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PSA velocity does not aid the detection of prostate cancer in men with a prior negative biopsy: data from the European Randomized Study of Prostate Cancer Screening in Göteborg, Sweden and Rotterdam, Netherlands

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Abstract

Purpose—Prostate specific antigen (PSA) velocity has been proposed as a marker to aid detection of prostate cancer. We sought to determine whether PSA velocity could predict the results of repeat biopsy in men with persistently elevated PSA after initial negative biopsy.

Materials and Methods—We identified 1,837 men who participated in the Göteborg or Rotterdam section of the European Randomized Screening study of Prostate Cancer (ERSPC), and who had one or more subsequent prostate biopsies after an initial negative finding. We evaluated whether PSA velocity improved predictive accuracy beyond that of PSA alone.

Results—There were a total of 2579 repeat biopsies, of which 363 (14%) were positive for prostate cancer, and 44 (1.7%) were high grade (Gleason score ≥ 7). Although PSA velocity was statistically associated with cancer risk ($p < 0.001$), it had very low predictive accuracy (area-under-the-curve [AUC] of 0.55). There was some evidence that PSA velocity improved AUC compared to PSA for high grade cancer. However, the small increase in risk associated with high PSA velocity – from 1.7 % to 2.8% as velocity increased from 0 to 1 ng / ml / year - is of questionable clinical relevance.

Conclusions—Men with a prior negative biopsy have a lower risk for prostate cancer at subsequent biopsies, with high grade disease particularly rare. We found little evidence to support the use of PSA velocity to aid decisions about repeat biopsy for prostate cancer.

Introduction

PSA velocity has been promoted as a marker to aid in the detection of prostate cancer^{1–4}. Several studies have shown that PSA velocity is strongly associated with risk of cancer on biopsy^{5–6}. Perhaps as a result, NCCN guidelines now state that men with a PSA velocity greater than 0.35ng/ml/year should consider a prostate biopsy, even with a PSA levels below the current biopsy thresholds⁷.

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Conflict of Interest Statement: Dr. Hans Lilja holds patents for free PSA and hK2 assays.

Despite a plausible biological association between PSA velocity and risk of prostate cancer, a systematic review found little direct evidence that PSA velocity helps to predict the outcome of a prostate biopsy⁸. We have subsequently published our own empirical research. In a cohort of 2742 men undergoing biopsy as part of the European Randomized Screening study of Prostate Cancer (ERSPC), we found little support for any clinically useful role for PSA velocity for helping to determine an initial biopsy. The predictive accuracy of a statistical model including PSA and age was improved slightly by the addition of PSA velocity, but there was little value for detection of high grade cancers, or when we excluded a small number of men with very high PSA velocity, which was associated with a reduced risk of prostate cancer⁹.

Critics have argued that PSA velocity improves the prediction of prostate biopsy outcome, but only in select groups of patients, such as in men with a prior negative biopsy^{10–11}. A declining PSA after a negative biopsy would indicate that the initial PSA rise resulted from a transient benign condition, whereas an increasing PSA would suggest a cancer missed on initial biopsy that continued to grow. Indeed, our own group has expressly advocated the potential value of PSA velocity for determining repeat biopsy in our prior work^{8–9}.

In this study, we evaluated whether PSA velocity aids the detection of prostate cancer on repeat biopsy in men with a prior negative biopsy. As in our previous paper on initial biopsy, we analyze data from two large, population-based cohorts from the ERSPC.

Methods

Patient methods

The study cohort included participants from the screening arms of the ERSPC in Göteborg, Sweden and Rotterdam, Netherlands. The study designs have been described previously^{12–14}. In brief, Göteborg participants were aged 50–70 and received biennial screening between 1995 and 2006; Rotterdam participants were aged 55–75 and underwent PSA tests every four years between 1995 and 2005. There was high compliance with both PSA screening (76% participation in Göteborg, 85% in Rotterdam) and biopsy after an elevated PSA (87% compliance). All biopsies were transrectal 6 core biopsies.

