Breast cancer in African-American women: an evolutionary perspective

Christine B. Ambrosone, PhD
Chair, Department of Cancer Prevention and Control
Roswell Park Cancer Institute
Breast Cancer in African-American Women

- Higher incidence overall of breast cancer in European-American (EA) women
- African-American (AA) 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 tumors extremely heterogeneous – can better classification by tumor subtypes clarify risk factors for breast cancer in AA women?

DNA microarray-based gene expression profiling (Perou, Sorlie) identified distinct breast cancer subtypes, later well represented with IHC markers.

Validated in numerous other populations.

Subtypes associated with prognosis.
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+

JAMA 2006, 295: 2492-2502
In CBCS (n=1,424 cases), 16% basal-like - different distributions by race, age (Millikan RC 2008)

More common in AA than EA women

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

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

- 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

• Clear differences in distributions of breast cancer subtypes and tumor characteristics by ancestry and by age

• What is driving these differences in tumor subtypes?
  - epidemiologic risk factors? (modifiable)
  - biology?
  - genetics?

• Initiated study in 2001 to examine role of reproductive and hormonal factors in ‘aggressive’ breast cancer
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)

Equal number of healthy controls identified through random digit dialing

Permission from physician to contact patient

In-home interviews, sample collection, body size and fat measures
Breast Cancer in African-American Women

‘African-Americans’ heterogeneous population, with varying admixture in populations

Ancestry informative markers (AIMs) can be used to estimate genetic ancestry and to test associations with disease risk

Collaboration with Elad Ziv, Laura Fejerman (UCSF), Esther John, genotyping 1,536 AIMs (333 women with breast cancer) with Illumina BeadStation 500GXDW
African Ancestry Among African American Breast Cancer Cases (n=333)

Extent of African ancestry associated with higher odds of ER-PR- breast cancer

ER+PR+ vs ER-PR- OR=4.73 (95% CI, 1.56-14.33), p=0.006

Fejerman et al, CEBP 2009
DNA Methylation: a Mechanism for Early/Aggressive Breast Cancer in African-American Women?

Stage 1 – genome wide scan for differential methylation in tumors from 100 AA and 100 EA women

Stage 2 – top hits in FFPE breast tumors from 500 AA and 500 EA women, self-report and using AlMs - in relation to age at onset, tumor characteristics, risk factors

R01 CA133264 Ambrosone, Higgins, Demissie (CINJ) – multiple PIs

- Evolution over millennia has resulted in numerous differences between populations from different continents of origin

- Are there factors related to ancestry that could be related to early, aggressive breast cancers in African-American women?

1. Africa home to origins of man – darker pigmentation the ancestral skin color

2. Adaptation to endemic infectious disease – robust immune/inflammatory responses
Vitamin D and Aggressive Breast Cancer

Higher pigmentation the ancestral skin color (lighter skin with migration to northern regions)
- adequate absorption of vitamin D in sub-Saharan environment, but deficiencies in African-Americans in urban our northern environments

Rodent models:
- vitamin D inhibits proliferation of breast cancer cells, induces apoptosis, prevents carcinogenesis,
- Vdr knock-out mice more likely to develop Er/Pr negative tumors than wild type mice

Epidemiologic data inconsistent for overall breast cancer
- could be related to subgroups of breast cancers
Proportion of vitamin D deficiency (<10 ng/ml) by ancestry among healthy women

Women’s Circle of Health Study (n=400)

25 OH-D levels lowest in women with highest African ancestry, using AIMS

Song Yao, PhD
Enrollment of newly diagnosed patients, prior to surgery

Banked serum, plasma, RBCs, DNA

Epidemiologic questionnaire completed

Linkage with clinical data, tumor tissue

Recruiting visitors as non-cancer controls
25OHD (ng/ml) and Breast Tumor Grade among Premenopausal Women

Data and samples from RPCI DataBank and BioRepository (> 500 cases)
25OHD and Breast Cancer Subtypes among Premenopausal Women

![Bar chart showing Vitamin D levels (ng/mL) for different breast cancer subtypes: Luminal A, Luminal B, HER2 overexpressing, and Triple Negative.](chart.png)
Vitamin D Receptor Polymorphisms and Breast Cancer Risk (WCHS)
Hypothesize that genetic profiles that evolved over millennia to adapt to endemic infectious disease may increase risk of early onset, aggressive cancers.

Distributions of polymorphisms in numerous cytokines and chemokines in both pathways differ markedly by continent of origin.

Number of cytokines associated with poor prognosis.
Examining levels of cytokines, chemokines in non-cancer controls

- IL-12: inhibitor of TH2 immune response, has anti-tumorigenic effects in mice, inhibiting establishment and/or inducing regression of tumors

- RANTES (CCL5): promotes breast cancer progression; co-expression with MCP-1 associated with more advanced breast tumors
Levels of IL-12 by Ancestry in WCHS

IL-12: inhibitor of TH2 immune response, has anti-tumorigenic effects in mice, inhibiting establishment and/or inducing regression of tumors

Chi-Chen Hong, PhD
Levels of RANTES by Ancestry in WCHS

RANTES (CCL5): promotes breast cancer progression; co-expression with MCP-1 associated with more advanced breast tumors
Examining serum levels of cytokines, chemokines relation to tumor characteristics in same population as vitamin D analyses

Forms basis of one of four projects in recently awarded Program Project grant
P01 CA151135

Epidemiology of Breast Cancer in African-American Women: a Consortium

PIs: Ambrosone, Palmer (BU), Millikan (UNC)

Pool data from 4 largest studies of breast cancer in African-American women - > 5000 cases, 5000 controls with tumor blocks, DNA, questionnaire data

4 projects, 4 cores, administered through RPCI
### 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</td>
<td>Referent</td>
<td>Referent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2, never</td>
<td>0.7 (0.6-0.9)</td>
<td>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>10%</td>
<td>26%</td>
</tr>
<tr>
<td>3+, never</td>
<td>0.7 (0.5-0.9)</td>
<td>1.9 (1.1-3.3)*</td>
<td>18%</td>
<td>30%</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>3+, ever</td>
<td>0.7 (0.5-0.9)</td>
<td>1.3 (0.7-2.3)</td>
<td>9%</td>
<td>10%</td>
<td>10%</td>
<td>26%</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, Rosenberg, PIs)

- 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)

- Increased risk with parity ameliorated with breastfeeding (unpublished data)

- 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)