Predictive value of Prostate Specific Antigen in a European HIV – positive cohort: Does one size fit all?

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Abstract: 244

Manuscript: 1475

Total inserts: 3 (**Figures:1, Tables**:2)

References: 20

Short title: Predictive value of Prostate Specific Antigen in a European HIV – positive cohort

Key words: HIV, Prostate specific antigen, prostate cancer, testosterone, biomarkers, nested case control study, screening.

Conflicts of interest

No other authors declare any conflicts of interest.

Funding

Primary support for EuroSIDA is provided by the European Commission BIOMED 1 (CT94-1637), BIOMED 2 (CT97-2713), the 5th Framework (QLK2-2000-00773), the 6th Framework (LSHP-CT-2006-018632), and the 7th Framework (FP7/2007-2013, EuroCoord n° 260694) programmes. Current support also includes unrestricted grants by Janssen R&D, Merck and Co. Inc., Pfizer Inc., GlaxoSmithKline LLC. The participation of centres from Switzerland was supported by The Swiss National Science Foundation (Grant 108787). The authors have no financial disclosures.

Abstract:

Background:

It is common practice to use PSA≥4.0 μg/L as a clinical indicator for men at risk of PCa, however this is unverified in HIV + men. We aimed to describe kinetics and predictive value of PSA for prostate-cancer (PCa) in HIV+ men.

Methods:

A nested-case-control study of 21 men with PCa and 40 matched-controls within EuroSIDA was conducted. Prospectively stored plasma samples before PCa (or matched date in controls) were measured for the following markers: Total PSA[tPSA], free PSA[fPSA], testosterone and sex hormone binding globulin[SHB]. Conditional logistic regression models investigated associations between markers and PCa. Mixed models were used to describe kinetics. Sensitivity and specificity of using tPSA >4 μg/L to predict PCa was calculated. ROC curves were used to identify optimal cut-offs in HIV+ men for total PSA

Results:

61 HIV+ men were included with a median 6(IQR 2-9) years follow-up. Levels of tPSA increased by 13.7% per year (95%CI:10.3,17.3) in cases, but was stable in controls (-0.4%;95%CI:-2.5,1.7). Elevated PSA was associated with higher odds of PCa at first (OR for 2-fold-higher 4.7;95%CI:1.7-12.9;P<0.01) and last sample (8.1;95%CI:1.1,58.9;P=0.04). A similar relationship was seen between fPSA and PCa. Testosterone and SHBG level were not associated with PCa. tPSA level>4ng/mL had 99% specificity and 38% sensitivity. The optimal PSA cut-off was 1.5ng/mL overall (specificity=84%, sensitivity=81%).

Conclusions:

PSA was highly predictive of PCa in HIV+ men; however the commonly used PSA>4ng/mL to indicate high PCa risk was not sensitive in our population and use of the lower cut-off of PSA>1.5ng/mL warrants consideration.

Introduction

Recent studies have consistently found a lower incidence of PCa in HIV+ than HIV- men in the combination antiretroviral therapy (cART) era [1-3], independently of screening patterns for PSA. However, the frequency of PCa diagnoses in HIV+ men increased significantly from 2001 to 2005, attributed to aging of the HIV+ population due to availability of effective treatment [4, 5]. As a result, PCa screening, detection and treatment are likely to become an integral component of future HIV care [6].

Men at high risk of PCa are generally identified through elevated prostate specific antigen (PSA) tests (PSA≥4.0 ng/ [7, 8]), an abnormal digital rectal exam (or both) and a biopsy[9]. Despite two large trials, the benefit of PSA testing as a screening tool remains unclear [9-12] and population based screening is not recommended by most urological societies [9]. The EACS guidelines currently recommends applying similar guidelines for HIV+ and -men [13]. However, the kinetics of PSA prior to PCa diagnosis in HIV+ men and use of a cut-off to identify high risk men remains largely unverified.

We performed a nested-case-control study to assess the association of total and free PSA (tPSA and fPSA) with PCa risk, including changes in marker levels prior to diagnosis. As PCa is a hormone dependent cancer, we also measured plasma levels of testosterone and sex hormone binding globulin (SHBG).

Patients and methods

A 1:2 nested-case-control study was performed within the EuroSIDA cohort (details at www.cphiv.dk). EuroSIDA has an established biobank, where prospective plasma samples have been collected at approximate 6 monthly intervals.

