Genetic Susceptibility to Prostate Cancer in Men of African Ancestry

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University of Southern California
Prostate cancer disparities

African Americans vs. Whites (and other populations):
- Incidence: 70% greater
  - diagnosed earlier, with more aggressive disease, with greater risk of progression
- Mortality: twice as likely to die from prostate cancer

Many factors likely contribute to prostate cancer disparities:
- sociodemographics, health behaviors, environmental factors, access to care, variation in screening, detection and treatment
- genetics
Genetic ancestry and prostate cancer

Admixture mapping identified risk alleles that track with local genetic ancestry in admixed population

- Admixture scan (n=1,600 AA men): reveals signal at 8q24 (~4 Mb).

Dense genotyping identified multiple risk alleles at 8q24 that contribute to prostate cancer risk.

- Multiethnic Cohort: 4,266 cases and 3,252 controls: African Americans, Whites, Japanese, Latinos, Native Hawaiians
- 7 independent risk alleles in 3 regions

Polygenic risk model for prostate cancer: 8q24

rs6983267

Risk Allele

Ref

ACB ASW ESN GWD LWK MSL YRI CLM MXL PEL PUR CDX CHB CHS JPT KHV CEU FIN GBR IBS TSI

| African | Hispanic | Asian | European |

African Americans, PAR=68%

Whites, PAR=32%

Relative risk compared with individuals carrying none of the seven risk alleles

Haiman et al. Nat Genet 2007
<table>
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<th>Study</th>
<th>Name</th>
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**TOTAL:** 10,368 10,986
GWAS in AAPC

Conti et al, JNCI 2017

rs72725854
p=5x10^{-105}
Freq=6%

vs. HOXB13: - 0.2% of Whites in U.S. G84E carriers (RR=3); accounts for 5% of hereditary PC
Population-specific risk alleles

13p34 - *IRS2*

17q12 - *ZNF652*

22q12 - *CHEK2*

- 2-5% in African ancestry populations
- 0% in other populations
- RR~1.6

17q12: rs7210100

Haiman et al, Nat Genet 2011
Conti et al, JNCI 2017
GWAS of cancer (through 2016)

- Over 700 cancer loci identified
  - ~80% first discovered in Whites
  - ~15% in East Asians,
  - ~3% in multiethnic scans
  - ~1% in African and Latin Americans.

N~478,000 cases

- European 84%
- African 11%
- East Asian 4%
- Latin American 1%
GWAS of prostate cancer

• PRACTICAL/ELLIPSE NCI GAME-ON Consortium: ~130 studies globally

Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci

Schumacher et al, Nat Genet 2018

• 181 common risk variants have been identified
  – >80% found in GWAS in whites
  – 37% of familial risk (FR) of prostate cancer in whites
  – modest effects (RR~1.05-1.40)

Polygenic Risk Score (PRS)

European Ancestry
~60,000 cases
~60,000 controls
Prostate cancer PRS by population

PRS summary (n=181 risk variants):
- Performance: European > Latino = African = Asian
Do genetic factors contribute to population differences in prostate cancer risk?

14 variants at 8q24

GWAS and fine-mapping in whites

All 181 variants
Multiethnic Studies

• Goal: To combine GWAS data across populations to identify stronger signals in known regions and novel variants with pan-ethnic effects.

• GWAS and fine-mapping meta-analysis:

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<td><strong>Total</strong></td>
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<td><strong>110,406</strong></td>
<td><strong>126,974</strong></td>
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Results (preliminary):
• ~60 novel risk variants (~240 total)
• ~90 of the 181 known risk (‘index’) variants have been replaced
Clinical Utility of GWAS-PRS

• Common risk variants (and the PRS) can’t discriminate between a man’s risk of aggressive vs. non-aggressive disease

• Ongoing prostate cancer screening studies that incorporate PRS in the UK and Sweden:
  – STHML3
  – BARCODE (includes AA men)
  – PROFILE

• Need genetic markers of aggressive disease

General male population

FamHist + PRS + rare mutations + PSA + biomarkers + ancestry

targeted screening MRI, biopsies

- Increase detection of aggressive/lethal disease
- Reduce # of biopsies, over-diagnosis of indolent disease
Rare pathogenic mutations in DNA repair genes

**BRCA1/2**
- 1% of prostate cancer cases carry a mutation
- BRCA1: RR>2
- BRCA2: RR>5
- Carriers develop more aggressive disease and have poor survival

Kote-Jarai et al, Br J Cancer 2011

Pritchard, NEJM 2016

Castro et al, JCO 2013

**Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer**

692 metastatic PC cases
53,105 ExAC controls

**Mutation carriers:**
- 12% of metastatic cases
- 3% of controls

Pritchard, NEJM 2016
Rare coding variants and prostate cancer risk in men of African ancestry

- DNA repair and cancer susceptibility gene panel (16 genes)
- Rare pathogenic mutations (protein truncating, ClinVar-missense)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Cases</th>
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<tr>
<td>African American</td>
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<td>1447</td>
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<tr>
<td>Ugandan</td>
<td>486</td>
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<td>Total</td>
<td>2098</td>
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Mutation carriers:
- 4% of cases
- 2% of controls
- RR=1.82, p=0.004
Rare coding variants and prostate cancer risk in men of African ancestry

• RR ~3-4 for overall prostate cancer (*BRCA2, ATM, PALB2, NBN*)
• Larger effects for aggressive phenotypes

