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Counterpoint: Prostate-specific antigen velocity is not of value for early detection of cancer

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Abstract

There is firm evidence that PSA velocity is statistically associated with many prostate cancer outcomes, including those related to early detection. But clinical use of a marker depends on clinical as well as statistical significance. Before using PSA velocity to inform decisions such as whether or not to biopsy a man, there should be clear evidence that doing so would improve clinical outcome. A systematic review on PSA velocity found that almost no studies had evaluated whether PSA velocity aids clinical decision-making. Since that time, several reports have indicated that including PSA in a statistical model alongside standard predictors (such as PSA and digital rectal exam) does not improve predictive accuracy. Specifically, biopsying men with high PSA velocity in the absence of other indications, as recommended by the NCCN guidelines, would lead to many millions of unnecessary biopsies, without a corresponding number of aggressive cancers being detected. Advocates of PSA velocity have been reduced to citing a single paper purporting to show that PSA velocity aids clinical decision-making. The paper involves selective reporting of an unusual subgroup analysis based on an extremely limited number of events. This is not to say that, in clinical practice, urologists should ignore prior PSA values: clinical judgment can be aided by careful longitudinal evaluation of PSA changes, interpreted in the context of symptoms and treatments. However, the literature clearly demonstrates that simplistic application of PSA velocity cut-offs is not of value for early detection of prostate cancer.

Keywords

prostate cancer; detection; screening; PSA

Introduction

For PSA velocity, as in all areas of clinical research, our first question should be: “What is the question?”. It cannot reasonably be doubted that PSA velocity is statistically associated with prostate cancer outcomes, including those related to early detection. Indeed, even a paper concluding that there was “little justification” for the use of PSA velocity did report that PSA velocity was a statistically significant ($p < 0.001$) predictor in a multivariable model¹. But there is a time-honored distinction between clinical and statistical significance:

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what we want to know about PSA velocity does not concern null hypotheses of no association, but whether incorporating PSA velocity in clinical decision-making will improve clinical outcomes. As it turns out, there is clear evidence that use of PSA velocity to make decisions about prostate biopsy does not do more good than harm.

Early data on PSA velocity for early detection of cancer

In 2008, my own group analyzed data on PSA velocity from what is known as the Malmö cohort, which involves archived blood samples from over 20,000 Swedish men followed for 20 – 30 years without PSA screening. Like prior authors, we found strong evidence that PSA velocity is associated with long-term risk of cancer, even after adjusting for PSA ($P < 0.001$). However, combining both PSA and PSA velocity into a single model did not improve the predictive accuracy of PSA alone: the area-under-the-curve (AUC) for both was identical to three decimal places $(0.771)^2$.

We were surprised by this result as it seemed to contradict the prior literature. To explore this issue further, we conducted a systematic review of all prior studies on PSA velocity and doubling time in localized prostate cancer³. A total of 87 studies were identified, 42 of which had biopsy outcomes as an endpoint. Although many studies did report a hypothesis test for the association between PSA velocity and prostate cancer outcome, only two addressed the question of whether PSA velocity added predictiveness to PSA alone. One study reported that “PSA velocity did not improve the out-of-sample prediction of prostate cancer risk”; the other reported that PSA velocity increased AUC by a small amount (0.83 vs. 0.81) but involved the unsound assumption that patients who were never biopsied did not have prostate cancer. No paper in the review evaluated the consequences of using PSA in clinical decisions.

Data on PSA velocity published after the systematic review

Since the publication of the review, numerous papers by my own group and others have specifically examined whether PSA velocity adds to established predictors such as PSA. The findings have been absolutely consistent: PSA velocity does not increase our ability to predict prostate cancer once PSA is known.

A particularly interesting set of papers comes from O’Brien et al. The authors first noted that changes in PSA could be defined in different ways, either in terms of velocity or doubling time, and with different rules as to which PSAs are included and how PSA kinetics are calculated. It was found that, for many definitions, PSA velocity can not be calculated for a significant proportion of patients. The second major finding of the O’Brien papers is that values of PSA kinetics can vary widely between different definitions. For example, one man in the data set had PSA velocities of 0.27, 0.76, 1.47, 2.64 and 32.0 ng/ ml / year depending on the definition used. Overall, the investigators found no evidence that PSA velocity or doubling time could help predict mortality after conservative management⁴ or recurrence or mortality after radical prostatectomy⁵. Similar findings were reported by Ross et al⁶, in an active surveillance cohort (PSA velocity an “unreliable trigger” for intervention), in the SPCG4 randomized trial of radical prostatectomy (PSA changes “poor predictor of lethal prostate cancer”)⁷ and in a large cohort of men treated surgically at academic centers⁸.

