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Prostate-Specific Antigen Velocity for Early Detection of Prostate Cancer:

Result from a Large, Representative, Population-based Cohort

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Abstract

Background—It has been suggested that changes in prostate-specific antigen (PSA) over time (ie, PSA velocity [PSAV]) aid prostate cancer detection. Some guidelines do incorporate PSAV cut points as an indication for biopsy.

Objective—To evaluate whether PSAV enhances prediction of biopsy outcome in a large, representative, population-based cohort.

Design, setting, and participants—There were 2742 screening-arm participants with PSA <3 ng/ml at initial screening in the European Randomized Study of Screening for Prostate Cancer in

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Take-home message Although there is a statistical association between prostate-specific antigen (PSA) velocity and prostate cancer, PSA velocity does not help detect prostate cancer once PSA and age are taken into consideration.

Rotterdam, Netherlands, or Göteborg, Sweden, and who were subsequently biopsied during rounds 2[en]6 due to elevated PSA.

Measurements—Total, free, and intact PSA and human kallikrein 2 were measured for 1[en]6 screening rounds at intervals of 2 or 4 yr. We created logistic regression models to predict prostate cancer based on age and PSA, with or without free-to-total PSA ratio (%fPSA). PSAV was added to each model and any enhancement in predictive accuracy assessed by area under the curve (AUC).

Results and limitations—PSAV led to small enhancements in predictive accuracy (AUC of 0.569 vs 0.531; 0.626 vs 0.609 if %fPSA was included), although not for high-grade disease. The enhancement depended on modeling a nonlinear relationship between PSAV and cancer. There was no benefit if we excluded men with higher velocities, which were associated with lower risk. These results apply to men in a screening program with elevated PSA; men with prior negative biopsy were not evaluated in this study.

Conclusions—In men with PSA of about ≥ 3 ng/ml, we found little justification for formal calculation of PSAV or for use of PSAV cut points to determine biopsy. Informal assessment of PSAV will likely aid clinical judgment, such as a sudden rise in PSA suggesting prostatitis, which could be further evaluated before biopsy.

Keywords

cancer detection; predictive models; prostate biopsy; prostate cancer; prostate-specific antigen; PSA velocity

1. Introduction

The change in prostate-specific antigen (PSA) level over time, PSA velocity (PSAV), has been suggested as an aid to detection of prostate cancer. It is argued that a rapidly rising PSA may indicate a greater risk of diagnosis of prostate cancer even if PSA levels are low. Accordingly, current National Comprehensive Cancer Network guidelines recommend that men whose PSAV is ≥ 0.35 ng/ml per year should consider biopsy even if PSA levels are below the usual threshold for biopsy [1]. The American Cancer Society makes a similar recommendation when PSAV is ≥ 0.75 ng/ml per year and PSA is 4[en]10 ng/ml [2]. The European Association of Urology (EAU) recommends biopsy if PSAV is above 0.60 ng/ml per year [3].

While conducting a systematic review on PSAV after diagnosis of prostate cancer, we were surprised to find little if any direct evidence that PSAV could help predict biopsy outcome [4]. In particular, we noted three problems with the existing literature on PSAV for detection of cancer. First, many analyses assumed that men who were not biopsied had no cancer, leading to “verification bias” [5], which can cause artifactual associations between a marker and cancer detection. Second, most studies made a perhaps unjustified assumption of a linear association between PSAV and cancer risk. Third, most studies have not addressed a key question for any marker: whether PSAV adds predictive value to established predictors. Clinicians deciding whether or not to recommend biopsy have a choice between basing this decision on the patient’s most recent laboratory report, or using the patient’s prior PSA values to calculate PSAV using, for example, ordinary least squares regression [6]. A statistically significant association between PSAV and cancer, or even an “independent” statistical association controlling for PSA level, does not tell us whether calculating PSAV would benefit patients.

In the light of these common methodological problems, we designed this study to evaluate whether PSAV aids decisions on whether to perform a prostate biopsy in men with moderate PSA elevations using a large, population-based cohort from the European Randomized Study

of Screening for Prostate Cancer (ERSPC). We also evaluated whether changes in the velocity of PSA forms and human kallikrein-related peptidase 2 (hK2) are of value.

