THE RACIAL DIFFERENCES THAT AFFECT PROSTATE CANCER

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University of North Carolina at Chapel Hill

African American Prostate Cancer Disparity Summit
Washington, DC    Sept 21-22, 2006
Prostate Cancer in Caucasian vs African Americans

- frequency of incidental prostate cancer same
- clinical prostate cancer, age < 65
  incidence 1.6 X
  mortality 2.8 X
- clinical prostate cancer, age ≥ 65
  incidence 1.3 X
  mortality 2.1 X  
  *Miller, NCI, 1996*
  
  *Fowler, Mono Urol, 1998*
MECHANISM of ANDROGEN ACTION

- Androgen binding
- Activation
- Dimerization
- DNA binding
- Transcription activation
- Translation

PROTEIN
Androgen Receptor Protein

• In a pilot study of 50 radical prostatectomy specimens, androgen receptor protein levels were 18% higher in benign prostate and 80% higher in prostate cancer in African than Caucasian Americans

• Androgen receptor protein is stabilized by androgens and dihydrotestosterone (DHT) is its preferred ligand
Racial Differences in AR Expression in AD CaP

<table>
<thead>
<tr>
<th></th>
<th>AA</th>
<th>CA</th>
<th>T-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>25</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>60 ± 8</td>
<td>62 ± 6</td>
<td>p = 0.303</td>
</tr>
<tr>
<td>PSA (ng/dl)</td>
<td>15.5 ± 12.2</td>
<td>9.7 ± 7.5</td>
<td>*p = 0.049</td>
</tr>
<tr>
<td>Gleason Grade</td>
<td>7.2 ± 1.1</td>
<td>6.5 ± 1.1</td>
<td>*p = 0.044</td>
</tr>
<tr>
<td>Path Stage</td>
<td>P2= 11, P3= 12, N+ = 2</td>
<td>P2 = 13, P3= 10, N+ = 2</td>
<td>p &gt; 0.75 (x2)</td>
</tr>
<tr>
<td>AR Visual Score</td>
<td>171 ± 40</td>
<td>149 ± 37</td>
<td>*p = 0.048</td>
</tr>
<tr>
<td>AR MOD</td>
<td>0.185 ± 0.09</td>
<td>0.107 ± 0.07</td>
<td>*p = 0.002</td>
</tr>
<tr>
<td>% Area Positive</td>
<td>75.2 ± 14.2</td>
<td>59.1 ± 26.2</td>
<td>*p = 0.01</td>
</tr>
</tbody>
</table>
Racial Differences in AR Expression
Androgen Receptor Protein

- In a pilot study of 50 radical prostatectomy specimens, androgen receptor protein levels were 18% higher in benign prostate and 80% higher in prostate cancer in African than Caucasian Americans (Gaston, J Urol, 2003)
- Androgen receptor protein is stabilized by androgens and dihydrotestosterone (DHT) is its preferred ligand
Does the African-American Prostate Receive Greater Androgenic Stimulation?

- serum testosterone levels 19% higher in LA college students  *Ross, JNCI, 1987*

- case-control studies associate prostate cancer with both higher and lower serum testosterone levels
Materials and Methods

- Steroid hormones were extracted from snap frozen radical prostatectomy specimens of 36 African and 59 Caucasian Americans.
- Testosterone, dihydrotestosterone (DHT), androstenedione (ASD), dehydroepiandrosterone (DHEA), DHEA sulfate (DHEA-SO₄), sex hormone-binding globulin (SHBG) and prostate-specific antigen (PSA) were measured using radioimmunoassay.
## Racial Differences in Prostate Androgen Levels

