



Editorial

PSA Velocity and Prostate Cancer Detection: The Absence of Evidence is not the Evidence of Absence

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The article by Schröder et al. [1] touches on an important topic and shows evidence that adds to the current confusion about the role of prostate-specific antigen velocity (PSAV) in prostate cancer early detection and screening: in a prescreened population for prostate cancer (second round) once the serum (total) PSA has reached the cut-off value of 4 ng/ml, the PSAV adds no new information about the presence of a cancer. This is disappointing, considering the urgent need to improve the discriminative power of serum total PSA to separate subjects with prostate cancer from those without.

When evaluating this study, its design needs to be kept in mind, since it deals with men who went from a PSA below 4 to a PSA above 4 during the four-year interval between screens in the programme. The conclusion of this article relates “only” to the use of PSAV as an addition to serum total PSA retrospectively once the PSA is above 4 and cannot be generalized to an *a priori* utilisation of PSAV in a second-round screening.

This article complements a previous report by the same group that highlights the lack of value of PSAV on prescreened men with a PSA below 4 ng/ml [2]. Again the design of the study suffers the same limitations described earlier: selection of the men who had a serum PSA below 4 and remained below 4 during the time of the study and excluding those where PSA rose above 4. A global analysis of the entire population (including men with PSA below

and above 4 ng/ml) may give a better view of the place of PSAV in a prescreened population.

There is an increasing body of evidence in favour of the use of PSAV to predict prostate cancer either in symptomatic patients or in the context of screening programmes. Carter et al. [3] were the first to advocate the use of PSAV to distinguish prostate cancer from benign lesions. The use of a PSAV cut-off of 0.1 ng/ml/yr is associated with an OR of 6.53 for men with a PSA between 2 and 4 ng/ml [4]. Berger et al. [5] in a screened population clearly demonstrated that the PSAV differs between cancer and no cancer (0.409 ng/ml versus 0.03 ng/ml). Nadler et al. [6] in men with PSA of 2.6–4 ng/ml noted a significantly greater PSAV in men with cancer (as opposed to those without (0.47 ng/ml versus 0.05 ng/ml). Eggener et al. [7], in a study of men with a previous negative biopsy, showed that PSAV is a significant risk factors among others, albeit weak. In a nomogram for predicting a positive repeat biopsy in prostate with previous negative biopsy, Lopez-Corona et al. [8] stressed the impact of PSA slope as a significant risk predictor.

Only the series from Lynn et al. [9] showed that the short-term PSAV alone had the same diagnostic accuracy as the serum PSA level. The absence of evidence is not the evidence of absence [10].

None of these studies prove the diagnostic value of PSAV, but a significant difference of PSAV between prostate cancer and no cancer is a sufficient indication to deserve a study on a

population that is representative of the question: Is PSAV better at predicting prostate cancer than a fixed serum total PSA cut-off in early detection or primary or secondary screening?

The amount of benign prostatic hyperplasia in the prostate gland may account for the lack of specificity of total PSA. It is one important reason why the evaluation of PSAV carries so much hope [6]. Even the Schröder group, when analyzing the second-round screening population with the whole range of PSA values included, was able to demonstrate a clear difference in PSAV between prostate cancer and prostate without cancer (0.62 ng/ml/yr versus 0.42 ng/ml/yr) and a modest diagnostic benefit over a PSA cut-off of 3 ng/ml (at a cut-off of 0.02 ng/ml/yr, PSAV will save 12.5% of unnecessary biopsies with a sensitivity of 95%) [11]. Noteworthy is the PSAV of the noncancer population that is among the highest reported in the literature.

To explain the lack of diagnostic value of PSAV in their prescreened population, the authors have postulated that the interval between the two rounds may not allow a difference in PSAV to appear in a screened population that has already been cleared from some prostate cancer with PSA above 4 ng/ml in round one. The graph from Berger [5] shows that the slopes take four years to diverge between population with cancer versus the population without cancer. This fact is already mentioned by Carter et al. [3] and Fang et al. [4].

The relationship between the aggressiveness of prostate cancer and PSAV is an important working track at present, especially since D'Amico et al. pointed out an increase risk of death for patients, treated by surgery [12] or radiation [13], with a PSA greater than 2 ng/ml/yr.

In addition to its potential better specificity, PSAV may allow earlier detection of men at risk of prostate cancer [14].

In conclusion, the clinical utility of PSAV has not yet been demonstrated. But there is an accumulation of good data that indicates its usefulness. Given the importance of the stakes: improved specificity of the diagnostic test, earlier detection of cancer, definition of aggressive cancer, we can only encourage the pursuit of the quest for evidence.

References

- [1] Schröder FH, et al. Does PSA velocity predict prostate cancer in pre-screened populations? *Eur Urol* 2006;49: 460–5.
- [2] Roobol MJ, et al. Prostate-specific antigen velocity at low prostate-specific antigen levels as screening tool for prostate cancer: results of second screening round of ERSPC (ROTTERDAM). *Urology* 2004;63(2):309–13, discussion 313–5.
- [3] Carter HB, et al. Recommended prostate-specific antigen testing intervals for the detection of curable prostate cancer. *JAMA* 1997;277(18):1456–60.
- [4] Fang J, et al. PSA velocity for assessing prostate cancer risk in men with PSA levels between 2.0 and 4.0 ng/ml. *Urology* 2002;59(6):889–93, discussion 893–4.
- [5] Berger AP, et al. Longitudinal PSA changes in men with and without prostate cancer: assessment of prostate cancer risk. *Prostate* 2005;64(3):240–5.
- [6] Nadler RB, et al. Use of 2.6 ng/ml prostate specific antigen prompt for biopsy in men older than 60 years. *J Urol* 2005;174(6):2154–7, discussion 2157.
- [7] Eggener SE, Roehl KA, Catalona WJ. Predictors of subsequent prostate cancer in men with a prostate specific antigen of 2.6 to 4.0 ng/ml and an initially negative biopsy. *J Urol* 2005;174(2):500–4.
- [8] Lopez-Corona E, et al. A nomogram for predicting a positive repeat prostate biopsy in patients with a previous negative biopsy session. *J Urol* 2003;170(4 Pt 1):1184–8, discussion 1188.
- [9] Lynn NN, Collins GN, O'Reilly PH. The short-term prostate-specific antigen velocity before biopsy can be used to predict prostatic histology. *BJU Int* 2000;85(7): 847–50.
- [10] Altman DG, Bland JM. Absence of evidence is not evidence of absence. *BMJ* 1995;311(7003):485.
- [11] Raaijmakers R, et al. Prostate-specific antigen change in the European Randomized Study of Screening for Prostate Cancer, section Rotterdam. *Urology* 2004;63(2): 316–20.
- [12] D'Amico AV, et al. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. *N Engl J Med* 2004;351(2):125–35.
- [13] D'Amico AV, et al. Pretreatment PSA velocity and risk of death from prostate cancer following external beam radiation therapy. *JAMA* 2005;294(4):440–7.
- [14] Riffenburgh RH, Amling CL. Use of early PSA velocity to predict eventual abnormal PSA values in men at risk for prostate cancer. *Prostate Cancer Prostatic Dis* 2003;6(1): 39–44.