2. Patients and methods

2.1. Patients

The study cohort included participants from the screening arms of the ERSPC in Göteborg, Sweden, and Rotterdam, Netherlands. The study designs have been described [7[en]9]. Briefly, about 30% of men aged 50[en]66 yr living in Göteborg were invited for an initial PSA test during 1995[en]1996; men not diagnosed with cancer were invited for up to five subsequent biennial screens or until they reached age 70. In Rotterdam, men aged 55[en]75 yr were invited for an initial PSA test during 1993[en]1999; men not diagnosed with cancer were invited for up to two subsequent screens every 4 yr until they reached age 75. This study is based on the measurements of total, free, intact PSA, and hK2 in serially collected blood samples in both cohorts taken between 1993 and 2006.

In both cohorts, biopsies were prompted by an elevated PSA. All total PSA and free PSA measurements used for statistical analysis are in accordance with World Health Organization (WHO) calibration standards [10]. The calibration of these assays was changed in 2004 to reflect the WHO standards; a correction factor was applied to the earlier measurements. Accordingly, the total PSA threshold for prostate biopsy varied slightly between 2.54 and 3.39 ng/ml. We excluded all participants who were biopsied in the first screening round because they had only one PSA measurement available and therefore PSAV could not be calculated. For the remaining participants, only a man's initial biopsy results were included; we excluded results from subsequent biopsies after an initial negative biopsy. Overall, our combined cohort included 2742 men (1241 from Göteborg, 1501 from Rotterdam) who had an elevated PSA (≥ 3 ng/ml) and were biopsied in rounds 2[en]6. The flow of study participants is given in Figure 1.

2.2. Laboratory methods

Laboratory methods were the same used by Vickers et al [8]. Total PSA and free PSA were measured using the dual-label Delfia Prostatatus total/free PSA-assay (Perkin-Elmer, Turku, Finland) and calibrated using the WHO standard. These analyses were performed within 2 wk of venipuncture for the Göteborg cohort. Rotterdam samples were processed within 3 h of venipuncture and then stored frozen at -80°C (conditions under which free PSA is stable [11, 12]). For this study, samples retrieved from the archival serum bank were shipped frozen on dry ice to Malmö, Sweden, for analyses in 2005[en]2007. Analyses of intact PSA and hK2 in samples from both centers were performed in 2005[en]2007 by in-house research assays [13]. Nicked PSA was calculated as free PSA minus intact PSA. All analyses were conducted blind to biopsy result at coauthor Hans Lilja's laboratory at Lund University, UMAS, Malmö, Sweden.

2.3. Statistical methods

Our principal analysis was determining whether PSAV could enhance the predictive accuracy of prostate cancer diagnosis above either of two base models. The base models were created by logistic regression; predictors were either total PSA and age, or total PSA, age, and free-to-total PSA ratio (%fPSA). We included %fPSA as a second base model in this and previous research [8] on the grounds that free PSA is widely used in clinical practice to determine indication for biopsy. PSAV was calculated using linear regression with no restrictions on the number of PSA values or interval between PSA values. PSAV was added separately to each base model. To model possible nonlinear relationships with risk, we used restricted cubic splines with knots at the tertiles for total PSA, free PSA, and PSAV. Predictive accuracy was

calculated as the area under the receiver operating characteristics curve (AUC); results were corrected for overfit using repeated 10-fold cross-validation. As a second end-point, we tested all models for prediction of high-grade prostate cancer (defined as biopsy Gleason score ≥ 7). Sensitivity analyses were performed to determine the effect of biopsy scheme: The ERSPC used sextant biopsy, which may have missed cancers that could have been detected with an extended biopsy scheme. For the sensitivity analyses, we considered participants with a positive biopsy within 4 yr of an initial negative biopsy as positive at their initial biopsy.

To characterize the clinical effects of the models, we used decision curve analysis [14]. This method estimates a “net benefit” for prediction models by summing the benefits (true positives) and subtracting the harms (false positives), with false positives weighted by a factor related to the relative harm of a missed cancer versus an unnecessary biopsy. The weighting is derived from the threshold probability of prostate cancer at which a patient would choose to be biopsied. As threshold probability varies among patients, we calculated net benefit across a range of threshold probabilities (10[en]40%) as reported previously [9]). We also examined whether the velocity of intact PSA, hK2, or free PSA could add to the predictive accuracy of a model including total PSA and age. All analyses were conducted using Stata 10.0 (Stata Corp., College Station, TX, USA).

