Hereditary Prostate Cancer: From Gene Discovery to Clinical Implementation

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(No disclosures to report)
Overview

• Prostate cancer epidemiology and risk factors
• Family-based gene discovery
• Lessons learned though tumor sequencing
• Clinical implications
Prostate cancer: common and lethal

### Estimated New Cases

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>174,650</td>
<td>268,800</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>116,440</td>
<td>111,710</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>78,500</td>
<td>67,100</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>61,700</td>
<td>61,880</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>57,220</td>
<td>39,260</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>44,120</td>
<td>37,810</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>41,090</td>
<td>33,110</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>36,140</td>
<td>29,700</td>
</tr>
<tr>
<td>Leukemia</td>
<td>35,920</td>
<td>26,830</td>
</tr>
<tr>
<td>Pancreas</td>
<td>29,940</td>
<td>25,860</td>
</tr>
<tr>
<td>All Sites</td>
<td>870,970</td>
<td>891,480</td>
</tr>
</tbody>
</table>

### Estimated Deaths

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>76,650</td>
<td>66,020</td>
</tr>
<tr>
<td>Prostate</td>
<td>31,620</td>
<td>41,760</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>27,840</td>
<td>23,380</td>
</tr>
<tr>
<td>Pancreas</td>
<td>23,800</td>
<td>21,950</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>21,800</td>
<td>13,980</td>
</tr>
<tr>
<td>Leukemia</td>
<td>13,150</td>
<td>12,160</td>
</tr>
<tr>
<td>Esophagus</td>
<td>13,020</td>
<td>10,180</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>12,870</td>
<td>9,690</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,510</td>
<td>8,460</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>9,910</td>
<td>7,850</td>
</tr>
<tr>
<td>All Sites</td>
<td>321,670</td>
<td>285,210</td>
</tr>
</tbody>
</table>

## Prostate cancer risk factors: age

<table>
<thead>
<tr>
<th>AGE</th>
<th>Probability of Developing Prostate Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 49</td>
<td>1 in 354</td>
</tr>
<tr>
<td>50 – 59</td>
<td>1 in 52</td>
</tr>
<tr>
<td>60 – 69</td>
<td>1 in 19</td>
</tr>
<tr>
<td>70 and Older</td>
<td>1 in 11</td>
</tr>
<tr>
<td>Birth to Death</td>
<td>1 in 8</td>
</tr>
</tbody>
</table>
Prostate cancer risk factors: race

Prostate cancer risk factors: family history

![Family tree indicating prostate cancer risk factors with ages and gender symbols.](image-url)
Important elements in family history

• Mode of inheritance
  – Most segregation analyses suggest autosomal dominant inheritance
  – Some evidence for recessive and/or X-linked models of inheritance

• Number of affected men in pedigree
  – Risk ↑ with ↑ number of affected men
  – FDR > SDR

• Early-onset prostate cancer
  – What is age cut-off?

• Other cancers types in pedigree
Heritability of prostate cancer: twin studies

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Heritability</th>
<th>Shared Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers</td>
<td>33 (30-37)</td>
<td>0</td>
</tr>
<tr>
<td>Melanoma</td>
<td>58 (43-73)</td>
<td>0</td>
</tr>
<tr>
<td>Prostate</td>
<td>57 (51-63)</td>
<td>0</td>
</tr>
<tr>
<td>Breast</td>
<td>31 (11-51)</td>
<td>16 (0-31)</td>
</tr>
<tr>
<td>Colon</td>
<td>15 (0-45)</td>
<td>16 (0-38)</td>
</tr>
<tr>
<td>Lung</td>
<td>18 (0-42)</td>
<td>24 (7-40)</td>
</tr>
</tbody>
</table>

UM Prostate Cancer Genetics Project (PGGP)

• Family-based study of PC susceptibility
• 1995-2016
• Collected FH, Med Hx, germline DNA and tumors
• Over 4000 participants
• New regions (LODs >2)
• New regions (LODs 1-2)
17q Prostate cancer linkage signal

147 families with 4+ cases and early-onset PC from UM and JHU

**BRCA1** mutations in HPC families?

- 93 families with linkage evidence to **BRCA1**
- Screened youngest case for **BRCA1** mutations using HPLC
- Only 1 proband identified with deleterious **BRCA1** mutation

**CONCLUSION:** **BRCA1** mutations do not explain PC linkage to chromosome 17q markers

Identification of a recurrent mutation which is a nonconservative substitution of glutamic acid for glycine at amino acid position 84 in the homeobox transcription factor gene HOXB13
Figure 1. Pedigrees of Four Subjects with the HOXB13 G84E Mutation on Initial Targeted Sequencing.