Laboratory methods

Seven milliliters of blood was collected by venipuncture in Vacutainer[®] tubes. The blood was allowed to clot, and serum was separated from blood cells by centrifugation at 3000g for 20 minutes, separated and frozen within 3 hours from collection, and kept frozen at –20°C until analysis. In the serum samples from Göteborg, PSA was measured within 2 weeks from the blood draw by Dr Lilja's laboratory at the Wallenberg Research Laboratories, Department of Laboratory Medicine, Lund University, University Hospital UMAS in Malmö, Sweden, using the dual-label DELFIA Prostatus[®] total/free PSA-Assay (Perkin-Elmer, Turku, Finland) as in our prior publication. Serum samples from Rotterdam were retrieved from the archival serum bank (where they had been stored frozen at –80°C after the initial processing within 3 hours from venipuncture) and shipped frozen on dry ice to Malmö, Sweden for analysis in 2005–2007 as reported. All analyses were conducted blind to biopsy result.

Statistical methods

A total of 1469 patients from Göteborg and 3394 from Rotterdam had at least one negative biopsy. Not all men had repeat biopsies, for example, if PSA was not elevated at subsequent screening. Our main analysis focuses on the subset of patients undergoing at least one repeat biopsy and who had a PSA value less than 20ng/ml: 862 in Göteborg and 975 in Rotterdam.

Only 30 men had a PSA greater than 20ng/ml and it is unlikely these men would forgo biopsy irrespective of their PSA velocity. Nonetheless, we planned a sensitivity analysis including these men. PSA velocity was calculated using ordinary least squares regression, separately for each biopsy outcome using all available PSA measurements up to the time of the respective biopsy.

The data set contained all biopsies subsequent to an initial negative biopsy, 2579 biopsies in total (1538 from Göteborg and 1041 from Rotterdam). Logistic regression was used to evaluate the association between PSA velocity and biopsy outcome (positive or negative), with adjustment for the PSA at biopsy and the number of prior negative biopsies (categorized as one or more than one). No other covariates (e.g. age, DRE) were used. Since participants could be represented more than once on the data set, generalized estimating equations were used to correct for within-subject correlation.

To determine the predictive value of PSA velocity above and beyond PSA level, we looked at predictive accuracy, given as the area under the receiver operating characteristics curve (AUC). Since the AUC is calculable only with one observation per participant, we included only the participants' first repeat biopsy for these purposes. We calculated the AUC for models including PSA level and PSA velocity separately and a model including both PSA level and PSA velocity (for the AUC analyses, the number of prior negative biopsies was one for all observations and therefore irrelevant). All AUCs were corrected for overfit using bootstrap methods. PSA level and velocity were entered into all models with restricted cubic splines to model any non-linear relationship with outcome. We did not observe a non-linear relationship between PSA or PSA velocity and risk of high-grade disease, and therefore, given the limited number of events for these analyses, we did not include non-linear terms. All statistical analyses were conducted using Stata 10.0 (StataCorp LP, College Station, TX).

Results

In Göteborg, approximately 50% of patients (n=452) had only one subsequent biopsy, while 28% (n=239) had two and 20% (n=171) had three or more; the most subsequent biopsies was five. In Rotterdam, with only three rounds of screening, the majority of patients (93%; n=906) had only one subsequent biopsy; 69 (7%) had two subsequent biopsies. The mean number of PSA measurements used to calculate PSA velocity was 2.6 and 4.4 for the first biopsy and all biopsies after an initial negative biopsy, respectively. Out of a total of 2579 biopsies, 363 (14%) were positive for prostate cancer, of which 44 (1.7%) were high grade (Table 1). PSA levels at the time of repeat biopsy were only slightly higher for men with positive compared to negative biopsies (median in Göteborg: 5.02 and 4.93 ng/ml and Rotterdam: 5.90 and 5.70ng/ml, respectively), as were PSA velocities (median in Göteborg: 0.33 and 0.25 ng/ml/year and Rotterdam: 0.32 and 0.23 ng/ml/year, respectively). Characteristics were similar when considering only the first biopsy after the initial negative biopsy.

