Predictive value of Prostate Specific Antigen for prostate cancer
A nested case control study in EuroSIDA

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Background

- cART has improved survival of HIV+ people and the proportion living past 50 is increasing.

- Cancers associated with older age, such as prostate cancer, are expected to become more prevalent.

- Prostate specific antigen (PSA) is a protein associated with higher prostate cancer risk.
Aims

“What is the predictive value of PSA in HIV+ men?”

Changes in markers prior to prostate diagnosis

How well does elevated PSA predict future prostate cancer?

Appropriateness of PSA>4 µg/mL
EuroSIDA is a large prospective cohort with 18,794 patients from 108 clinics in 34 European countries, Israel and Argentina. Regularly collecting:

- CD4 counts, HIV viral loads
- Non-AIDS events (since 2001)
- Prospectively stored plasma samples.
Methods – Study design

Nested case control study
Methods – Study design

Nested case control study

Follow-up

Prostate cancer

After 1 Jan 2001

Prior plasma sample

PCa
Methods – Study design

Nested case control study

Follow-up

PCa
Methods – Study design

Nested case control study

First sample

±2 year window

Latest sample

±2 year window

PCa

EuroSIDA
Methods – Study design

Nested case control study

Age (1\textsuperscript{st} sample)
± 10 years

CD4 (1\textsuperscript{st} sample)
±200 cells/mm\textsuperscript{3}

Region of Europe
Methods – Samples

All samples prior to diagnosis (or equivalent date in controls)

- Total PSA
- Free PSA
- Testosterone
- Sex hormone binding globulin (SHBG)
Methods – Study design

Nested case control study

EuroSIDA
4978 men
After 2001
Nested case control study

EuroSIDA
4978 men
After 2001

Controls
N=40

Prostate cancers
N=21
Methods – Study design

Nested case control study

Controls N=40

Baseline: First sample date

Follow-up
Median: 6 IQR: 2 – 9 years

Last sample - Prostate cancer
Median: 7 IQR: 4-11 months
## Baseline characteristics (first sample)

<table>
<thead>
<tr>
<th>Factors</th>
<th>Total</th>
<th>Prostate cancer</th>
<th></th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>Cases</td>
<td>Controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>61 (100.0)</td>
<td>21 (100.0)</td>
<td>40 (100.0)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Risk group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homosexual</td>
<td>47 (77.0)</td>
<td>17 (81.0)</td>
<td>30 (75.0)</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>7 (11.5)</td>
<td>2 (9.5)</td>
<td>5 (12.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDU</td>
<td>2 (3.3)</td>
<td>0 (0.0)</td>
<td>2 (5.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White ethnicity</td>
<td>57 (93.4)</td>
<td>21 (100.0)</td>
<td>36 (90.0)</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>No prior NADM</td>
<td>59 (96.7)</td>
<td>19 (90.5)</td>
<td>40 (100.0)</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>No prior ADM</td>
<td>55 (90.2)</td>
<td>21 (100.0)</td>
<td>34 (85.0)</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>On cART</td>
<td>58 (95.1)</td>
<td>20 (95.2)</td>
<td>38 (95.0)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>51 (48,57)</td>
<td>52 (49,57)</td>
<td>51 (47,56)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>CD4 count (cells/mm³)</td>
<td>437 (243,610)</td>
<td>460 (260,610)</td>
<td>426 (230,595)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>log₁₀ HIV VL (copies/ml)</td>
<td>1.9 (1.6,2.6)</td>
<td>1.9 (1.6,2.6)</td>
<td>2.0 (1.6,2.6)</td>
<td>0.40</td>
<td></td>
</tr>
</tbody>
</table>
total PSA by time before diagnosis

Annual % change in Cases: 15 (10,20)%  P<0.01

Annual % change in Controls: 0 (-2, 3)%  P=0.71

Difference in rate between cases and controls: P<0.01
Free PSA by time before diagnosis

Annual % change in Cases: 11 (7,16)\% P<0.01

Annual % change in Controls: 0 (-2, 3)\% P=0.70

Difference in rate between cases and controls: P<0.01
Testosterone & SHBG by time before diagnosis