The proband who was selected for sequencing is indicated by the arrow in each pedigree. The remaining symbols are described in the key. Squares indicate male sex, and circles female sex. Ages of subjects, rounded to the nearest 5-year interval, are shown under the symbols. A slash through the symbol indicates that the subject is deceased. Two subjects in two families, Family 1 from the University of Michigan Prostate Cancer Genetics Project (UM) and Family 1 from Johns Hopkins University (JHU), who were inferred to be obligate carriers of the HOXB13 G84E mutation, died from prostate cancer. The unaffected G84E carrier in JHU Family 1 was 70 years of age at last contact.
**HOXB13 G84E is more common in men with + FH and EO disease**

<table>
<thead>
<tr>
<th>Variable</th>
<th>G84E Carrier Freq. (%)</th>
<th>Odds Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family History Positive (N=2064)</td>
<td>2.2</td>
<td>2.8</td>
<td>1.2x10^-4</td>
</tr>
<tr>
<td>Family History Negative (N=2410)</td>
<td>0.8</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Age at Diagnosis ≤55 (N=2310)</td>
<td>2.2</td>
<td>2.7</td>
<td>1.1x10^-4</td>
</tr>
<tr>
<td>Age at Diagnosis &gt;55 (N=2703)</td>
<td>0.8</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pos. FH &amp; Age of Dx ≤55 (N=1050)</td>
<td>3.1</td>
<td>5.1</td>
<td>2.0x10^-6</td>
</tr>
<tr>
<td>Neg. FH &amp; Age of Dx &gt;55 (N=1456)</td>
<td>0.6</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
• **HOXB13** R229G and G216C each observed in 1 AA family
• **HOXB13** L144P in LNCaP and Y88D in LAPC4 PC cell lines
Many confirmatory studies

- **HOXB13** associated with PC
- \( OR = 3.38 \ (95\% \ CI = 2.45-4.46) \)
- Variant assoc’d with:
  - Early-onset disease
  - Affected relatives
  - Aggressive disease
  - ? Other cancers
- 5% of hereditary PC families
- Common haplotype =>founder allele
Pathological characteristics of HOXB13 G84E cases

• Prominent multifocality
• Pseudohyperplastic features
  – Dilated glands
  – Pink amorphous secretions
• More cases with SPINK overexpression and fewer cases ERG+
Targeted resequencing of 17q21-22 linkage region led to recognition of \textit{HOXB13} as a PC risk locus
UM Precision Medicine Tumor Board

Roychowdhury S et al. Sci Transl Med 2011
Patient diagnosed with metastatic prostate cancer

55 yo patient with T4N1M1 Gleason 10 PCa

Pelvic LN Bx

MiOncoseq

Sequencing results:
• TMPRSS2-ERG +
• Somatic and germline BRCA2 mutations
Pedigree of pt with germline BRCA2 mutation
## Other rare germline mutations

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Risk of Prostate Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Breast and Ovarian Cancer</td>
<td><em>BRCA2</em></td>
<td></td>
</tr>
<tr>
<td>Hereditary Breast and Ovarian Cancer</td>
<td><em>BRCA1</em></td>
<td></td>
</tr>
<tr>
<td>Lynch Syndrome</td>
<td>Mismatch Repair Genes</td>
<td>+/−</td>
</tr>
</tbody>
</table>
Prostate Cancer Sequencing Studies

- Large sequencing studies of metastatic PC
- Germline mutations in 8-12% of cases
- DNA repair genes
- Implications for Rx

