Genomic Profiling of Early-Onset Breast Cancer in African-American and European-American Women

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Cancer Health Disparities Summit 2008
Bethesda North Marriott Hotel and Conference Center
Breast Cancer Incidence Rates

Age-Specific SEER Incidence Rates by Race, Breast Cancer, Females SEER 13 Registries for 1995-2004
Breast Cancer Mortality

Age-Specific Total US Mortality Rates For Breast Cancer, Females, For 1995-2004 by 'Expanded' Race

Breast Cancer Survival

Factors Influencing Breast Cancer Disparities

- Access to healthcare (breast cancer screening)
- Socioeconomic status
- Other environmental factors (diet, exogenous hormone exposure)
- Genetics

*Disparities persist after controlling for sociodemographic factors, eg, education, reproductive experiences and access to healthcare* [Chen VW et al, 1994; Miller BA 2002; Chlebowski RT, 2005]
## Biological differences reported between AA and EA breast tumors

<table>
<thead>
<tr>
<th>Biological Feature</th>
<th>AA</th>
<th>EA</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone Receptor Expression</td>
<td>Negative</td>
<td>Positive</td>
<td>VW Chen 1994, BA Miller 2002</td>
</tr>
<tr>
<td>Histological and Nuclear Grade</td>
<td>High</td>
<td>Low</td>
<td>VW Chen 1994, CA Kotwall 2003</td>
</tr>
<tr>
<td>AJCC Stage</td>
<td>Late stage at presentation</td>
<td>Early stage at presentation</td>
<td>PL Porter 2004, BA Jones 2004</td>
</tr>
<tr>
<td>p53 Mutations</td>
<td>Positive</td>
<td>Negative</td>
<td>BA Jones 2004, PL Porter 2004</td>
</tr>
<tr>
<td>Breast Tumor Subtype</td>
<td>Basal</td>
<td>LA/LB</td>
<td>LA Carey 2006, CU Ihemelandu 2007</td>
</tr>
<tr>
<td>Disease Onset</td>
<td>Early (before age 50)</td>
<td>Late (after age 50)</td>
<td>CA Kotwall 2003, PL Porter 2004</td>
</tr>
</tbody>
</table>
HYPOTHESIS

The differences in tumor phenotype observed between African-American and European-American early onset (age≤50yrs) breast cancer correlate with specific patterns of genomic aberrations and these patterns represent different pathways of breast cancer development.
APPROACH

- Characterize the biological differences in breast tumors from Alabama AA and EA early onset breast cancer patients.

- Use array-based comparative genomic hybridization to identify candidate loci that are differentially altered in breast tumors from Alabama AA and EA patients.

- Correlate the genomic aberrations occurring at candidate loci with tumor biological differences.
Classification of Breast Tumors by Ethnicity and Histological Grade

AA n=39, EA n=46; \( P<0.001 \)

Classification of Breast Tumors by Ethnicity and Subtype

AA n=40, EA n=47; \( p=0.112 \)
Array Comparative Genomic Hybridization

Sample DNA + Reference DNA → Hybridization → BAC DNAs → Analysis
Chromosome 8p Aberrations by Ethnicity

- More common in premenopausal breast tumors
- Associated with ER negativity, high tumor grade
- Contains putative TS loci which play a role in breast and prostate cancer

Linnaeus Center for Bioinformatics Data Warehouse: [http://dw.lcb.uu.se](http://dw.lcb.uu.se)
Chromosome 17q12 Deletion Differentially Altered by Ethnicity

- The deletion occurs in 100% of EA samples and ~35% of AA samples.
- This region contains a family of structurally related Rab-GTPases recently implicated in prostate cancer.

CGH Explorer 3.1. described in OC Lingjærde et al, Bioinformatics 2005
## Frequency of Specific Alterations Occurring in AA and EA Breast Tumors

<table>
<thead>
<tr>
<th>Aberration</th>
<th>Chrm.</th>
<th>Locus Span (bp)</th>
<th>Genes</th>
<th>AA</th>
<th>EA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deletion</td>
<td>1q12</td>
<td>141485039-141653087</td>
<td>Q9UMX8, Q8NF67</td>
<td>27%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>7p22.3</td>
<td>1228336-1327504</td>
<td>UNCX</td>
<td>18%</td>
<td>56%</td>
</tr>
<tr>
<td></td>
<td>10q22.2</td>
<td>77136739-77177473</td>
<td>c10orf11</td>
<td>27%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>17q12</td>
<td>33354803-33591769</td>
<td>TBC1D3</td>
<td>27%</td>
<td>56%</td>
</tr>
<tr>
<td>Amplification</td>
<td>5p15.32</td>
<td>5830137-6021315</td>
<td></td>
<td>27%</td>
<td>44%</td>
</tr>
<tr>
<td></td>
<td>5p13.3</td>
<td>33976871-34066975</td>
<td>RXFP3, SLC45A2, C1QTNF3</td>
<td>27%</td>
<td>44%</td>
</tr>
<tr>
<td></td>
<td>8q24.13</td>
<td>126120940-126291775</td>
<td>SQLE, KIAA0196, NSMCE2</td>
<td>27%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>17q24.3</td>
<td>67503237-67689459</td>
<td>Q8IVH9, SOX9</td>
<td>27%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>19p13.2</td>
<td>8665785-8729253</td>
<td>NP_848620.1, OR2Z1</td>
<td>27%</td>
<td>56%</td>
</tr>
<tr>
<td></td>
<td>19p13.11</td>
<td>16791343-16933322</td>
<td>SIN3B, F2RL3, CPAMD8</td>
<td>9%</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>19q13.2</td>
<td>43776562-43945405</td>
<td>MAP4K1, EIF3K, ACTN4, CAPN12</td>
<td>27%</td>
<td>0%</td>
</tr>
</tbody>
</table>
In our sample dataset, higher grade aggressive subtype breast tumors were more frequent in AA patients compared to EA patients, and this trend is consistent with previous reports.

Both AA and EA breast tumors exhibit complex genome copy number alterations.

Several loci were found to be differentially altered in AA vs. EA breast tumors (i.e. 2p13, 4p, 7q22.1 8p, 9q, 10p, 12p, 13q and X).

Currently, the dataset is being expanded to examine ethnicity-based differences by subtype.
ADDITIONAL STUDIES AND IMPLICATIONS

- Explore the ancestry of frequent amplifications and deletions to determine whether specific African or European alleles segregate with aberration events.

- Compare array CGH profiles from corresponding normal breast tissue with those from breast cancer tissue samples.

- Data from this investigation will inform additional studies of candidate genes with tumor suppressive and oncogenic properties.

- An understanding of the genetic drivers of aggressive early onset breast cancer in the African-American population may uncover novel therapeutic targets for breast cancer.
ACKNOWLEDGMENTS

UAB Breast SPORE Tissue Repository
Kathy Sexton
Amanda Mitchell
Bill Grizzle

UAB Comprehensive Cancer Center
Renee Desmond
Natalya Frolova

UAB Heflin Center for Human Genetics
Arek Piotrowski
Bruno Poplawski

UAB Minority Health & Research Center
Mona Fouad
Ann Smith

NIH/NCI-CRCHD/CURE
LeeAnn Bailey
Mary Ann Van Duyn

DISSERTATION COMMITTEE
Theresa Strong, Advisor
Jan Dumanski
Mona Fouad
Andra Frost
Bruce Korf
Susan Sell

SUPPORT
NIH/NCI National Research Service Award
Predoctoral Fellowship 1F31CA126473-01A1
Sigma Xi National Scientific Research Society
GIAR Award
UAB Breast SPORE Pilot Project