3. Results

Of the 2742 men biopsied, 710 (26%) were diagnosed with prostate cancer (322 of 1241 in the Göteborg cohort and 388 of 1501 in the Rotterdam cohort). Participant characteristics are shown in Table 1. Participants in Rotterdam were older at biopsy (median 67 vs 63 yr) and had slightly higher Gleason scores (23% of cancers were Gleason ≥ 7 in Rotterdam vs 16% in Göteborg); other characteristics were very similar between sites. Total PSA levels were extremely homogenous (75% were between 3 and 5 ng/ml) and similar in men with prostate cancer compared to those with negative biopsy (median of 3.8 vs 3.7 ng/ml).

Figure 2 shows the predicted probability of prostate cancer with increasing PSAV after controlling for PSA and age. The risk of cancer peaked at approximately 0.5 ng/ml per year and declines above and below this point. The predictive accuracy of the models is shown in Table 2. The base model with only total PSA and age had an AUC of 0.531, which increased to 0.609 with the addition of %fPSA. PSAV enhanced the predictive accuracy of both base models slightly (without %fPSA the AUC increased from 0.531 to 0.569; with %fPSA it increased from 0.609 to 0.626). Similar results were seen from sensitivity analyses simulating the effects of a biopsy more extensive than sextant (without %fPSA the AUC increased from 0.512 to 0.556; with %fPSA it increased from 0.596 to 0.617) and when the Rotterdam or Göteborg cohorts were analyzed independently (Table 2). When PSAV was modeled using only linear terms, the enhancement of predictive accuracy was smaller in both the model with only total PSA and age (AUC increased from 0.531 to 0.545) and with %fPSA (AUC increased from 0.609 to 0.618). All of these predictive accuracies were poor.

When the outcome was defined as high-grade cancer (Gleason score ≥ 7), predictive accuracy of all models increased. However, the predictive accuracy of total PSA and age (AUC 0.683) was not significantly improved by adding PSAV (AUC 0.689). Dynamics of other kallikreins (intact PSA, hK2, nicked PSA, or free PSA) did not significantly enhance predictive accuracy above that of the base model plus the respective marker (Table 3).

The nonlinear relationship between PSAV and cancer risk (Fig. 2) suggests that simple PSAV cut points would not be of value. Indeed, among men with a PSA of 4[en]10 ng/ml, those with PSAV >0.75 ng/ml per year were significantly *less* likely to be diagnosed with prostate cancer than men with PSAV below the cut point (24% vs 30%; $p = 0.034$). Similar results were found

for other cut points (Table 4). Results were also similar when the analysis included all men or those with PSA ≥ 4 ng/ml (data not shown).

To put these results in a clinical context, we plotted decision curves for prostate cancer diagnosis (Fig. 3 and 4). These show that, although no model is of value for risk-averse men with threshold probabilities $<20\%$ (ie, men who would opt for biopsy even if they had a lower risk of cancer), PSAV improves clinical net benefit slightly for men who would choose biopsy only at a risk of $\geq 20\%$. However, Figure 4 demonstrates that the clinical benefit of PSAV is restricted to a small number of men with high PSAV: When the analysis excludes men with PSAV >0.75 ng/ml per year (corresponding to approximately 15% of our current study cohort), PSAV confers no benefit. This suggests that formal calculation of PSAV and incorporation into a multivariable model may be unnecessary and that a simple clinical algorithm will suffice: Men with a sudden rise in PSA should be considered for evaluation for prostatitis before being referred for biopsy. As PSAV did not appear to significantly enhance predictive accuracy in our main analysis, we undertook six post hoc analyses to evaluate PSAV using slightly different definitions. First, it is possible that more recent PSA measurements are more predictive of prostate cancer; thus, we repeated our analyses with only the two most recent PSA measurements before the biopsy. Second, accurate calculation of PSAV may require many PSA measurements; we restricted our analysis to patients with at least four PSA measurements taken over 6 yr. Third, the utility of PSAV may lie in assessment of its variability: Prostate cancer may plausibly be more likely in a patient with a steadily rising PSA than in a patient whose PSA rises, drops, and then rises again. To explore this hypothesis, we calculated the residual sum of squares from each patient's dynamics calculation (when three or more PSA measurements were available) as a predictor in the model with its respective velocity measurement. Fourth, to model the acceleration of PSA, Benecchi et al [6] recommend log-transforming the PSA values; thus we also calculated the total PSAV with log-transformed total PSA values. Fifth, several studies have used doubling time as a method for modeling the changes in PSA [15,16], and thus we repeated our analyses with doubling time, with and without %fPSA. Finally, we examined whether including transrectal ultrasound volume in the model alongside PSA and age influenced the additional value of PSAV. None of these additional analyses significantly affected our results (Table 5). The largest enhancement came from log-transformed total PSA measurements; however, the improvement was smaller when %fPSA was included in the model (AUC 0.594 vs 0.619 including PSAV) or when the outcome was high-grade cancer (AUC 0.683 vs 0.693 including PSAV).

