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The Optimal Application of Prostate-Specific Antigen (PSA) Velocity to Predict High-Risk Disease

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Keywords

PSA velocity; PSA kinetics; prostate cancer; aggressiveness; high-risk

Consider the following clinical scenario: Two white men aged 55 yr present with a prostate-specific antigen (PSA) level of 3.0 ng/ml and normal digital rectal examination. Neither individual has a family history of prostate cancer. At this point, these patients might appear to have a similar risk for prostate cancer. We subsequently learn that 1 yr prior, the PSA level was 1.0 ng/ml in the first patient and 3.0 ng/ml in the second patient. Now which patient is at greater risk for prostate cancer? Further, if both patients were diagnosed with prostate cancer, which patient is more likely to have aggressive disease?

It seems intuitive that a demonstrably rising PSA would increase the risk of prostate cancer as well as the likelihood of adverse treatment outcomes. Indeed, numerous studies have shown that PSA velocity (PSAV) is associated with prostate cancer risk and disease-specific survival [1,2]. Nevertheless, as described in the accompanying editorial comment by Professor Heidenreich [3], other recent studies have called into question the “additional informative role” of PSAV.

Ulmert et al, for example, reported on PSAV in 4907 unscreened men from the Malmo Preventive Medicine study with two PSA measurements drawn approximately 6 yr apart [4]. In this population, men with a PSAV in the 50th percentile (0.029 ng/ml per year) had a 9.1% probability of prostate cancer detection at 20 yr, compared with a 14.1% probability for men with a PSAV in the 90th percentile (0.256 ng/ml per year). PSAV remained a significant predictor of prostate cancer risk after adjusting for PSA ($p < 0.0005$) but did not lead to a significant increase in the concordance index. Thus, the authors concluded that PSAV does not improve the predictive accuracy beyond a single PSA measurement in this unscreened

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Conflicts of interest

The authors have nothing to disclose.

population. However, the use of only two PSA measurements separated by a lengthy 6-yr interval may have considerably reduced the potential predictive value of PSA velocity.

In the European Randomized Study of Screening for Prostate Cancer, Schroder et al reported on a different form of PSAV [5]. In this case, two PSA measurements approximately 4 yr apart were used in the calculation. The study population consisted of 588 men with a PSA level <4.0 ng/ml at the initial screening visit whose PSA increased to ≥ 4.0 ng/ml over the 4-yr interval. Within this prospective yet highly selected population, PSAV was not associated with overall prostate cancer risk but was associated with an increasing likelihood of “aggressive” prostate cancer (clinical stage $\geq T1c$, Gleason score ≥ 7). The proportion of aggressive tumors was 55%, 60%, 65%, and 65% for men with a PSAV >0.25, >0.50, >0.75, and >1.0 ng/ml per year, respectively.

Nevertheless, because Schroder et al [5] did not find an improvement in the prediction of overall prostate cancer detection using PSAV beyond a total PSA threshold of 4.0 ng/ml, this study is often quoted as evidence against a role of PSA kinetics in screening. As with the prior study, however, a major limitation is the use of only two PSA measurements separated by a 4-yr interval for the PSAV calculation, increasing the likelihood of confounding from PSA “noise.” Instead, we recommend a PSAV calculation based upon at least three PSA measurements over approximately 18 mo.

To illustrate the importance of time interval in the PSAV calculation, we examined a previously described population ($n = 980$) from the Baltimore Longitudinal Study of Aging [6]. Specifically, we calculated PSAV using two PSA measurements derived from modeling of PSA values beginning 5 yr prior to diagnosis. For men ultimately diagnosed with high-risk prostate cancer (PSA ≥ 20 ng/ml, Gleason 8[en]10 or confirmed prostate cancer death), the PSAV was 0.53, 0.40, and 0.32 ng/ml per year using a 2-, 4-, or 6-yr time interval, respectively (unpublished data).

Additionally, dividing the PSA change over a 4-yr interval by four (or a 6-yr interval by six) makes the assumption that annual PSA changes are constant, thus overlooking the potential prognostic value of acceleration or deceleration over time. Our group has previously described the concept of a “risk count,” wherein men whose PSAV exceeded a specific threshold more than once had a greater likelihood of life-threatening prostate cancer [7]. Further studies are warranted to further evaluate the role of PSA acceleration in predicting prostate cancer risk and prognosis.

Returning to the initial case scenario, a long-term PSA history with numerous measurements helps to provide a context for the current clinical picture. When interpreting the results of Ulmert et al [4] and Schroder et al [5], it is important to recognize that not all PSAV calculations are equivalent. The time interval between PSA measures, the number of component PSA measurements, and the method used for calculating PSAV can have a significant impact on the results [8]. An important goal for future studies is to define the optimal method of calculation and specific patient populations in which PSAV provides incremental value for the detection of prostate cancer and the prediction of biologic potential.

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