Trials

3. Personalized Care
   - More effectively using genomics for:
     - Preventative care
     - Treatment
   - Clinical Trial Awareness
   - Efficient Patient Recruitment
   - Clinical Trial Participation
Final Thoughts

• Physician Scientists can accelerate discovery and translation of research that benefit patients
  ✓ 21\textsuperscript{st} Century Medicine is interdisciplinary, patient centered, community based and networked
  ✓ Diverse team of investigators --- basic science, clinical trials, behavioral science, population science, policy, implementation science and health economics etc.
  ✓ Address global burden of disease – cancer predicted to be leading cause of death globally
  ✓ Education mission is robust - prepare a diverse workforce to serve diverse populations
  ✓ Leverage public private partnerships to accelerate progress
Acknowledgement

**Univ. Chicago**
Olopade Lab
Dezheng Huo
Nkem Chineme
Dominique Sighoko
Yonglan Zheng
Galina Khramtsova
Lise Sveen

**IGSB/White Lab**
Kevin White
Jason Grundstad
Jason Pitt
Jigyasa Tuteja

**Dept. Health Studies**
Dezheng Huo

**Univ. Ibadan**
Dept. Ob/Gyn
Oladosu Ojengbede
Omobolanle Oyedele
Stella Odedina
Imaria Anetor

**Dept. Pathology**
Abideen Oluwasola
Mustapha Ajani

**Dept. Surgery**
Temidayo Ogundiran
Adeyinka Ademola
Kelechi Williams
Chibuzor Afolabi

**IAMRAT**
Chinedum Babalola
Abayomi Odetunde
Ifeanyi Nwosu
Jide Okedire
Odunayo Akinyele

**LASUTH**
John Obafunwa
Abiodum Popoola
Olorunde Ifeoluwa
Victor Aderoju
Anne Ayodele
Mobolaji Oludara
Nasiru Ibrahim
Ayodele Sanni
Felix Sanni
Esther Obasi

**Novartis**
Dimitris Papoutsakis
Jordi Barretina
Scott Mahan

**University of Washington**
Seattle
MC King
Tom Walsh
Acknowledgement

TCGA breast cancer analytical working group
• **Dezheng Huo**, U of Chicago
• Jason Pitt, U of Chicago
• Shengfeng Wang, U of Chicago
• **Chuck Perou**, U of North Carolina
• Katherine A. Hoadley, U of North Carolina
• Hai Hu, Windber Research Institute
• Jianfang Liu, Windber Research Institute
• Suhn Kyong Rhie, U of South California
• Peter Laird, Van Andel Institute
• Andrew D. Cherniack, Broad Institute