4. Discussion

In an analysis of a large, population-based cohort, we found little evidence that PSAV can enhance cancer detection in men with elevated PSA. The increment in predictive accuracy was small, decreased if %fPSA was taken into account, and most likely not sufficient to influence clinical decision making. Any enhancement in predictive accuracy contributed by PSAV depended on careful nonlinear modeling. Moreover, PSAV did not help prediction of high-grade prostate cancer after adjustment for PSA and age. We also found little evidence that the velocities of other PSA forms or hK2 were of value.

Our approach involved three methodological safeguards. First, we avoided the assumption that men without biopsy are cancer free. Second, we did not assume that the association between PSAV and cancer is linear; instead, we used nonlinear modeling to allow the relationship between PSAV and cancer to follow a curve. Third, we examined whether PSAV adds predictive value beyond that provided by PSA and age. Although several analyses of PSAV in the ERSPC have been published [17,18], none have involved multiple screening rounds, used data from more than one center, assessed increments in predictive accuracy offered by PSAV, or modeled PSAV using nonlinear terms.

Several possible limitations of our study may explain why we found no important role for PSAV. First, PSA measurements were taken only every 2 yr or 4 yr. Plausibly, more frequent PSA assessments might allow a more accurate assessment of true changes in PSA over time. That said, a recent study of patients receiving yearly screening reported very similar results: An AUC of 0.58 for a base model of age and PSA increased to 0.61 for base model plus PSAV [19]. This increment, 0.03, is very close to our primary analysis. The authors also reported a lower risk of prostate cancer at high PSAV. Moreover, we saw no evidence that PSAV performed significantly better in Göteborg (with biennial PSA measurements) than in Rotterdam, with a 4-yr screening interval.

A second possible limitation of our study is that we did not include men with PSA <3 ng/ml, as these men were not biopsied in the ERSPC. Accordingly, our results apply only to men with elevated PSA, and we are unable to test whether PSAV might be of value for men with low PSA. The Prostate Cancer Prevention Trial (PCPT) was unique in biopsying men irrespective of their PSA level. The PCPT investigators found that PSAV was not an independent predictor of cancer risk and did not add predictive value to a multivariable prediction model [20]. A third limitation is that we analyzed only the outcome of a first biopsy. Changes in PSA might plausibly be particularly valuable as indicator for rebiopsy after a first negative biopsy. For example, a declining PSA after a negative biopsy might indicate that the initial PSA rise resulted from a transient benign condition, whereas an increasing PSA would suggest a cancer that was missed on initial biopsy. We plan to evaluate this hypothesis in a separate paper.

It has also been suggested to us that PSAV is sensitive to slight changes in assay characteristics [21]. However, to minimize any measurement-related biases, we performed all PSA measurements in a single laboratory using an assay protocol calibrated with a PSA standard endorsed by WHO. We anticipate that routine clinical use of PSAV would typically involve calculation of PSAV from measurements adhering to far less standardization. Furthermore, our study was nested within a randomized controlled trial in which the same standard operating procedures for specimen procurement were used at both sites. It has also been suggested to us that these results may be affected by the use of sextant biopsy in the ERSPC. However, our sensitivity analyses indicate that the results are unlikely to have differed if the ERSPC had performed extended biopsies.