Robinson et al. *Cell* 2015;161(5):1215-1228
# Importance of populations studied

<table>
<thead>
<tr>
<th>Gene</th>
<th>All Mutations</th>
<th>Ashkenazi Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pritchard N = 692</td>
<td>Utah* N = 351</td>
</tr>
<tr>
<td>BRCA1</td>
<td>6 (0.9%)</td>
<td>4 (1.1%)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>37 (5.3%)</td>
<td>6 (1.7%)</td>
</tr>
<tr>
<td>All DR Genes</td>
<td>82 (11.8%)</td>
<td>26 (7.1%)^</td>
</tr>
</tbody>
</table>


*Boyle et al. manuscript in preparation

^One patient harbors 2 of the 26 DR mutations
Are germline DNA repair gene mutations more common in lethal prostate cancer?

- 313 lethal cases vs. 486 indolent cases
- *BRCA1/2* and *ATM* mutations
- Mutation carriers die at an earlier age

Na et al. *Eur Urol* 2017
Germline prostate cancer gene mutations are assoc’d with:

- Early age at cancer diagnosis
- Multiple cases of prostate cancer
- Metastatic prostate cancer
- What about multiple primary cancers?
PC and multiple primary cancers

- 102 men with PC and 1+ add’l cancers
  - Age <56 at dx for initial cancer
  - Rare cancers
- Multigene panel testing
- 11/102 men had pathogenic germline mutation
  - BRCA2, ATM, MLHI, BRIP1, PALB2, FGFR3, CHEK2, HOXB13
- Over half of mutation carriers would not have been offered testing based on current clinical standards

Cancer 2017 Oct 15;123(20):3925-3932
Proband with *BRCA2* mutation

*Cancer* 2017 Oct 15;123(20):3925-3932
140+ SNPs associated with prostate cancer

- Identified using large case: control studies
- Majority not in genes
- Individually modest effect
- Larger cumulative effect

www.ebi.ac.uk/gwas
PRS Modifies BRCA1/2 Effect in PCa

- 1,802 male carriers of BRCA1/2 mutations
- Risk is 40% for BRCA2 carriers (average)
- Risk is 70% if PRS at top 5th percentile
- Risk is 24% if PRS at bottom 5th percentile
Clinical Implications

- +FH of PCa
- +FH suggestive of cancer syndrome
- Refer to cancer genetics
- *HOXB13, BRCA1/2, other genes*
- Prostate cancer screening
  - PSA other biomarker
  - MRI
Clinical Implications

- Men with metastatic PCa
- Tumor and germline testing for PCa genes
- Order? Panel?
The future?

- 3607 men with PC who met NCCN guidelines for genetic testing
- 17.2% of men had pathologic mutations
  - 1/3 in *BRCA1/2*
  - *HOXB13* G84E in 4.5%
  - FH and Gleason grade were “imperfect predictors” of mutations
- Should all men with PC be offered germline tests?
- Nicolosi et al. *JAMA Oncol* Feb 2019
Conclusions

• Successful identification of PCa genes
  – Rare, moderately penetrant mutations
  – GWAS SNPs

• Challenges
  – Better population-level data: allele frequencies and penetrance
  – Phenotype:
    • 1 in 8 men with be dx’d with PCa over lifetime
    • But only 1 in 41 men with die of PCa over lifetime
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  – Anna Johnson, Kim Zuhlke, Linda Okoth, Scott Tomlins

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• Johns Hopkins University
  – Bill Isaacs

• NorthShore University HealthSystem
  – Jianfeng Xu

• Funding: NIH, DOD, UM, University of Utah Health Sciences
Clinical implications (NCCN):

• Men with strong FH of PC
  – Father or bro or >1 fam member with PC before age 60
  – Family suggestive of cancer syndrome

• These men are at increased risk of PC and this should impact early detection discussion
Clinical implications (NCCN):

- Men with M1 CRPC
  - Consider testing for MSI-H or IHC for dMMR: possible treatment with pembrolizumab
  - Consider testing (tumor and germline) for *BRCA1, BRCA2, ATM, PALB2, FANCA*
    - Refer to genetic counseling if +
    - Early use of PARPi and/or platinum chemo or trial