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>37</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>60 (44-73)</td>
<td>65 (51-76)</td>
<td>*p= 0.009</td>
</tr>
<tr>
<td><strong>PSA (ng/dl)</strong></td>
<td>6.5 (3.8-35)</td>
<td>8.2 (4-27.5)</td>
<td>p= 0.50</td>
</tr>
<tr>
<td><strong>Gleason Sum</strong></td>
<td>7 (5-9)</td>
<td>7 (38)</td>
<td>p= 0.45</td>
</tr>
<tr>
<td><strong>Path Stage</strong></td>
<td>P0=1, P2=20, P3=16</td>
<td>P0=1, P2=46, P3=26</td>
<td>p= 0.95</td>
</tr>
<tr>
<td><strong>Testosterone (pmol/g)</strong></td>
<td>2.4 (1-5.4)</td>
<td>2.5 (1.2-15)</td>
<td>p= 0.06</td>
</tr>
<tr>
<td><strong>DHT (pmol/g)</strong></td>
<td>4.4 (2-5.6)</td>
<td>5.2 (2.5-23)</td>
<td>p= 0.06</td>
</tr>
<tr>
<td><strong>tPSA (nmol/g)</strong></td>
<td>74.2 (7-205)</td>
<td>85.6 (11-288)</td>
<td>p= 0.6</td>
</tr>
</tbody>
</table>
# Racial Differences in Prostate Androgen Levels

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<tr>
<th>pmol/g</th>
<th>AA</th>
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<tbody>
<tr>
<td>ASD</td>
<td>4.1 (0.9-10)</td>
<td>2.8 (2.5-23)</td>
<td>p = 0.005</td>
</tr>
<tr>
<td>DHEA</td>
<td>79.5 (11-448)</td>
<td>52.2 (8-209)</td>
<td>p = 0.31</td>
</tr>
<tr>
<td>DHEA-SO₄</td>
<td>93.9 (17-753)</td>
<td>58.1 (17-366)</td>
<td>p = 0.084</td>
</tr>
<tr>
<td>SHBG</td>
<td>6.0 (4.3-19)</td>
<td>4.5 (1.6-10)</td>
<td>*p = 0.017</td>
</tr>
</tbody>
</table>
Conclusions

• Tissue levels of testosterone and DHT did not differ by race
• African Americans had higher SHBG tissue levels and more Androgen Receptor than Caucasian Americans
• Higher SHBG tissue levels may activate the androgen receptor through cAMP-dependent pathways
• Higher Androgen Receptor levels may allow racially similar levels of tissue androgens to stimulate prostate (cancer) growth more in African than Caucasian Americans
UNC Prostate Cancer Observation Study

- 1989 to present
- grade, stage, PSA
- uniform counseling
  - life expectancy
  - tumor-limited life expectancy
  - chance of CaP death
  - chance of cure
  - risks of treatment
- PSA, Hct, Cr, DRE q 6 months
Progression Criteria

• Clinical Progression
  change in DRE
  gross hematuria
  UTI
  prostatism/retention
  metastatic disease

• Biochemical Progression
  PSA ↑ x 3 and > 5 ng/ml
Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>AA</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>59</td>
<td>111</td>
</tr>
<tr>
<td>Mean Age (yrs)</td>
<td>71 ± 7</td>
<td>72 ± 6</td>
</tr>
<tr>
<td>PSA (ng/ml)*</td>
<td>18.0 ± 24.0</td>
<td>9.9 ± 0.9</td>
</tr>
<tr>
<td>Gleason Sum</td>
<td>6 ± 2</td>
<td>6 ± 2</td>
</tr>
<tr>
<td>Follow-up (mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>44</td>
<td>43</td>
</tr>
<tr>
<td>Range</td>
<td>3-96</td>
<td>3-138</td>
</tr>
</tbody>
</table>
# Progression

<table>
<thead>
<tr>
<th></th>
<th>AA</th>
<th>CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA Progression</td>
<td>46%</td>
<td>46%</td>
</tr>
<tr>
<td>Clinical Progression</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Time to Progression (mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Range</td>
<td>6-138</td>
<td>3-84</td>
</tr>
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</table>
## Stage-Specific Progression