Cases were defined as men with a primary PCa diagnosis after 1 January 2001, the date after which all malignancies have been routinely collected in EuroSIDA, with at least one plasma sample prior to the date of diagnosis. For each case, up to 2 matched-controls were selected from men with follow-up after 1 January 2001 with no history of PCa and at least one plasma sample prior to the date of diagnosis for each case. Cases and controls were matched on region of Europe, date of (±2

years), age (± 5 years), and CD4 (± 200 cells/mm^3) at first plasma sample, and date of latest plasma sample date (±2 years). Date of first plasma sample was considered as baseline.

Serial plasma samples for cases and controls were analysed for total PSA (tPSA), free PSA (fPSA), sex hormone binding globulin (SHBG) and testosterone. The ratio of tPSA to fPSA (f/tPSA) was calculated. Plasma samples were centrally analysed by a technician blinded to events on frozen stored plasma at the Department of Clinical Biochemistry at Rigshospitalet. TPSA, fPSA and testosterone were measured by competitive electrochemiluminescense immunoassays using Cobas 8000 (Roche Diagnostics, Indianapolis, IN). SHBG was measured by a sandwich chemiluminescence immunometric assay using Immunulite 2000 (Siemens Healthcare Diagnostics, Flanders, NJ). Lower limits of detection were 0.03 µg/L for tPSA, 0.02 µg/L for fPSA, 0.42 nmol/L for testosterone, and 2 nmol/L for SHBG. 277 samples were analyzed.

Mixed models were used to describe kinetics of each marker in the period prior to diagnosis (or latest sample in controls) by testing for an interaction between marker level and time. Unadjusted conditional logistic regression models investigated the association between PCa and levels of each marker at baseline and latest sample. Area-under-the curve statistics (AUC), and sensitivity and specificity of varying cut offs were used to assess the predictive performance of each marker.

All statistical tests were two sided with a type I error rate of 5%. All statistical analyses were performed using SAS 9.3 (Statistical Analysis Software, Cary NC, USA).

Results

Cases (N=21) and controls (N=40) were well balanced on non-matched characteristics (table 1) with a median of 6 years (IQR1-9) between first and last plasma sample. Of men with tPSA available at first sample, 53/59 (89.8%) of cases and controls had tPSA≤ 4 ng/mL. Levels of tPSA and fPSA were higher in cases relative to controls at baseline and even more so at latest sample, whereas f/tPSA ratio was lower in cases than controls. Baseline and latest testosterone and SHBG levels were similar for cases and controls.

The trajectories of the markers prior to diagnosis are shown in figure 1. Level of tPSA (A) and fPSA (B) increased in cases, but remained stable in controls. This difference was significant in both univariate analysis and after adjustment (Both P<0.01). The ratio of fPSA to tPSA declined in cases but was stable in controls (C). The difference in rates between cases and controls was significant in univariate analysis (P=0.04), but not after adjustment (P=0.11). There was little change over time in testosterone (D) and SHBG (E) both before (Testosterone: P=0.09 and SHBG: 0.11) and after adjustment (P=0.58 and 0.96).

A two-fold increase in baseline tPSA was associated with almost a 5-fold increase in odds of PCa, and latest tPSA with an 8-fold increase in odds of PCa (results were similar for fPSA) (table 2). This association was detectable up to 5 years prior to PCa (OR for two-fold higher tPSA: 2.92; 95%CI: 1.38, 8.07; P<0.01 and fPSA: 5.46; 95%CI:1.54,29.05; P<0.01, respectively). Conversely, a higher fPSA to tPSA ratio was associated with lower odds of PCa at both first and latest sample. There was no significant association with testosterone or SHBG.

The most informative predictor of PCa was tPSA (AUC=0.90), followed by fPSA (0.82) and the ratio of fPSA to tPSA (0.82). Testosterone (AUC=0.51) and SHBG (0.51) did not predict PCa. Combining all four markers resulted in an AUC of 0.91, only marginally improving on tPSA alone. The usual cut-off of tPSA >4 ng/mL had 99% specificity and 38% sensitivity, meaning 99% of men who were PCa free were correctly identified as “low risk” using a PSA test (I.e. had a PSA ≤4 ng/mL), however only 38% with PCa were correctly identified as “high risk” (i.e. had a PSA>4 ng/mL). The optimal cut-off which maximised both sensitivity and specificity was 1.5 ng/mL overall (specificity=84%, sensitivity=81%) although cut-offs between 1.4 – 1.6 provided >80% sensitivity and specificity. This was similar in those aged <50 with an optimal cut-off 1.4 ng/mL (specificity=94%,sensitivity=86%, in 22 people and 41 samples, with cut-offs 1.2 – 2.8 ng/mL providing >80% sensitivity and specificity) and ≥50 with an optimal cut-off 1.5 ng/mL (specificity=82%, sensitivity=81%, N=54 people and 236 samples, no other cut-offs had >80% sensitivity and specificity) at current sample.