PSA velocity appeared very homogeneous (Figure 1; PSA velocity density plot), and there are no large changes in risk with increasing velocity. Using all biopsy results and adjusting for the number of prior negative biopsies, PSA level was significantly associated with high grade disease (p=0.023), but not with any cancer (p=0.12); PSA velocity was significantly associated both with any cancer on biopsy (p<0.001, Figure 1) and with high grade disease (p<0.001; Figure 2). After adjustment for both PSA and number of negative biopsies, PSA velocity remained a significant predictor of any cancer (p<0.001) and high-grade disease (p=0.035).

In all analyses, the number of prior negative biopsies was associated with biopsy outcome (all $p < 0.02$), with the risk of a positive biopsy being lower with more biopsies. For example, in the model including both PSA level and PSA velocity, the odds of a positive biopsy was 71% lower with two or more prior negative biopsies compared to one prior negative biopsy.

Considering only the first biopsy following after the initial negative biopsy, both PSA level and PSA velocity exhibited poor discrimination for predicting any cancer (corrected AUC 0.522 and 0.551; $p = 0.04$ and $p = 0.004$). For the outcome of high grade disease, PSA velocity was more predictive than PSA alone (corrected AUC of 0.621 and 0.558; $p = 0.001$ and $p = 0.016$, respectively). When both PSA and PSA velocity were included in the model, the predictive accuracy of a model with PSA was not importantly improved for the prediction of any cancer (AUC: 0.557); the predictive accuracy of high grade disease was slightly improved (AUC: 0.598). However, due to the very low number high grade cancers, the confidence intervals are very wide (95% CI: 0.503, 0.681).

The Rotterdam and Göteborg cohorts are different with respect to screening strategies: men were screened either every two years in Göteborg or every four years in Rotterdam. It was plausible that the predictiveness of PSA velocity is higher among men who were screened less regularly. Therefore we evaluated whether the effect of PSA velocity differed by cohort. We did find some evidence that PSA velocity was more strongly associated with risk of high grade disease in the Rotterdam cohort (OR for a 1 ng/ml/year increase in PSA velocity: 7.6; 95% CI: 1.4, 41.4) than for the Göteborg cohort (OR: 1.5; 95% CI: 0.89, 2.6); the interaction term testing whether the effects of velocity depended on cohort was not significant ($p = 0.061$).

None of our results were materially affected if we included men with PSA above 20 ng / ml. For example, the AUC of PSA velocity for any cancer was 0.560 compared to 0.551 in the main analysis.

Discussion

We have previously hypothesized that PSA velocity could predict the outcome of repeat biopsy. Our empirical analyses do not support this hypothesis: in a large, population-based cohort, PSA velocity was associated with very low predictive accuracy. There was some evidence that PSA velocity was predictive of high grade disease, particularly for men with a four year interval between PSA tests. However, this effect is of questionable clinical value as risk of high grade disease after a prior negative biopsy is very low and PSA velocity relatively homogenous. For example, take two men with negative biopsy, one of whom has a stable PSA (i.e. PSA velocity of 0 ng / ml / year) and the other who had a PSA velocity of 1 ng / ml / year. These two men would typically be seen as having quite distinct risks, and indeed they constitute the 20th and 90th percentile of PSA velocity. However, the change in risk from 1.7 % vs 2.8% for high grade disease seems unlikely to lead to differences in clinical decision making. Only 1.6% of the cohort had PSA velocity above the widely cited threshold of 2 ng/ml /year¹⁵.