These data are important because they suggest that PSA velocity is not a strong marker of cancer aggressiveness and thus is unlikely to be an important consideration in the decision whether or not to biopsy.

PSA velocity and prostate biopsy outcomes

Several groups have reported that PSA velocity does not importantly improve the specificity of PSA, that is, it does not help the decision to biopsy men with elevated PSA^{1,9-13}. In a study based on data from the European Randomized trial of Screening for Prostate Cancer (ERSPC), PSA velocity increased AUC by small amount compared to standard predictors, but this effect was driven by *lower* prostate cancer risk in men with high PSA velocities¹. This effect has been replicated independently. Exclusion of a small number of men with high PSA velocities abolished the effect of PSA velocity; moreover, PSA velocity did not help predict high grade cancers¹³.

Similar findings were found for repeat biopsy after initial negative biopsy. In a large study based on the ERSPC, with over 2500 repeat biopsies and 363 cancers, PSA velocity was strongly associated with cancer risk ($p < 0.001$) but had very low AUC (0.55). There was some evidence PSA velocity helped improve detection of high-grade cancer, but the confidence intervals were very wide and the clinical implications questionable as the increase in risk with higher PSA velocity was less than 1%.⁹ Similar findings were reported in the REDUCE trial¹⁴.

It has also been argued that PSA velocity could help detect prostate cancer in men with low PSA, in other words, that PSA velocity may improve the sensitivity of PSA. For many years, the guidelines of the National Cancer Centers Network (NCCN) recommended biopsy for men with a PSA risk of 0.35 ng / ml / year or more even if they had no other indication for biopsy, such as a positive DRE or elevated PSA¹⁵. The origin of this recommendation is interesting. In a study with only 20 events, and no attempt to determine whether PSA velocity added predictive value to PSA alone, Carter et al. reported a statistical association between PSA velocity and prostate cancer death 10 – 15 years before diagnosis¹⁶. The cut-point of 0.35 ng / ml was “suggested” as one reasonable choice amongst others based on a visual inspection of the receiving-operating-characteristic curve. A small study that is not about biopsy and does not examine the clinical value of PSA velocity, derives a possible cut-point based on an informal analysis, which then becomes hardened into a biopsy recommendation.

As it turns out, there is only a single data set that can be used to examine whether men with a high PSA velocity should be biopsied in the absence of other indications, the Prostate Cancer Prevention Trial (PCPT), in which all patients were biopsied at the end of the trial as part of the study protocol. The control arm of the PCPT in fact closely reflects the NCCN guidelines as it involved yearly PSA and DRE tests. Accordingly, the data can be used to empirically test what would happen were the guidelines to be implemented in practice. The results of a study on the PCPT were extremely clear. First, PSA velocity added almost nothing to the AUC of PSA alone, 0.709 vs. 0.702. Second, improvements in PSA were even smaller for the endpoint of clinically significant or high-grade cancer. Third, the

recommendation to biopsy men with low PSA and negative DRE if PSA velocity exceeded 0.35 ng / ml / year would lead to a very large number of biopsies, approximately one in seven men of screening age. Implementation of the NCCN guidelines would therefore lead to many millions of men in the US every year being referred to biopsy. Fourth, the yield of biopsies based on PSA velocity was very low and PSA cut-points had far greater sensitivity for equivalent specificity (e.g. 41% vs. 25% for high-grade cancer). As a result, clinicians who feel that current PSA thresholds are insufficiently sensitive would be better off using a lower PSA threshold, than biopsying on the basis of PSA velocity. Fifth, the data were independent of the method of calculating PSA: numerous different algorithms were tried, including the risk count method, and none were found of benefit¹⁰. Finally, the data were reanalyzed excluding older men and the results were nearly identical¹⁷.

Response to the recent data on PSA velocity

A summary of some of the most well-known and characteristic studies on PSA velocity in localized prostate cancer are given in Table 1. In general, the studies supporting PSA velocity are based on clinical cohorts (i.e. men who happened to be treated at a particular hospital), with small numbers of events. Most critically, none examined the marginal value of PSA velocity, that is, whether it increased the predictive accuracy of standard predictors such as PSA. In contrast, the papers suggesting that PSA velocity is not helpful are typically based on randomized trials or prospective cohort studies with large numbers of events, and did address the specific question of whether PSA velocity increases predictiveness.