P<0.001 for most RR’s
Rare coding variants and prostate cancer risk in men of African ancestry

Metastatic disease:

- African Americans: <70 metastatic cases
- Ugandans: no information on stage; 32% of cases with PSA>100 ng/ml at dx

P’s<0.001
Rare variant discovery for aggressive prostate cancer: 20,000 cases of European ancestry

Stage 1: Exome seq
- 2,770 Agg cases
- 2,775 Non-agg cases

Stage 2: 500 genes
- 7,300 Agg cases
- 7,300 Non-agg cases

Stage 3/4 & Gleason 8+ or death due to PCa
Stage 1/2 & Gleason < 7

R01 CA196931 selected for validation (Spring 2019)
Research on Prostate Cancer in Men of African Ancestry: Defining the Roles of Genetics, Tumor Markers and Social Stress

- U19 in collaboration with NCI-DCEG Intramural investigators
- Objective: to define sociological and biological factors and their inter-relationships that contribute to aggressive PCa in African American men
- Recruit 10,000 African American men with prostate cancer
  - baseline survey, saliva and tumor samples
- Scientific questions to be addressed:
  - genetic susceptibility (GWAS and exome seq)
  - social factors that contribute to lifetime stress
  - lifestyle factors and health behaviors
  - medical care-related factors (e.g. access to care and screening)
  - tumor-related features: somatic mutations and local inflammation
- Cores: admin, pathology, recruitment, data analysis
- Funding: NCI, NIMHD and PCF

www.RESPONDstudy.org
## RESPOND Investigators

<table>
<thead>
<tr>
<th>NAME</th>
<th>INSTITUTION</th>
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<tbody>
<tr>
<td>Christopher Haiman, ScD</td>
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<td>Ann Hamilton, PhD</td>
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<td>David Conti, PhD</td>
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<td>William Gauderman, PhD</td>
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<td>Scarlett Gomez, PhD, MPH</td>
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<td>Iona Cheng, PhD, MPH</td>
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<td>Mindy DeRouen, PhD, MPH</td>
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<td>Salma Shariff-Marco, PhD, MPH</td>
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<td>Rosemary Cress, PhD</td>
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<td>Kevin Ward, PhD, MPH</td>
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<td>Antoinette Stroup, PhD</td>
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<td>Jong Park, PhD, MPH</td>
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<td>Thomas Sellers, PhD, MPH</td>
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<td>Jennifer Beebe-Dimmer, PhD, MPH</td>
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<td>Melissa Bondy, PhD</td>
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<td>Stephen Chanock, MD</td>
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<td>Sonja Berndt, PhD</td>
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<td>Michael Cook, PhD</td>
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<td>Meredith Yeager, PhD</td>
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**Multi-disciplinary team**: epidemiologists, oncologists, urologists, pathologists, genomicists, bioinformaticians and biostatisticians with track records in population-based and clinical prostate cancer and health disparities research

**EAC**: Lee Green (Moffitt), Scott Tomlins (Michigan), Daniel Schaid (Mayo), Isaac Powell (Wayne St.), Amani Allen (Berkeley), Westley Sholes (Advocate)

[www.RESPONDstudy.org](http://www.RESPONDstudy.org)
• Goal: Recruitment of 10,000 African American prostate cancer cases
• Contact and recruitment through SEER and NPCR cancer registries covering 7 states representing ~40% of African American men in the U.S.

www.RESPONDstudy.org
Challenges in Recruitment

Focus groups of African American prostate cancer patients at each recruitment site (n=7-10) reviewed study materials and were asked about how we can build trust:

- What is the benefit for me or my family?
- Clearly define the disparity.
- Research vs. testing
- Transparency
- Confidentiality of data/results
- Buy-in from Black community leaders, institutions, organizations & churches, etc.
- Include African American researchers/colleges
- A celebrity face for the study would build credibility
- Include Black study staff members and face to face interaction
- Publicize to build credibility
- Health education & literacy
- Keep us informed
GWAS of Cancer

AAPC:
- >30 studies over >25 years
- 10,000 cases (2,700 aggressive)

RESPOND:
- 5 years
- 10,000 cases (3,000 aggressive)
- GWAS: ~20,000 cases (5,700 aggressive)
- Exome seq: ~20,000 cases + controls
## Acknowledgements

### Multiethnic Cohort
- David Conti
- Fred Schumacher
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- Loic Le Marchand
- Lynne Wilkens

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- Doug Easton
- Ali Amin Al Olama
- Hidewaki Nakagawa
- Fredrik Wiklund
- Graham Giles

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- Stephen Watya
- Alex Lubwama

### AAPC Consortium
- Bill Blot
- Stephen Chanock
- Sue Ingles
- Sonja Berndt
- Sara Strom
- Janet Stanford
- Rick Kittles
- William Isaacs
- Susan Gapstur
- Ryan Diver
- Victoria Stevens
- Curtis Pettaway
- Edward Yeboah,
- Yao Tettey
- Richard B. Biritwum
- Andrew A. Adjei
- Evelyn Tay
- Jianfeng Xu
- Michael Cook
- Fergus Couch

### AAPC Consortium
- Lisa B. Signorello
- Wei Zheng
- Barbara Nemesure
- John Carpten
- Anselm Hennis
- Adam S. Kibel
- Benjamin Rybicki
- Christine Neslund-Dudas
- Ann Hsing
- Phyllis J. Goodman
- Eric A Klein
- Graham Casey
- John S. Witte

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