% change in Cases: -2 (-4, 0)%  P=0.13

% change in Controls: -2 (-3, -1)%  P<0.01

Difference in rate between cases and controls:  P=0.96
Testosterone & SHBG by time before diagnosis

% change in Cases: -2 (-4, 0)% $P=0.13$
% change in Controls: -2 (-3, -1)% $P<0.01$

Difference in rate between cases and controls: $P=0.96$

% change in Cases: 0 (-1,2)% $P=0.82$
% change in Controls: 0 (-2, 2)% $P=0.65$

Difference in rate between cases and controls: $P=0.58$

Case – ○
Control – △
Median total PSA

Baseline
- Median (Case): [value]
- Median (Control): [value]
- N = 21

Latest
- Median (Case): [value]
- Median (Control): [value]
- N = 21

P<0.01
P=0.04

N = 38
N = 39
Median free PSA

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Latest</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median (Case)</strong></td>
<td>0.4 N = 21</td>
<td>0.8 N = 21</td>
</tr>
<tr>
<td><strong>Median (Control)</strong></td>
<td>0.2 N = 38</td>
<td>0.2 N = 39</td>
</tr>
</tbody>
</table>

P < 0.01
Baseline: cases = 21, controls = 38; Event: cases = 21, controls = 39.

Median testosterone and SHBG

P=0.73   P=0.92   P=0.83   P=0.99
Oddsratio of prostate cancer for 2x higher marker

<table>
<thead>
<tr>
<th>Marker</th>
<th>Baseline</th>
<th>Latest</th>
<th>cOR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total PSA</td>
<td></td>
<td></td>
<td>4.7 (1.7,12.9)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td>8.1 (1.1,58.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Latest</td>
<td></td>
<td></td>
<td>10.4 (1.9,55.6)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Free PSA</td>
<td></td>
<td></td>
<td>5.4 (1.7,17.4)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td>10.4 (1.9,55.6)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Latest</td>
<td></td>
<td></td>
<td>10.4 (1.9,55.6)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Testosterone</td>
<td></td>
<td></td>
<td>0.8 (0.3,2.4)</td>
<td>0.73</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td>1.1 (0.3,3.3)</td>
<td>0.92</td>
</tr>
<tr>
<td>Latest</td>
<td></td>
<td></td>
<td>1.1 (0.3,3.3)</td>
<td>0.92</td>
</tr>
<tr>
<td>SHBG</td>
<td></td>
<td></td>
<td>0.9 (0.4,2.1)</td>
<td>0.83</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td>1.0 (0.4,2.7)</td>
<td>0.99</td>
</tr>
<tr>
<td>Latest</td>
<td></td>
<td></td>
<td>1.0 (0.4,2.7)</td>
<td>0.99</td>
</tr>
</tbody>
</table>
Predictive value of markers

AUC statistic

- Total PSA: 0.9
- Free PSA: 0
- Testosterone: 0
- SHBG: 0
Predictive value of markers

- Total PSA: 0.90
- Free PSA: 0.82
- Testosterone
- SHBG
Predictive value of markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>AUC Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total PSA</td>
<td>0.90</td>
</tr>
<tr>
<td>Free PSA</td>
<td>0.82</td>
</tr>
<tr>
<td>Testosterone</td>
<td>0.51</td>
</tr>
<tr>
<td>SHBG</td>
<td>0.51</td>
</tr>
</tbody>
</table>
Predictive value of markers

- Total PSA: 0.90
- Free PSA: 0.82
- Testosterone: 0.51
- SHBG: 0.51
- All markers: 0.91
Total PSA >4 µg/mL

Sensitivity: 37%

Specificity: 99%
Limitations

• Small number of prostate cancers

• Other markers: ProPSA

• No information on cancer treatment
Strengths

• Many prostate cancers (relatively)

• Prospective and independent plasma samples
Conclusions

PSA highly predictive of PCa in HIV+ men

PSA is elevated more than 5 years before prostate cancer

Further analysis to identify age-specific PSA cut-offs for maximum sensitivity and specificity for identifying high risk patients for further testing
The multi-centre study group, EuroSIDA (national coordinators in parenthesis).

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