Our results are consistent with our previous work on the ERSPC cohort that failed to find a role for PSA velocity for predicting the result of initial biopsy^{9, 16–18}, as well as an independent study that failed to find evidence that PSA velocity enhances the prediction of prostate cancer in men with a prior negative biopsy¹⁹. Similarly, a nomogram developed to predict the probability of prostate cancer on repeat biopsy did not find that PSA velocity was an important predictor²⁰.

In contrast to our findings on PSA, Thompson et al. found that PSA did not lose predictive value for the detection of prostate cancer after a prior negative biopsy²¹. Our findings differ

– PSA level did not help predict prostate cancer on subsequent biopsy – most likely because men in our cohort were prompted to undergo biopsy only after a persistently elevated PSA. Thompson et al. biopsied all men regardless of their subsequent PSA level: more than 50% of the men undergoing a second biopsy had PSA levels below the usual threshold for biopsy. Biopsying a large number of men with low PSA levels who were at low risk of being diagnosed would improve the performance characteristics of PSA; the clinical relevance of this finding is questionable, however, because in clinical practice men with low PSA are not referred for a second biopsy.

Although our findings do not support the hypothesis that formal calculation of PSA velocity provides a decision rule for rebiopsy of men following a negative biopsy, we do not want to discount informal consideration of prior PSA values. For example, a dramatic increase in PSA is more likely to signal benign inflammation rather than cancer: in our cohort, five men had PSA velocities greater than 10ng/ml, none of whom were subsequently diagnosed with prostate cancer.

There are several possible limitations of our study that may explain why we did not find an important role for PSA velocity in men with a prior negative biopsy. First, our calculation of PSA velocity relied on PSA measurements taken every two or four years. It is plausible that more frequent PSA assessments may have improved our ability to assess the true changes in PSA velocity. Yet Eggener et al analyzed a cohort of men receiving yearly PSA tests and reported similar results to ours: men with an annual PSA velocity of 0 ng/ml or greater were at statistically greater risk of prostate cancer than those whose PSA fell, but predictive accuracy was low (AUC of 0.58)¹⁰. Moreover, Bittner et al.¹⁹ reported no significant association between PSA velocity and the result of rebiopsy despite patients having 3 or more PSA measurements in the year before biopsy. Furthermore, a recent study of US men who were re-biopsied after a prior negative biopsy due to a persistently elevated PSA and/or abnormal DRE found that PSA velocity was not an independent predictor of prostate cancer due to its strong correlation with PSA level²².

Second, our study did not include men with PSA less than 2.5 ng/ml, as these men were not biopsied in the ERPSC. However, in an analysis of PCPT data, in which men were given a biopsy irrespective of their PSA level, Thompson et al did not find any evidence that PSA velocity was informative of biopsy outcome²³. Furthermore, common clinical practice would dictate that men whose PSA fell below 2.5 ng / ml should not be referred to biopsy. As such, our findings reflect usual clinical care. A final possible limitation is that patients in our study received only sextant biopsy, and it could be that a more extensive biopsy scheme would have uncovered cancers associated with PSA velocity. However, it seems unlikely that PSA velocity would differentially detect tumors that can be identified on extended but not sextant biopsy. Again the data of Bittner et al.¹⁹ are pertinent: there was no association between PSA velocity and outcome of a transperineal template-guided mapping biopsy, where a median of more than 50 cores were taken.

In sum, we found PSA velocity is statistically associated with the result of repeat biopsy, but is not a strong predictor of outcome. Our findings are in line with previous studies, which have also failed to find PSA velocity a valuable clinical tool in the detection of prostate cancer in several other groups of men^{8, 24–25}. There is therefore little justification for the formal calculation of PSA velocity, use of PSA velocity cut-offs or inclusion of PSA velocity in statistical models to determine which men with a prior negative prostate biopsy should be referred for repeat biopsies.

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Figure 1. Predicted probability of a positive biopsy by PSA velocity, with adjustment for the number of prior negative biopsies. The shaded region represents the population-based quartiles of PSA velocity.