That said, my own systematic review on PSA velocity was conducted some time ago, and in preparation for this paper, I contacted several noted advocates of PSA velocity asking for any recent data suggesting that PSA velocity added predictiveness to PSA alone. I was referred to a single paper by Loeb et al.¹⁸. This paper does indeed compare the predictive accuracy of PSA velocity, calculated in terms of risk count, plus PSA with that of PSA alone, with PSA velocity increasing AUC by 0.01. Such a trivial increase in AUC is hardly a ringing endorsement of the clinical value of PSA velocity. Moreover, the analysis is badly flawed by the assumption that men who were never biopsied did not have prostate cancer: because men who had an elevated PSA are referred to biopsy, and are therefore at risk of having cancer detected, this finding is no more than a demonstration that men with a high PSA velocity end up with high PSAs. The authors are not unaware of this problem and, in the methods section, state that they planned a subgroup analysis including only those men with who were biopsied. Remarkably, the results of this analysis are not presented, we are never told the AUC of PSA vs. PSA plus PSA velocity for biopsy outcomes. The authors do present a subgroup of a subgroup analysis, claiming that the AUC of PSA increases dramatically when incorporating PSA velocity for the prediction of high grade disease, where, unconventionally, high grade is defined as Gleason 8 – 10. This analysis is based on only 21 cases, highly problematic given the context of multivariable modeling.

Conclusion

There is little question that PSA velocity has a statistical association with prostate biopsy outcomes, even after adjusting for PSA. However, a systematic review including studies

published to March 2007 found that essentially no papers had addressed the critical question of whether use of PSA velocity aids prediction or clinical decision making once PSA is known. Numerous papers published since that time have clearly addressed this question in the negative: statistical models including both PSA and PSA velocity do not importantly predict any better than models based on PSA alone, and clinical decisions based on PSA velocity do not improve clinical outcome. Advocates of PSA velocity have been reduced to citing a single paper purporting to show that PSA velocity aids clinical decision-making. The paper involves selective reporting of an unusual subgroup analysis based on an extremely limited number of events.

This is not to say that, in clinical practice, urologists should ignore prior PSA values. Clinical judgment can be aided by careful longitudinal evaluation of PSA changes, interpreted in the context of symptoms and treatments. As a simple example, a PSA of 5 ng / ml may be considered very differently in a man who has experienced a gradual rise over time in comparison to a man experiencing a fall from 12 ng / ml, following treatment for signs of prostatitis. However, the literature clearly demonstrates that simplistic application of PSA velocity cut-offs is not of value for early detection of prostate cancer.

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Table 1

Examples of the results of typical studies on PSA velocity in men before treatment.

Study	Design	Events	Endpoint	Examined marginal value?	PSA velocity helpful?
BLSA ¹⁶	Prospective cohort study	20	Prostate cancer death in men prior to diagnosis	No	Yes
Malmö ²	Prospective cohort study	82	Advanced cancer in men prior to diagnosis	Yes	No
Loeb ¹⁹	Prospective cohort	346	Diagnosis of prostate cancer during screening	No	Yes
PCPT ¹⁰	Randomized trial	1211 (any) 256 (high grade)	Prostate cancer on biopsy	Yes	No
ERSPC ¹	Randomized trial	710 (any) 144 (high grade)	Prostate cancer on biopsy	Yes	No
ERSPC ⁹	Randomized trial	363 (any) 44 (high grade)	Prostate cancer on repeat biopsy	Yes	No
D'Amico ²⁰	Clinical cohort	28	Prostate cancer death in men treated with radiotherapy	No	Yes
D'Amico ²¹	Clinical cohort	27	Prostate cancer death in men treated with surgery	No	Yes
Stephenson ⁸	Clinical cohort	117	Prostate cancer death in men treated with surgery	Yes	No
Khatami ²²	Clinical cohort	104	Progression on active surveillance	No	Yes
Ross ⁶	Prospective cohort study	102	Progression on active surveillance	No	No
SPCG4 ⁷	Randomized trial	34	Prostate cancer death in men managed conservatively after diagnosis	Yes	No
O'Brien ⁴	Prospective cohort study	119	Prostate cancer death in men treated conservatively	Yes	No