Breast Cancer in African-American Women

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Breast Cancer in African-American Women

- Higher incidence overall of breast cancer in European-American women
- African-American women more likely to be diagnosed before age 40
- More aggressive tumors in African-American women
  - High grade
  - Negative for estrogen receptor expression
  - High mitotic index
Breast Cancer in African-American Women

Breast cancers among young women have poorer prognosis

Is the higher incidence of more aggressive cancers among African-American women due to the earlier age at onset?
Proportion of ER-/PR- tumors by race in 13,239 women within age quartiles

IHC surrogates for gene expression profiling

Nielson et al. IHC subtypes
ER+ / HER2-    HER2+ / ER+ or -    ER- / HER2- / CK5/6+ and/or HER1+

Current Study IHC subtypes
ER+ and/or PR+ / HER2-    ER+ and/or PR+ / HER2+    ER- / PR- / HER2+    ER- / PR- / HER2- / CK5/6+ and/or HER1+

Slide courtesy of R Millikan
More common in African-American than European-American women

In CBCS (n=1,424 cases), 16% basal-like - different distributions by race, age (Millikan RC 2008)

Women < 40 years have 4.5 times the risk of basal like breast cancer than those > 60, in comparison to luminal A

<table>
<thead>
<tr>
<th>Menopausal status</th>
<th>EA (%)</th>
<th>AA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>14.5</td>
<td>27.2</td>
</tr>
<tr>
<td>Post</td>
<td>9.3</td>
<td>16</td>
</tr>
</tbody>
</table>
Race, Age and Breast Cancer Characteristics

Unique molecular characteristics of tumors among younger women
- Immune function, mTOR/rapamycin pathway, hypoxia, BRCA1, stem cell biology, apoptosis, histone deacetylase, signaling (Anders 2008)

Differential tumor epithelial and stromal gene expression patterns between African-American and European-American women (Martin 2009)
- Genes regulating angiogenesis and chemotaxis; unique interferon signature
  - Higher microvessel density and macrophage infiltration in tumors from African-American women
Breast Cancer in African-American Women

What is driving these differences in tumor subtypes?
- epidemiologic risk factors? (modifiable)
- biology?
- genetics?
What Risk Factors Differ by Subtype?

Carolina Breast Cancer Study, 1803 cases, 1,564 controls

<table>
<thead>
<tr>
<th>Waist hip ratio</th>
<th>Luminal A OR (95% CI)</th>
<th>Basal-like OR (95% CI)</th>
<th>Basal-like Premenopausal</th>
<th>Basal-like Postmenopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.77</td>
<td>Referent 1.1 (1.1-1.7)</td>
<td>Referent 2.3 (1.5-3.5)</td>
<td>Referent 2.3 (1.3-4.1)</td>
<td>Referent 1.4 (0.7-2.8)</td>
</tr>
<tr>
<td>0.77-0.83</td>
<td>1.5 (1.1-1.9)</td>
<td>2.3 (1.4-3.6)</td>
<td>1.9 (1.0-3.6)</td>
<td>1.4 (0.7-2.7)</td>
</tr>
<tr>
<td>0.84+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## What Risk Factors Differ by Subtype?

<table>
<thead>
<tr>
<th>Case-control analysis</th>
<th>Luminal A OR (95% CI)</th>
<th>Basal-like OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>1</td>
<td>0.7 (0.5-1.0)</td>
<td>1.7 (0.9-3.0)</td>
</tr>
<tr>
<td>2</td>
<td>0.7 (0.6-1.0)</td>
<td>1.8 (1.1-3.1)</td>
</tr>
<tr>
<td>3+</td>
<td>0.7 (0.5-0.9)</td>
<td>1.9 (1.1-3.3)</td>
</tr>
<tr>
<td><strong>Months breastfeeding per child</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>0-3.9</td>
<td>0.8 (0.7-1.0)</td>
<td>0.8 (0.6-1.2)</td>
</tr>
<tr>
<td>4+</td>
<td>0.9 (0.7-1.2)</td>
<td>0.6 (0.4-0.9)</td>
</tr>
</tbody>
</table>

Carolina Breast Cancer Study; Millikan Br Ca Trt Res 2008
### Carolina Breast Cancer Study

<table>
<thead>
<tr>
<th>Parity and lactation</th>
<th>Luminal A OR (95% CI)</th>
<th>Basal-like OR (95% CI)</th>
<th>AA &lt; 40y</th>
<th>AA 40-49y</th>
<th>EA &lt; 40y</th>
<th>EA 40-49y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulliparous 1-2, never</td>
<td>Referent 0.7 (0.6-0.9)</td>
<td>Referent 1.8 (1.1-3.0)*</td>
<td>18%</td>
<td>30%</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>1-2, ever</td>
<td>0.7 (0.5-0.9)</td>
<td>1.1 (0.6-2.0)</td>
<td>9%</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3+, never</td>
<td>0.7 (0.5-0.9)</td>
<td>1.9 (1.1-3.3)*</td>
<td>10%</td>
<td>26%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3+, ever</td>
<td>0.7 (0.5-0.9)</td>
<td>1.3 (0.7-2.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For luminal A, parity reduces risk, regardless of number of children or breastfeeding; importance of terminal differentiation of breast ductal cells.