Discussion

The commonly used PSA >4ng/mL as a marker of high PCa risk in HIV+ men was substantially less sensitive (38%) than a lower threshold of 1.5ng/mL or more (81%). Various forms of PSA were predictive of PCa in this study, namely tPSA, fPSA, and f/tPSA, however the strongest predictor was

tPSA. This is consistent with the literature [14]. We found elevated tPSA levels to be detectable more than 5 years prior to PSA diagnosis, however, testosterone and SHBG levels were not associated with PCa and did not affect PSA predictability, which is consistent with other studies [1, 15].

Median tPSA levels were low in our study, possibly reflecting comparatively younger age at PCa diagnosis, a higher prevalence of hypogonadism in HIV+ men (20%) [16], or an alternate biological relationship between PCa and PSA in the presence of HIV. Two American studies reported similar PSA ranges in HIV+ men to that reported here[17, 18] and previous studies have shown lower latest PSA levels when PCa is present in HIV+ compared to – men prior to diagnosis[1].

Studies have shown that using PSA to screen for PCa is associated with lower PCa stage and grade at diagnosis in the general population, but not overall mortality[10]. However, higher PSA level is increasingly associated with higher risk and therefore no "ideal" cut-off exists[9] and raised levels can be caused by other prostate related conditions such as chronic prostatitis. Furthermore, PSA screening may have potential harms such as complications of prostate biopsies and over diagnosis resulting in needless and expensive treatments. These concerns have prevented the recommendation of a population wide PSA screening.

The major strength of this study is availability of prospectively stored plasma samples collected independent of PCa. However, due to lack of information on method of PCa diagnosis, stage, subsequent treatment or prognosis, we cannot rule out that PCa was diagnosed earlier and at a lower level of PSA than in other studies. A further limitation is that we cannot show the impact of PSA testing on outcomes in in HIV+ men. Our sample size is small and although matching between cases and controls improved the efficiency of our analysis, this data needs to be validated in larger studies.

In conclusion, although overall levels were low, a clinically relevant increase in tPSA and fPSA in the years preceding PCa diagnosis was observed, and was evident at least 5 years prior to diagnosis.The commonly used PSA>4ng/mL to indicate high PCa risk was not sensitive in our population and use of the lower cut-off of PSA>1.5ng/mL warrants consideration.

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Table 1 Baseline characteristics for cases and controls.

Factors	***Cases***	***Controls***	***p-value***
all	21 (100)	40 (100)	-
Region[1,6]			
East and East central	5 (23.8)	10 (25.0)	Na
Argentina	1 (4.8)	1 (2.5)	
South	2 (9.5)	3 (7.5)	
North	6 (28.6)	12 (30.0)	
West	7 (33.3)	14 (35.0)	
Risk group			
MSM	17 (81.0)	30 (75.0)	0.98
IDU	0 (0.0)	2 (5.0)	
Heterosexual	2 (9.5)	5 (12.5)	
Other/Missing	2 (9.5)	3 (7.5)	
Non-white ethnicity	0 (0.0)	4 (10.0)	0.99
prior AIDS[2]	4 (19.0)	13 (32.5)	0.17
prior Non-AIDS event[3]	17 (81.0)	39 (97.5)	0.10
prior NADM	19 (90.5)	40 (100)	0.99
prior ADM	21 (100)	34 (85.0)	0.99
Ever ART/cART [4]	20 (95.2)	38 (95.0)	1.00
HIV VL > 400 cps/mL[2]	4 (19.0)	10 (25.0)	0.58
Median (IQR)			
Age at sample[1]	51.9 (48.6,56.7)	51.1 (47.3,55.5)	0.18
First sample date[1]	OCT 1999 (MAR 1999, APR 2006)	AUG 2000 (JAN 1998, JUN 2006)	0.91
Last sample date[1]	JUL 2008 (DEC 2004, MAR 2011)	SEP 2007 (SEP 2004, OCT 2010)	0.52
Time till PCa	6.6 (2.8,10.1)	-	-
CD4 count/mm3[1]	460.0 (260.0,610.0)	426.0 (229.5,595.0)	0.07
tPSA (ng/mL) [5]			
baseline	2.8 (1.6,4.6)	0.8 (0.5,1.2)	<0.01
latest	6.1 (4.7,9.5)	0.8 (0.5,1.4)	0.04
fPSA (ng/mL) [5]			
baseline	0.4 (0.2,0.8)	0.3 (0.2,0.4)	<0.01
latest	0.9 (0.6,1.3)	0.2 (0.2,0.4)	<0.01
f/t PSA ratio [5]			
baseline	0.2 (0.1,0.3)	0.3 (0.3,0.4)	<0.01
latest	0.1 (0.1,0.2)	0.3 (0.2,0.5)	<0.01
Testosterone (nmol/L) [5]			
baseline	19.3 (14.5,22.2)	19.7 (15.8,25.9)	0.73

