XMRV and Prostate Cancer
A Clinician's View

Eric A. Klein, M.D.

Glickman Urologic and Kidney Institute
and Lerner Research Institute

Cleveland Clinic
Disclosures

• Research Support
  – Genomic Health
  – Abbott Laboratories

• Patent Licenses
  – Abbott Laboratories
Questions

• Why is prostate cancer important?
• Is prostate cancer an infectious disease?
• What’s the role of XMRV in prostate cancer?
• What are the implications?
Prostate Cancer World Wide

- 782,600 new cases in 2007
- 5th most common cancer overall (11.7%)
- 2nd most common cancer in men
- 254,000 deaths (2007)

Rate Per 100,000

Prostate
Lung & bronchus
Colon and rectum
Urinary bladder
Non-Hodgkin lymphoma
Melanoma of the skin

Lifetime risk = 1/6 (17%)

*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting.

Presented at the 1st Intl. Workshop on XMRV 7-8 September 2010, Bethesda USA
Cancer Death Rates* Among Men, US, 1930-2006

Rate Per 100,000

100
90
80
70
60
50
40
30
20
10
0


Lung & bronchus
Stomach
Colon & rectum
Prostate
Pancreas
Leukemia
Liver

Lifetime risk = 1/34 (3%)

*Age-adjusted to the 2000 US standard population.
National Center for Health Statistics, Centers for Disease Control and Prevention, 2009.
Prostate Cancer 2010

• Risk Factors
  – Age
  – Race
  – Family History
  – Genetic Factors (largely undefined)

• Clinical Challenges
  – Large discrepancy between incidence and mortality
  – PSA-based screening detects many indolent cancers
  – Can’t accurately identify who needs therapy
  – All therapies have significant morbidity
Questions

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Infection and Cancer

Mackay et al, Cancer Atlas, ACS (cancer.org)
<table>
<thead>
<tr>
<th>Virus</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV</td>
<td>Cervical, anogenital, laryngeal carcinoma</td>
</tr>
<tr>
<td>EBV</td>
<td>Burkitt’s lymphoma, Nasopharyngeal carcinoma, Hodgkin’s lymphoma, AIDS associated lymphoma</td>
</tr>
<tr>
<td>HHV-8</td>
<td>Kaposi’s sarcoma, primary effusion lymphoma</td>
</tr>
<tr>
<td>HTLV-1</td>
<td>Adult T-cell leukemia, (tropical spastic paraparesis)</td>
</tr>
<tr>
<td>HBV, HCV</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>MC polyoma</td>
<td>Merkel cell carcinoma</td>
</tr>
<tr>
<td>MMTV/HMTV</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>CMV</td>
<td>Glioblastoma</td>
</tr>
<tr>
<td>XMRV</td>
<td>Prostate cancer (chronic fatigue syndrome)</td>
</tr>
</tbody>
</table>

Established Etiological Agent
Possible Etiological Agent
Is Prostate Cancer an Infectious Disease?

Epidemiologic Data

- Increased Risk of Prostate Cancer with
  - Early sexual activity *Honda et al, 1988*
  - Number of partners *Honda et al, 1988; Sarma et al, 2006*

- Decreased Risk of Prostate Cancer with
  - Frequent ejaculation *Giles et al, 2003; Willet et al, 2004*
  - Eunuchs
Infection and Prostate Cancer Risk Meta-Analysis

29 studies, Medline 1966 – 2004
6,022 cases, 7,023 controls

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonorrhea</td>
<td>1.35</td>
</tr>
<tr>
<td>HPV</td>
<td>1.39</td>
</tr>
<tr>
<td>Any STD</td>
<td>1.48</td>
</tr>
</tbody>
</table>

Taylor et al, Family Med 37:506-12, 2005
Is Prostate Cancer an Infectious Disease?

Genetic Data

– Variants in \( RNaseL, MSR1, \) & \( TLR4 \)

associated with increased risk for

• Infections in animals

• Prostate cancer in humans
Questions

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Genome-Wide Search

Smith et al, Science 274:1371, 1996
**Epidemiology**

- Maps to 1q24-25
- Early age of onset
- Many affected family members
- Rare allele with high penetrance

**Biology**

[Diagram showing the biological processes involving RNase L and viral replication]
## R462Q Variant and Prostate Cancer

<table>
<thead>
<tr>
<th>Genotype</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (WT)</td>
<td>1.00</td>
</tr>
<tr>
<td>RQ</td>
<td>1.46</td>
</tr>
<tr>
<td>QQ</td>
<td>2.12</td>
</tr>
</tbody>
</table>