Basal like – increased risk with parity ameliorated by breastfeeding.
Risk Factors for Early Onset Breast Cancer among African-American Women

Black Women’s Health Study (Palmer, PI)

- High parity IRR = 2.4 (CI = 1.1-5.1) in women < 45; reduced risk in older women IRR = 0.5 (CI 0.3-0.9) (JNCI 2003)

- High BMI inversely associated with risk in premenopausal women IRR = 0.71, (CI 0.53-0.93); no association in postmenopausal (IRR = 0.84, CI 0.63-1.12) (CEBP 2007)

- Reduced risk with strenuous activity at age 21 for premenopausal (IRR = 0.5, CI 0.3-0.8), but not postmenopausal women (J Nat Med Assoc 2001)
Breast Cancer in African-American Women

Need for very large sample sizes to subtype tumors, evaluate risk factors for subtypes by race, age

Developing P01 to pool studies (CBCS, Millikan; BWHS, Palmer; WCHS, Ambrosone)
Women’s Circle of Health Study

- Grant developed in 2000
  - African-American women (and girls) have higher levels of estrogens, higher BNI, earlier age at menarche, earlier age at first birth, more children
  - Distribution of polymorphisms differs across racial and ethnic groups
  - Could these differences account for earlier onset and more aggressive disease?

2. To examine risk factors related to earlier age at diagnosis and more aggressive disease (ER-, high grade tumors).

3. To determine proportion of early age/aggressive breast cancer due to differential racial distribution of risk factors.
First funded by DOD as part of Breast Cancer Center of Excellence for Biobehavioral Research (Bovbjerg, Center PI; Ambrosone, Project 1 [case control study] PI), Mount Sinai School of Medicine

Obtained NCI funding to expand sample size, extend to Caucasians
Study Design

- Ascertainment of African-American (n=1200) and European-American (n=1200) women with incident, primary breast cancer through hospitals in the NY metropolitan area, and through NJ State Tumor Registry (SEER site)
  - Now limited to enrollment in NJ

- Equal number of healthy controls identified through random digit dialing

- Permission from physician to contact patient

- In-home interviews, sample collection
The Women’s Circle of Health: Recruitment (as of May 5, 2009)

<table>
<thead>
<tr>
<th></th>
<th>Cases=1,249</th>
<th>Controls=1,085</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA*</td>
<td>White</td>
</tr>
<tr>
<td>NYC</td>
<td>338</td>
<td>340</td>
</tr>
<tr>
<td>NJ</td>
<td>251</td>
<td>320</td>
</tr>
<tr>
<td>Total</td>
<td>589</td>
<td>660</td>
</tr>
<tr>
<td>Goal:</td>
<td>1,200</td>
<td>1,200</td>
</tr>
</tbody>
</table>

*AA: African American
Breast Cancer Detection among Younger and Older Women

<table>
<thead>
<tr>
<th>How was your breast cancer found?</th>
<th>AA (%)</th>
<th>EA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 40</td>
<td>≥ 40</td>
</tr>
<tr>
<td>Self-exam</td>
<td>31</td>
<td>25</td>
</tr>
<tr>
<td>Accidental</td>
<td>40</td>
<td>22</td>
</tr>
<tr>
<td>MD exam</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Mammogram</td>
<td>8</td>
<td>40</td>
</tr>
</tbody>
</table>

Ever have a screening mammogram

<table>
<thead>
<tr>
<th></th>
<th>AA</th>
<th></th>
<th>EA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td>40%</td>
<td>≥ 40</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>≥ 40</td>
<td>47%</td>
<td>&lt; 40</td>
<td>93%</td>
<td></td>
</tr>
</tbody>
</table>
Classification of Subtypes

- Collection of tumor tissue blocks from hospitals
- Standardized grading by one pathologist at RPCI
- Construction of TMAs, staining for ER, PR, HER2, cytokeratins
Estrogen Receptor Status by Race and Age (WCHS)

Race and ER Status

%
Tumor Differentiation by Race and Age (WCHS)

Race and Grade

- AA 1
- AA 2
- AA 3
- EA 1
- EA 2
- EA 3

%
Parity by Race among Cases (WCHS)

Race

African-American

Caucasian

Age

0
1 or 2
3 or 4
5+

%
Age at First Full Term Pregnancy by Race (WCHS)

Race
- African-American
- Caucasian

Age
- < 19
- 20-24
- 25-29
- 30+

%
GWAS of Breast Cancer in African-American Women (Haiman, PI)

- 12 Participating studies
  - 4,684 cases, 4,506 controls
- Illumina 1M chip
- Risk variants found in EA GWAs – slight associations in AAs (FGFR2, 8q24, MAP3K1)
- Additional unique SNPs identified (ORs=1.2), specific to ER- breast cancer
- Stratify by age at onset

- Higher pigmentation in Africans –
  - adequate absorption of vitamin D in sub-Saharan environment
  - High prevalence of vitamin D deficiencies in African-Americans
  - Distributions of polymorphisms in Vitamin D receptor and VDR metabolism varies by ancestry

- Relationship between Vitamin D levels and basal-like breast cancers?
Vitamin D levels according to clinical characteristics by menopausal status

Funded by BCRF
Vitamin D and Early, Aggressive Breast Cancers in African-American Women

- Low vitamin D levels associated with high grade, triple negative breast cancers ONLY among premenopausal women

- Ongoing assessment in relation to early onset, aggressive breast cancer in African-American women in WCHS study; vitamin D receptor polymorphisms

- Adaptation to endemic infectious disease (malaria) in Africa

- Development of robust immune/inflammatory response – differential distributions of SNPs in these pathways

- Relationship with high grade, early onset breast cancers?
Early, Aggressive Breast Cancers in African-American Women

- Racial differences in tumor characteristics *appear to be* independent of early age at onset

- Intensive research to identify modifiable risk factors for early aggressive breast cancers
In collaboration with......

Elisa Bandera, CINJ

Karen Pawlish, NJ Dept. Health and Senior Services

Dana Bovbjerg, U Pittsburgh

Lina Jandorf, MSSM

Gregory Ciupak, Warren Davis, RPCI

Multiple clinical and scientific collaborators
Number of Children by Race and Age among Breast Cancer Cases (WCHS)