latest	17.7 (16.6,21.7)	18.0 (14.0,23.7)	0.92
SHBG (nmol/L) [5]			
baseline	48.0 (34.0,69.0)	53.5 (34.0,64.0)	0.83
latest	54.0 (34.0,63.0)	49.0 (36.0,65.0)	0.83

Abbreviations: tPSA: total PSA, fPSA: free PSA, SHBG: Sex hormone binding globulin. IQR, interquartile range.
Baseline was date of first plasma sample
[1] Matching variables.
[2] AIDS defining events (excl. ADM) as defined by the 1993 CDC clinical definition[19]
[3]Non-AIDS defining events (Excl. NADM) pancreatitis, grade 3 or 4 hepatic encephalopathy or liver-related death, myocardial infarction, stroke, coronary artery bypass graft, coronary angioplasty, carotid endarterectomy (grouped together as serious CV events), and end-stage renal disease [20].
[4] Highest level of treatment received is ARV regimen involving 1 or more drugs.
[5] Marker levels were available on all cases at baseline and latest sample, and 38/41 and 39/41 controls at baseline and latest sample.
[6] Argentina: Argentina; South: Greece, Israel, Italy, Portugal, Spain; West: Austria, Belgium, France, Germany, Luxembourg, Switzerland; North: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East and East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovakia; Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.),

Table 2 Unadjusted conditional odds ratio of PCa for a two-fold increase in each marker

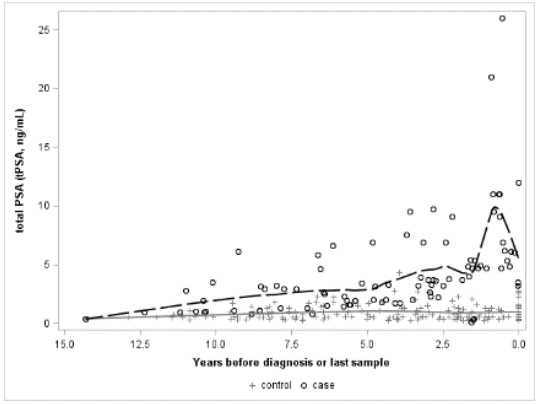
Marker	Baseline		Latest	
	OR of* 2 fold increase in marker level *(95%CI)	***P-value***	***OR of* 2 fold increase in marker level *(95%CI)***	***P-value***
tPSA (ng/mL)	4.67 (1.69,12.89)	<.01	8.09 (1.11,58.86)	0.04
fPSA (ng/mL)	5.41 (1.68,17.44)	<.01	10.38 (1.94,55.55)	<.01
f/t PSA ratio	0.31 (0.14,0.67)	<.01	0.08 (0.01,0.40)	<.01
Testosterone (nmol/L)	0.83 (0.29,2.35)	0.73	1.06 (0.34,3.31)	0.92
SHBG (nmol/L)	0.91 (0.40,2.08)	0.83	1.00 (0.37,2.68)	0.99

Models are conditional on matching variables only. No other adjustments were made.

Baseline was date of first plasma sample. Latest sample was last sample prior to PCa diagnosis in cases or matched sample in controls.

Figure 1 A – E: Trajectories of marker level in the time prior to PCa diagnosis (or last sample in controls) for cases and controls. Change in marker levels per year (%) before and after adjustment are shown in tables.

