Why Is It So Difficult to Eliminate Prostate Cancer Disparities

Timothy R. Rebbeck, PhD
Prostate Cancer Mortality Rate Ratio 1975-2012
African American : European American

US Mortality Files, National Center for Health Statistics, CDC.

Reality: Rate Ratio>2 (Disparity)
Goal: Rate Ratio=1 (No Disparity)
What Causes Disparities?

Differences*  Inequities*

Genetics  Discrimination
Race/Ethnicity  Segregation
Environment  Access
Biology/Physiology

What Causes Disparities?

Differences

- Genetics
- Race/Ethnicity
- Environment

Inequities

- Discrimination
- Segregation
- Access

Who is at risk?

- Genetics
- Race/Ethnicity
- Environment

Can we intervene?

- Environment
- Biology/Physiology
Disparities Framework

Self-Identified Race or Ethnicity

Culture

Environment

Behavior

Phenotype

Ancestry

Genomic Variation

Disease-Causative Genetic Variation

Tissue-specific Changes

Disease/Outcome

Prevention, Treatment

Adapted from: Rebbeck and Sankar CEBP 2005, Rebbeck et al. JCO 2006
MADCaP: Men of African Descent and Carcinoma of the Prostate
(Supported by AACR Landon Foundation, U01-CA184374, Fulbright Program, R01-CA085074, P50-CA105641, P60-MD006900)
Overweight and Obesity among Adults Age 20 and Older, USA
Estimated Percentage by Race/Ethnicity (NHANES 2009-2011)
Rate of Post-Prostatectomy Gleason Upgrading in Obese and Non-Obese Men

Yamoah et al. 2016
# Heritability of Common Cancers

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Heritability estimate (%)</th>
<th>Silventoinen 2015</th>
<th>Mucci 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testicular</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Familial Risk, % (95% CI)</th>
<th>Heritability</th>
<th>Shared Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cancer</td>
<td>33 (30-37)</td>
<td>0</td>
</tr>
<tr>
<td>Head and neck</td>
<td>9 (0-60)</td>
<td>26 (0-65)</td>
</tr>
<tr>
<td>Stomach</td>
<td>22 (0-55)</td>
<td>6 (0-31)</td>
</tr>
<tr>
<td>Colon</td>
<td>15 (0-45)</td>
<td>16 (0-38)</td>
</tr>
<tr>
<td>Rectum and anus</td>
<td>14 (0-50)</td>
<td>10 (0-38)</td>
</tr>
<tr>
<td>Lung</td>
<td>18 (0-42)</td>
<td>24 (7-40)</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>58 (43-73)</td>
<td>0</td>
</tr>
<tr>
<td>Nonmelanoma</td>
<td>43 (26-59)</td>
<td>0</td>
</tr>
<tr>
<td>Breast</td>
<td>31 (11-51)</td>
<td>16 (0-31)</td>
</tr>
<tr>
<td>Corpus uteri</td>
<td>27 (11-43)</td>
<td>0</td>
</tr>
<tr>
<td>Ovary</td>
<td>39 (23-55)</td>
<td>0</td>
</tr>
<tr>
<td>Prostate</td>
<td>57 (51-63)</td>
<td>0</td>
</tr>
<tr>
<td>Testis</td>
<td>37 (0-93)</td>
<td>24 (0-70)</td>
</tr>
<tr>
<td>Kidney</td>
<td>38 (21-55)</td>
<td>0</td>
</tr>
<tr>
<td>Bladder, other urinary organs</td>
<td>30 (0-67)</td>
<td>0</td>
</tr>
<tr>
<td>Leukemia, other</td>
<td>57 (0-100)</td>
<td>0</td>
</tr>
</tbody>
</table>
What Genes Are We Looking For?

- **High Relative Risk**
  - Mostly Known: BRCA2, HOXB13
  - Probably Don’t Exist

- **Low Relative Risk**
  - Sequencing
  - “Common Disease, Common Variant”
    - 401 Associations,
      - 167 loci, 17 Traits

**Allele/Genotype Frequency**

- Common
- Rare
Prostate Cancer GWAS Hits Validation in African Descent Men

4,853 African American Cases
4,678 African American Controls

82 GWAS Hits

68 (83%) Directionally Consistent

30 (37%) Significant at p<0.05

Han et al., *Int J Cancer* 2014
Prostate Tissue Biomarker Differences in African American vs. European American Men

Sample biomarkers - Red: European-American  Blue: African-American

Inference:
A set of biomarkers demonstrate racial dependence in predicting locally-advanced prostate cancer.

Yamoah et al., JCO 2015
Marker H-Score Distribution by Race

- cPTEN: p=0.002
- nPTEN: p<0.001
- PSMA: p<0.001
- RACEMASE: p=0.008
- CMYC: p<0.001
- AR: p<0.001
- P53: p=0.66
- cRB: p<0.001
- nRB: p<0.001
- EZH2: p=0.007

Colors:
- European-American
- African-American
- Senegalese
Outlook

• Prostate cancer is etiologically complex.
• Single risk factors are unlikely to explain a large proportion of etiology or disparity.
• Causal factors may impact risk on multiple levels: biological, individual risk factors, contextual.
• Interventions to eliminate disparities may require interventions at multiple levels.
Ancestrally, Socially, or Phenotypically Similar Groups
Different Disease Patterns
Observed Between These Groups

Infer “Disparities” Exist
Risk Factors May Also Cluster in Groups
Group is an Imperfect Surrogate for Phenotypes or Risk Factors of Interest
Regroup Based on Individual’s Risk, not Socially-Defined Group Membership
Goal: Develop a “Precision” Approach to Disparities

- Self-identified race/ethnicity is:
  - A complex, multifactorial trait.
  - Misclassified with respect to the entity we probably care about in defining disparities.
- Develop “precision” approaches to screening and treatment based on:
  - Genomics/Biomarkers
  - Risk Factors
- Maximize benefit and minimize harm
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