Figure 2.

Predicted probability of a high grade disease on biopsy by PSA velocity, with adjustment for the number of prior negative biopsies. The shaded region represents the population-based quartiles of PSA velocity.

Participant characteristics. Data are given as median (interquartile range) or frequency (percentage). *8 biopsies were repeat biopsies occurring in the first round

Table 1

Göteborg Cohort	All biopsies after initial negative biopsy		First biopsy after initial negative biopsy	
	No Cancer N=1290	Cancer N=248	No Cancer N=693	Cancer N=169
Age at biopsy (years)	64 (61, 67)	65 (62, 67)	64 (61, 67)	65 (62, 67)
Round of biopsy				
2*	263 (20%)	71 (29%)	248 (36%)	69 (41%)
3	341 (26%)	61 (25%)	196 (28%)	39 (23%)
4	295 (23%)	46 (19%)	127 (18%)	28 (17%)
5	230 (18%)	43 (17%)	81 (12%)	21 (12%)
6	161 (12%)	27 (11%)	41 (6%)	12 (7%)
Total PSA (ng/ml)	4.93 (3.89, 6.71)	5.02 (3.98, 7.15)	4.47 (3.64, 5.86)	4.69 (3.70, 6.43)
Total PSA velocity (ng/ml/year)	0.25 (0.10, 0.50)	0.33 (0.17, 0.63)	0.26 (0.09, 0.53)	0.28 (0.15, 0.60)
<0	206 (16%)	26 (10%)	117 (17%)	23 (14%)
0 – 0.5	760 (59%)	142 (57%)	392 (57%)	95 (56%)
0.5 – 1	216 (17%)	51 (21%)	127 (18%)	33 (20%)
>1	108 (8%)	29 (12%)	57 (8%)	18 (11%)
Abnormal DRE	108 (8%)	40 (16%)	69 (10%)	31 (18%)
Biopsy Gleason grade				
6		219 (88%)		145 (86%)
7		25 (10%)		15 (12%)
8		4 (2%)		4 (2%)
Prostate volume (cc) [n=1213]	49 (39, 66)	37 (30, 51)	47 (37, 60)	36 (30, 49)
Rotterdam Cohort	No Cancer N=926	Cancer N=115	No Cancer N=862	Cancer N=113
Age at biopsy (years)	64 (61, 67)	65 (61, 68)	64 (61, 67)	65 (61, 68)
Round of biopsy				
2	722 (78%)	90 (78%)	722 (84%)	90 (80%)
3	204 (22%)	25 (22%)	140 (16%)	23 (20%)

Göteborg Cohort	All biopsies after initial negative biopsy		First biopsy after initial negative biopsy	
	No Cancer N=1290	Cancer N=248	No Cancer N=693	Cancer N=169
Total PSA (ng/ml)	5.70 (4.40, 7.90)	5.90 (4.40, 8.80)	5.60 (4.30, 7.70)	5.90 (4.40, 8.80)
Total PSA velocity (ng/ml/year)	0.23 (0.00, 0.54)	0.32 (0.05, 0.83)	0.24 (0.00, 0.56)	0.32 (0.05, 0.83)
<0	225 (24%)	24 (21%)	208 (24%)	23 (20%)
0–0.5	446 (48%)	49 (43%)	410 (48%)	48 (42%)
0.5–1	169 (18%)	17 (15%)	162 (19%)	17 (15%)
>1	86 (9%)	25 (22%)	82 (10%)	25 (22%)
Abnormal DRE	188 (20%)	34 (30%)	171 (20%)	34 (30%)
Biopsy Gleason grade				
6		100 (87%)		98 (87%)
7		11 (10%)		11 (10%)
8		4 (3%)		4 (4%)
Prostate volume (cc) [n=1038]	58 (47, 73)	51 (39, 68)	58 (47, 72)	51 (39, 66)