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RESEARCH HIGHLIGHT

Should prostate-specific antigen velocity be abandoned?

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Prostate-specific antigen (PSA) is the most widely used biomarker for prostate cancer, but may also be elevated in non-malignant conditions such as benign prostatic hyperplasia. Studies in the early 1990s suggested that rapid increases in PSA over time—a concept known as PSA velocity (PSAV)—may be useful to distinguish prostate cancer from the generally slower rise in PSA that may be seen in benign conditions.[1] Subsequent studies demonstrated that PSAV predicts not only the presence of prostate cancer but also tumour grade, biochemical recurrence and disease-specific mortality.[2,3] Accordingly, the National Comprehensive Cancer Network Guidelines suggest that PSAV should be considered along with PSA when considering whether to recommend a prostate biopsy.[4]

A new study by Vickers *et al.* evaluated the use of PSAV in 5519 men from the placebo arm of the Prostate Cancer Prevention Trial, a 7-year randomized controlled trial of finasteride versus placebo for prostate cancer prevention.[5] PSAV was calculated by linear regression of PSA values from the 2 years prior to prostate biopsy.

On univariable analysis, increasing age, African-American race, positive family history and prior prostate biopsy were all significantly associated with prostate cancer detection. There was also a robust association between increasing PSAV and positive biopsy results ($P<0.001$).

Similarly, on multivariate analysis with other standard clinical predictors, PSAV was associated with a 5.24-fold increased odds of prostate cancer on biopsy ($P<0.001$). However, the addition of PSAV to the multivariable model led to only a small improvement in the area under the curve (AUC) on receiver operating characteristic analysis (0.709 from 0.702). Based upon these findings, the authors concluded that there is insufficient evidence to support the inclusion of PSAV in a guideline.

An important caveat of the study is to consider whether the study population reflects the target population. Among men from a large prostate cancer screening study, it was previously reported that the PSAV measured during the fifth decade had the best performance characteristics for prostate cancer detection (AUC 0.800 in 40s, 0.697 in 50s, 0.693 in 60s and 0.668 at age 70 and older).[6] Unfortunately, the study by Vickers *et al.* did not include men aged $\leqslant$55 years and only 1% were aged 55–60 years.[5] Accordingly, these results may not be generalized to younger men. On the contrary, 32% of the study population were aged 65–69 years, and 47% were aged 70 years or older. Because screening is controversial in elderly men with a more limited life expectancy,[7] an assessment of PSAV in a younger population would provide more useful clinical information.

In light of current controversies regarding the overdiagnosis of clinically insignificant prostate cancer, a critical question is the utility of PSAV to aid in the identification of life-threatening disease. Vickers *et al.* sought to address this issue by examining the association between PSAV with prostate cancer features on biopsy.[5] Compared to a base model with log PSA, family history, digital rectal examination and prior biopsy, the addition of PSAV led to modest increases in the discrimination of clinically significant (AUC 0.772 from 0.767) and Gleason scores 7–10 prostate cancer on biopsy (AUC 0.792 from 0.791). Limitations of this analysis are that the criteria for 'clinically significant' disease (clinical stage >T1c, PSA density $\geqslant$0.15, Gleason score $\geqslant$7, $\geqslant$3 positive cores or >50% core involvement with cancer) are subject to debate and also could not be evaluated in approximately one-quarter of the study population who had missing pathological data. Moreover, no long-term follow-up data beyond the biopsy are reported in the manuscript.

By contrast, previous studies with longer follow-up have demonstrated robust associations between PSAV and aggressive prostate cancer. For example, D'Amico *et al.* reported that a preoperative PSAV greater than 2 ng/ml/year was independently associated with a significantly increased risk of disease-specific mortality after radical prostatectomy and radiation therapy.[2,8]

More recently, our group examined the incremental predictive value of PSAV compared to PSA alone for the prediction of life-threatening prostate cancer in men from the Baltimore Longitudinal Study of Aging, a prospective cohort study initiated by the National Institute on Aging.[9] For observations at a PSA <3, the probability of life-threatening prostate cancer was 3% considering PSA alone. However, with the additional information of a PSAV >0.4 ng/ml/year, this probability increased to 13.6%. For observations at PSA levels of 3–10 ng ml^{-1}, the probability of life-threatening prostate cancer was 9.8%, which increased to 12% with PSAV >0.4 ng/ml/year. Thus, PSAV significantly reclassified the risk of life-threatening prostate cancer beyond total PSA, particularly at low PSA levels.

A potential explanation for the disparity between these results and the Vickers study is that the majority of their participants did not have a clinical indication (PSA or digital rectal examination abnormality) and underwent empiric biopsy at the end of the 7-year Prostate Cancer Prevention Trial study protocol.[5] As a result, this population was likely enriched in indolent tumours which would not have caused clinical consequences. It is difficult to establish more definitive conclusions regarding PSAV and life-threatening disease without long-term follow-up on these patients.

In conclusion, the study by Vickers *et al.* demonstrated a strong independent association between PSAV and prostate biopsy outcomes, though the improvement in discrimination was

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small in this elderly prescreened population that were selected for PSA levels below 3 ng ml^{-1}. Although the authors concluded that PSAV should not be included in practice guidelines on the basis of their results, long-term data in a younger population will be necessary to clarify the role of PSAV in the prediction of clinically significant prostate cancer.

1 Carter HB, Pearson JD, Metter EJ, Brant LJ, Chan DW *et al*. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. *JAMA* 1992; **267**: 2215–20.
2 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.
3 Carter HB, Ferrucci L, Kettermann A, Landis P, Wright EJ *et al*. Detection of life-threatening prostate cancer with prostate-specific antigen velocity during a window of curability. *J Natl Cancer Inst* 2006; **98**: 1521–7.
4 National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology version 2011. http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf (accessed 14 January 2011).
5 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.
6 Loeb S, Roehl KA, Catalona WJ, Nadler RB. Is the utility of prostate-specific antigen velocity for prostate cancer detection affected by age? *BJU Int* 2008; **101**: 817–21.
7 Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2008; **149**: 185–91.
8 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.
9 Loeb S, Carter HB, Schaeffer EM, Kettermann A, Ferrucci L *et al*. Distribution of PSA velocity by total PSA levels: data from the Baltimore Longitudinal Study of Aging. *Urology* 2011; **77**: 143–7.