<table>
<thead>
<tr>
<th>Stage</th>
<th>AA</th>
<th>CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a/b</td>
<td>29% (17)</td>
<td>28% (21)</td>
</tr>
<tr>
<td>T1c</td>
<td>42% (12)</td>
<td>33% (24)</td>
</tr>
<tr>
<td>T2a/b</td>
<td>44% (18)</td>
<td>50% (48)</td>
</tr>
<tr>
<td>T2c</td>
<td>80% (5)</td>
<td>80% (10)</td>
</tr>
<tr>
<td>T3/4</td>
<td>85% (7)</td>
<td>50% (8)</td>
</tr>
<tr>
<td>N+, M+</td>
<td>86% (8)</td>
<td>91% (11)</td>
</tr>
</tbody>
</table>
## Progression by Gleason Grade

<table>
<thead>
<tr>
<th>Gleason Sum</th>
<th>AA</th>
<th>CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 - 6</td>
<td>41% (32)</td>
<td>31% (70)</td>
</tr>
<tr>
<td>7</td>
<td>75% (16)</td>
<td>64% (25)</td>
</tr>
<tr>
<td>8 - 10</td>
<td>44% (9)</td>
<td>75% (16)</td>
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</table>
Progression by PSA at Diagnosis

<table>
<thead>
<tr>
<th>PSA</th>
<th>AA</th>
<th>CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10</td>
<td>24% (25)</td>
<td>30% (77)</td>
</tr>
<tr>
<td>10-20</td>
<td>54% (13)</td>
<td>76% (21)</td>
</tr>
<tr>
<td>20 - 30</td>
<td>88% (8)</td>
<td>83% (6)</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>62% (13)</td>
<td>86% (7)</td>
</tr>
</tbody>
</table>
Deaths (7.1%)

- from prostate cancer 0
- from other causes 12
Actuarial Progression of CaP in Caucasian and African Americans

![Graph showing the probability of non-progression in months for Caucasian (CA) and African American (AA) groups. The graph indicates a decrease in the probability of non-progression with increasing months.]
Mohler’s Take Home Message

Prostate cancer may be more common and aggressive in African Americans because higher levels of androgen receptor and SHBG in African Americans enhance the effect of racially similar levels of tissue androgens but clinical evidence for racial differences in prostate cancer behavior, once diagnosed, remains lacking.
Racial Differences in Prostate Cancer: Influence of Health Care Interaction and Host and Tumor Biology

Hypothesis

The mortality rate from prostate cancer is more than two-fold higher in African Americans compared to Caucasian Americans due to racial differences in 1) interaction with the health care system, 2) diet and biology of the host and/or 3) characteristics of the tumor.

Consortium Members

1) University of North Carolina
2) Louisiana State University
3) Roswell Park Cancer Institute
4) Harvard University
5) Johns Hopkins Medical Center
6) University of California-Irvine
7) University of South Carolina
8) Natl. Inst. Environ. Health Sciences
9) National Cancer Institute
10) Food and Drug Administration
11) Boston University
12) Wake Forest University
NC – LA Prostate Cancer Project (PCaP)

Core 1
EPIDEMIOLOGY
Schroeder (UNC)
Fontham, Su (LSU)

Core 2
BLOOD & TISSUE PROCUREMENT
Smith (RPCI)
Ruiz (LSU)

Core 3
TISSUE MICROARRAY & IMMUNOANALYSIS
Mohler (RPCI)
Ruiz (LSU)

Core 4
ADMINISTRATION
Mohler (RPCI)
Bensen (UNC)

P1. EARLY DETECTION
Godley (UNC)

P2. HEALTH CARE ATTITUDES/BEHAVIOR
Mishel (UNC)

P3. DIET
Su (LSU)

P4. CAP SUSEPTIBILITY GENES
Taylor (NIEHS)

P5. HEREDITARY GENES
Isaacs (JH)
Xu (WFU)

P6. PROTEOMICS
Ornstein (UC-I)
Petricoin (GMU)

P7. ANDROGEN AXIS
Mohler (RPCI)

P8. AR-REGULATED GENES/COACTIVATORS
Wilson (UNC)

P9. STEM CELLS
Smith (RPCI)

LEVEL 1
PATIENT-HEALTH CARE SYSTEM INTERACTION

LEVEL 2
HOST BIOLOGY

LEVEL 3
TUMOR BIOLOGY
Research Subjects

2000 men with newly-diagnosed CaP, 1000 from NC of whom 500 are African American and 500 are Caucasian, and 1000 from LA of whom 500 are African American and 500 are Caucasian, will be identified by rapid case ascertainment. African Americans in NC have one of the highest, and African Americans in LA have one of the lowest mortality rates from CaP in the US while Caucasian Americans in the two states have similar CaP mortality that is less than that in either African American group.

