Asian Journal of Andrology (2011) 13, 616–617

www.nature.com/aja

RESEARCH HIGHLIGHT

PSA velocity may not be of value in prostate cancer detection

Derrick Johnston and Martha K Terris

Asian Journal of Andrology (2011) **13,** 616–617; doi:10.1038/aja.2011.43; Published online: 23 May 2011

Prostate cancer is the most prevalent non-skin cancer and is the third leading cause of cancer death in the United States. It is estimated to affect millions of men worldwide and is a significant cause of morbidity and mortality.[1] The detection and treatment of prostate cancer has changed significantly since the discovery of prostate-specific antigen (PSA) in the 1970s and the development of the first PSA serum assay in the 1980s. PSA testing has been implemented as a tumor marker and as a screening instrument for prostate cancer. Much data have been generated regarding the properties and usefulness of PSA in both roles. PSA velocity (PSAV), or the rate of increase in serum PSA levels over time, has been discussed and studied for many years as an adjunct to PSA alone in predicting prostate cancer.

A recent article by Vickers *et al.* in the *Journal of the National Cancer Institute* evaluated the accuracy of PSAV in predicting prostate cancer.[2] They analyzed prospectively gathered data from the placebo arm of the Prostate Cancer Prevention Trial (PCPT). In brief, the trial followed men with baseline PSA <3.0 for 7 years with serial rectal exams and PSA levels who were treated with finasteride or placebo. The placebo arm of this trial represents an excellent population for studying the value of PSA and PSAV in prostate cancer screening. The 5519 men over the age of 55 years underwent yearly PSA testing and digital rectal exam. Prostate biopsy was performed during the study when indicated (by PSA >4.0 or abnormal digital rectal exam) and at the end of the study in all patients who had not yet been diagnosed with prostate cancer (regardless of whether they had a prior biopsy). These data afford the opportunity to track PSA changes over time and compare with the known prostate biopsy pathology.

Vickers *et al.* created a multitude of different models to predict prostate cancer with different combinations of 'cut points' for PSA and PSAV. For example, PSA velocities of 0.35, 0.5 or 0.75 ng/ml/year combined with PSA levels of 2.5 or 4.0 ng ml^{-1}. These predictive models were then compared with the PSA and PSAV data from the study patients including the final biopsy results. Comparison was made between the different models' accuracy using receiver-operating characteristic curves which evaluate both sensitivity and specificity. They showed that PSA and PSAV correlated very closely together. Models using PSA and PSAV did not significantly outperform models using PSA alone. In fact, they showed that adding PSAV to a screening model may increase the number of unnecessary biopsies. They showed that in the PCPT study population, increased cancer detection could be attained by reducing the PSA threshold to 2.5 ng ml^{-1} which would increase unnecessary biopsies at the same rate as the 0.35 ng/ml/year PSAV model but would result in higher detection. In other words, using PSA alone at a cutoff of 2.5 ng ml^{-1} resulted in more sensitivity at the same specificity as using PSA cutoff of 4.0 ng ml^{-1} and a PSAV cutoff of 0.35 ng/ml/year. When they repeated the analysis for higher-grade prostate cancers only (Gleason score 7 and above) as well as 'clinically significant' cancers by Epstein criteria, they had the same results. The authors conclude that PSAV is not of significant added value compared to PSA alone for predicting prostate cancer detection.

The finding that PSAV is of poor predictive value in a screening population has been reported before. Analysis from the large European prostate cancer screening study, the European Randomised Study of Screening for Prostate Cancer (ERSPC),[3] also showed that PSAV did not add accuracy to predict prostate cancer in that population. This conclusion was discounted by some as there were questions about inconsistencies in indications for biopsy in the ERSPC study. The PCPT data avoid these shortcomings and still demonstrate that PSAV is not an independent predictor of prostate cancer detection.

These findings are controversial as they seem to contradict current practices. Many clinical guidelines, including the American Urological Association (AUA) and the NCCN prostate cancer screening guidelines, recommend consideration of biopsy for patient with PSAV above 0.35 ng/ml/year even with low PSA. It is certainly true that PSAV has been shown by many studies to be a good prognostic indicator for patients with known prostate cancer, predicting disease-specific and all cause mortality in patients treated with external radiation therapy as well as pathological stage, final Gleason's score and prostate cancer-specific mortality in patients undergoing prostatectomy.[4,5] Post-biochemical recurrence PSA doubling time, a correlate of PSAV, has also been well validated as a predictor of post-treatment prostate cancer progression, morbidity and mortality.

It does seem logical that higher PSAV would correlate with faster growing, more aggressive cancers. So why does PSAV not perform well at predicting significant prostate cancer detection? Perhaps at low PSAs, benign causes are more likely contribute to PSAV elevations. Perhaps, this is simply another example of the usefulness of PSA as a tumor marker but its limitations for screening. Etzioni *et al.*[6] hypothesize that lead time bias and variations in PSAV calculation (including how many values are used in the regression and the timeframe between measurements) explain its inaccuracy in screening. There has yet to be a prospective trial performed which specifically examines the result of using PSAV to indicate biopsy compared to PSA alone. Controversy continues regarding PSA

Section of Urology, Georgia Health Sciences University, Augusta, GA 30904, USA

Correspondence: Dr MK Terris (mterris@mcg.edu)

screening in general and there are several unanswered questions regarding PSAV. Further work may shed light on these issues. The placebo arm of the PCPT study and the previously reported ERSPC outcomes represent the largest prospectively gathered data sets which demonstrate the limitations of PSAV in detecting prostate cancer.

1 Haas GP, Delongchamps N, Brawley OW, Wang CY, de la Roza G. The worldwide epidemiology of prostate cancer: perspectives from autopsy studies. *Can J Urol* 2008; **15**: 3866–71.
2 Vickers AJ, Till C, Tangen CM, Lilja H, Thompson IM. An empirical evaluation of guidelines on prostate-specific antigen velocity in prostate cancer detection. *J Natl Cancer Inst* 2011; **103**: 462–9.
3 Roobol MJ, Kranse R, de Koning HJ, Schröder FH. Prostate-specific antigen velocity at low prostate-specific antigen levels as screening tool for prostate cancer: results of second screening round of ERSPC. *Urology* 2004; **63**: 309–13; discussion 313–5.
4 D'Amico AV, Renshaw AA, Sussman B, Chen MH. Pretreatment PSA velocity and risk of death from prostate cancer following external beam radiation therapy. *JAMA* 2005; **294**: 440–7.
5 D'Amico AV, Chen MH, Roehl KA, Catalona WJ. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. *N Engl J Med* 2004; **351**: 125–35.
6 Etzioni RD, Ankerst DP, Weiss NS, Inoue LY, Thompson IM. Is prostate-specific antigen velocity useful in early detection of prostate cancer? A critical appraisal of the evidence. *J Natl Cancer Inst* 2007; **99**: 1510–5.