A



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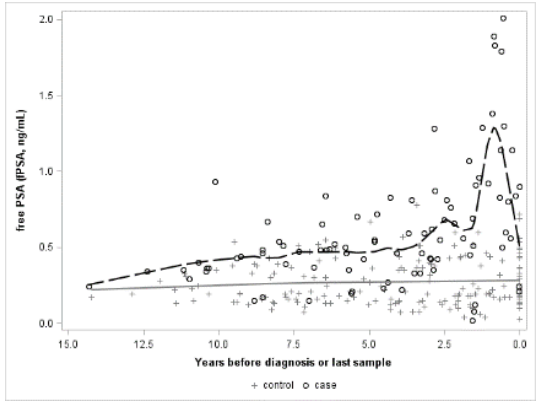
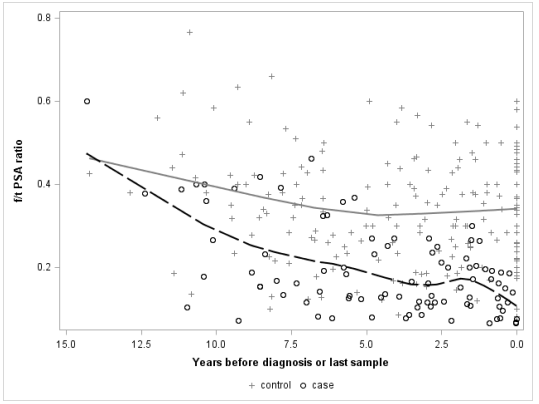
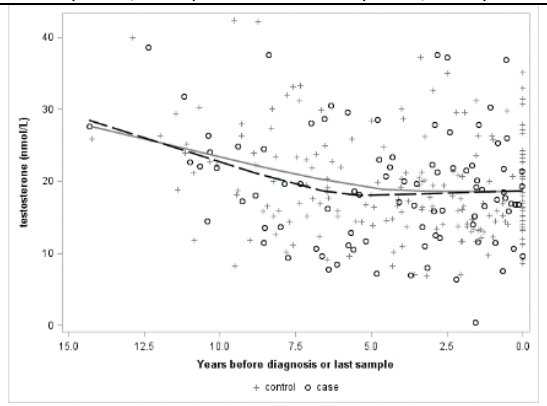


C

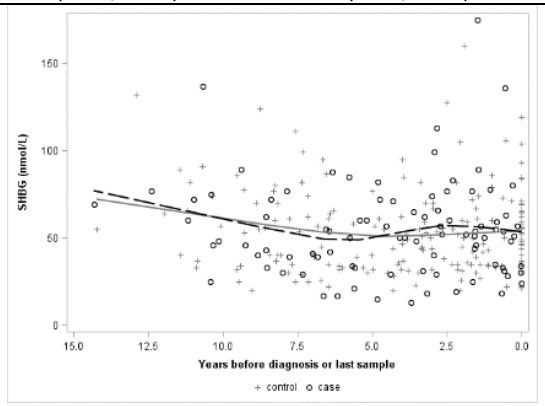


	Unadjusted		Adjusted[1]		Unadjusted		Adjusted[1]		Unadjusted		Adjusted[1]	
	% change (95% CI)	P	% change (95% CI)	P	% change (95% CI)	P	% change (95% CI)	P	% change (95% CI)	P	% change (95% CI)	P
Control	-0.44 (-2.49, 1.65)	0.67	1.19 (-1.38, 3.82)	0.37	-0.95 (-2.97, 1.10)	0.36	0.97 (-1.42, 3.42)	0.43	-0.52 (-2.18, 1.16)	0.54	-0.38 (-2.21, 1.49)	0.69
Cases	13.74 (10.29,17.29)	<.01	15.47 (10.69,20.46)	<.01	7.93 (4.73,11.21)	<.01	11.84 (7.62,16.24)	<.01	-3.49 (-5.70,-1.23)	<.01	-3.15 (-5.98,-0.23)	0.03

D



E



	Unadjusted		Adjusted[1]		Unadjusted		Adjusted[1]	
	% change (95% CI)	P	% change (95% CI)	P	% change (95% CI)	P	% change (95% CI)	P
Control	-3.01 (-4.37,-1.63)	<.01	0.37 (-1.24, 2.00)	0.65	-0.87 (-2.55, 0.83)	0.31	-2.42 (-3.56,-1.26)	<.01
Cases	-0.89 (-2.94, 1.21)	0.4	0.29 (-2.18, 2.82)	0.82	1.51 (-0.83, 3.91)	0.21	-1.79 (-3.78, 0.25)	0.09

[1]Models were adjusted for age at first sample, and current CD4 and HIV-RNA viral load. Models for fPSA and tPSA were further adjusted for current testosterone and SHBG level.