Data Collection

In-home computer-assisted interview and blood, urine, toenail and adipose tissue sampling. Tissue microarrays will be constructed from diagnostic biopsy specimens.
Why a consortium? (See Figure)

Rapid Case Ascertainment

Physician Contact

Home Visit

Patient contact - Enrollment Specialists

Hospital/Physician Office

Interview Consent

Computer-Assisted Interview

- Diet
- Puberty
- Alternative medicine use
- Care access
- SES
- Early detection behavior
- Attitudes, beliefs, knowledge
- Treatment choice

Adipose Tissue, Urine, Toenails

- Fatty acids
- Carotenoids
- Tocopherols
- Heavy Metals

Blood – DNA, Plasma Erythrocytes, WBC for Immortalization

- CaP susceptibility genes
- Hereditary CaP genes
- Proteomics
- Racial admixture
- Carotenoid, tocopherol
- Serum androgens
- AR trinucleotide repeats
- DNA damage/repair

Diagnostic Biopsy Blocks for Tissue MicroArrays

- Ki-67
- Apoptosis
- Androgen receptor
- AR co-activators
- Androgen-regulated genes
- Cell signaling molecules
- Growth factors
- Stem-like cells

Office Record Elements

- Clinical stage
- Medical history
- PSA
- Treatment choice

Mortality / 100,000

- US: 22.0 (22.0 – 22.1)
- LA: 21.5 (21.0 – 22.1)
- NC: 22.4 (22.0 – 22.9)


Mortality / 100,000

US: 47.2 (46.9 – 47.5)
LA: 42.2 (41.0 – 43.5)
NC: 55.4 (54.0 – 56.8)
North Carolina Study Area

>4,000,000 lbs. Tobacco

>100,000 Hogs
Louisiana Study Area
HYPOTHESIS TESTING

Reasons for the disparity in prostate cancer outcome by race will be tested on three levels:

Level 1)

Racial differences in interaction with the health care system will be evaluated by examining early detection behavior; socioeconomic status; attitudes, beliefs and knowledge; health care access; patient-physician communication; patient decision-making; alternative treatment use and treatment choices.
HYPOTHESIS TESTING

Level 2)

Racial differences in host biology may affect CaP aggressiveness due to genetic, environmental or gene-environmental interaction. Racial differences will be sought in diet with an emphasis upon antioxidant and fat consumption; serum androgens; exposure to carcinogens; expression of CaP susceptibility genes such as androgen metabolism pathway, detoxification, DNA repair and hereditary CaP genes; and serum protein profiles associated with the aggressive CaP phenotype.
HYPOTHESIS TESTING

Level 3)

Racial differences in **tumor characteristics** will be examined in tumor extent (clinical stage and serum PSA, a tumor volume surrogate), tumor differentiation (Gleason grade) and tumor growth rate (apoptosis and cellular proliferation); expression of androgen receptor, androgen receptor co-activators and androgen-regulated genes; and stem-like cells.
DOD CONSORTIUM GOAL

To demonstrate whether public health resources should be focused upon altering critical patient-health care system interaction or altering patient or tumor biology to reduce CaP mortality, in general, and CaP mortality in African Americans, specifically.
References


• Schroeder JC. The North Carolina – Louisiana Prostate Cancer Project (PCaP): Methods and design of a multidisciplinary population-based cohort study of racial differences in prostate cancer outcomes. Prostate 2006;66:1162-76.