**P value** .011

**PAF = .13**

Casey et al, Nature Genet 32:581, 2002

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Expressed in RNase L⁻/⁻ Cells

Mock  | R462Q  | G296V  | Y529C  | I220V  |
---    | -----  | -------|--------|--------|
    |       |        |        |        |

Wild Type

G59S  | S322F  | I97L  | D541E  |
---    | -------|-------|--------|
    |        |       |        |
Discovery of XMRV in Prostate Cancer

Prostate Cancer Tissue → RNA → Virochip

New Gamma Retrovirus Related to Murine Leukemia Viruses

Hybridization Pattern & RT-PCR
Red VP= homozygous for R462Q RNase L Variant


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XMRV is Related to MLVs

In mice, MLVs and related viruses cause
• Immune deficiency
• Neurodegenerative disease
• Cancer
XMRV and Prostate Cancer
Confirmatory Studies

• Miller (Univ Wash)\(^1\)
  – 2 strains XMRV isolated from a QQ human prostate cancer xenograft established in 1991 (CWRU22Rv1)

• Singh (Columbia/Utah)\(^2\)
  – XMRV in 23% of cancers (n=233) vs. 6% benign
  – Found in tumor epithelium
  – Associated with higher grade disease
  – Not associated with RNaseL genotype

\(^1\)Knouf et al, J Virol 83:7353, 2009
\(^2\)Schlaberg et at, PNAS 106:16351, 2009
XMRV and Prostate Cancer
Confirmatory Studies

- Petros (Emory)\(^1\)
  - XMRV serum Ab in 28% of RP patients (n=40)
  - Highest titers in QQ patients
  - FISH confirmed presence in stroma

- (Baylor)\(^2\)
  - XMRV in RP specimens
  - Detection sensitive to the technique used

\(^1\)Arnold et al, Urology 75:755, 2010
\(^2\)1st Int’l Workshop on XMRV
Why are the Negative Studies Negative?

- XMRV is not truly associated with human disease
- Technique
  - PCR details
  - Unrecognized sequence variation
- Geography
Global Distribution of HTLV-1

Proietti et al, Oncogene 24:058, 2005
Prevalence of KoRV in Geographically Distinct Koala Populations

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Sexual Activity

RR, RQ, QQ

XMRV - PAP FIBRILS

RR, RQ, QQ

Antiviral Defenses

No Tumor

RR or RQ

Viral Clearance

RR or RQ

QQ

Persistent Infection

Clinically Detectable Cancer

QQ

Tumor Initiation & Promotion

QQ

Stable Viral Integration
Viral Oncogenesis

- Insertional mutagenesis
  - Androgen regulation of normally androgen insensitive genes
- Proinflammatory environment
- Oncogenic Protein
- Immune suppression
- Role of epithelial vs. stromal infection
Stromal-Epithelial Interaction in Prostate Carcinogenesis

Questions

• Why is prostate cancer important?
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• What’s the role of XMRV in prostate cancer?
• What are the implications?
What if XMRV causes prostate cancer?

• Implications
  – Screening
  – Prognosis
  – Therapy
  – Prevention
    – Pharmacologic agents
    – Vaccine
Detection of XMRV in Urine

**Voided (VB1)**

**Voided (VB3)**

<table>
<thead>
<tr>
<th>Sample #</th>
<th>Pre-massage</th>
<th>Post-massage</th>
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<tbody>
<tr>
<td>899</td>
<td>1/2</td>
<td>0/2</td>
</tr>
<tr>
<td>900</td>
<td>0/2</td>
<td>1/2</td>
</tr>
<tr>
<td>902</td>
<td>0/2</td>
<td>1/2</td>
</tr>
<tr>
<td>904</td>
<td>0/2</td>
<td>1/2</td>
</tr>
<tr>
<td>905</td>
<td>1/2</td>
<td>1/2</td>
</tr>
<tr>
<td>906</td>
<td>1/2</td>
<td>1/2</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td><strong>3/6</strong></td>
<td><strong>5/6</strong></td>
</tr>
</tbody>
</table>

Negative for mouse mtDNA

Das Gupta et al (unpublished)
XMRV and Prostate Cancer Aggressiveness

Schlaberg et al, PNAS 2009

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WASHINGTON, June 8 — Federal drug officials announced today that they had approved a vaccine against cervical cancer that could eventually save thousands of lives in the United States each year and hundreds of thousands in the rest of the world.

Called Gardasil, the vaccine is the culmination of a 15-year scientific effort that began at the National Cancer Institute and a research center in Australia, and it may one day be seen as one of the major health advances of the early 21st century.
No PSA or DRE for me...
I’m immune to XMRV
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