Our study has several strengths. It included a very large number of men in a randomized trial, who were therefore subject to highly standardized testing and follow-up procedures. We avoided verification bias and addressed the key question of whether PSAV adds information beyond that provided by PSA alone. We also used decision analysis to examine the clinical impact of decisions based on PSAV. Few of these methodological safeguards have been prominent in the literature purporting to show that PSAV is of value. For example, a paper concluding that “PSAV had additional value over ... PSA” did not report a multivariate analysis including both PSA and PSAV [22]. Similarly, a study reporting that “PSA velocity enhanced the detection of high-grade cancer” did not compare the predictive accuracy of a statistical model including both PSA and PSAV with a model including PSA alone. Other papers have reported only statistical associations [23] or have made the assumption that men who did not have a biopsy were free of cancer [24]. Our findings support those of several prominent reviews that have questioned the value of PSAV [25,26].

5. Conclusions

We found that PSAV adds very little predictive value for determining the outcome of a first prostate biopsy in men with elevated PSA. Our findings are very similar to those of earlier studies, which found no real value of using PSAV [19,20]. Accordingly, we see little justification for formal calculation of PSAV and subsequent incorporation into a statistical

model, and no justification for velocity cut points, in determining indication for biopsy. This suggests that current guidelines on the use of PSAV to guide biopsy should be revised [1,3, 14]. However, we encourage use of clinical judgment in decisions about biopsy: A sudden rise in PSA might suggest prostatitis, triggering further evaluation of symptoms, laboratory tests, or empirical antibiotic therapy. If evidence of prostatitis is absent, a biopsy might well be advisable. This type of sophisticated, sequential, clinical decision making cannot easily be evaluated in analyses of population-based screening studies.

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Fig. 1.
[en] Flow of participants through the study.

Fig. 2.

[en] Predicted probability of a positive biopsy with increasing prostate-specific antigen (PSA) velocity, controlling for PSA. Probabilities are for a subject with a PSA level of 4.3 ng/ml, which was the mean PSA for the cohort. Black line: modeled with nonlinear terms; gray line: modeled with only a linear term; dashed lines: 95% confidence intervals.

Fig. 3.

[en] Decision curve analysis. The curves show the clinical benefit for basing biopsy decisions on the models with total prostate-specific antigen (PSA) plus age (dotted line), total PSA plus age plus free-to-total PSA ratio (%fPSA; dashed line), and total PSA plus age plus %fPSA plus PSA velocity (thin solid line); biopsy all men (thick grey line); and biopsy no man (thick black line).

Fig. 4.
 [en] Decision curve analysis for men with prostate-specific antigen (PSA) velocity <0.75 ng/ml per year. Total PSA plus age (dotted line), total PSA plus age plus free-to-total PSA ratio (%fPSA; dashed line), total PSA plus age plus %fPSA plus PSA velocity (thin solid line), biopsy all men (thick grey line), biopsy no man (thick black line).

Table 1
[en] Participant characteristics stratified by European Randomized Screening for Prostate Cancer site and cancer status*

	Göteborg (<i>n</i> = 1241)		Rotterdam (<i>n</i> = 1501)	
	No cancer <i>n</i> = 919	Cancer <i>n</i> = 322	No cancer <i>n</i> = 1113	Cancer <i>n</i> = 388
Age at biopsy, yr	63 (60, 66)	65 (61, 67)	67 (63, 71)	67 (64, 71)
Round of biopsy				
2	296 (32%)	72 (22%)	936 (84%)	324 (84%)
3	268 (29%)	88 (27%)	177 (16%)	64 (16%)
4	168 (18%)	75 (23%)	[en]	[en]
5	85 (9%)	47 (15%)	[en]	[en]
6	102 (11%)	40 (12%)	[en]	[en]
Absolute measurements**				
Total PSA	3.5 (3.1, 4.2)	3.5 (3.1, 4.3)	3.8 (3.3, 4.8)	4.0 (3.4, 5.2)
Free PSA ***	0.74 (0.59, 1.00)	0.69 (0.51, 0.90)	0.84 (0.66, 1.10)	0.75 (0.58, 1.02)
% Free PSA ***	20.7 (16.1, 26.8)	18.8 (13.8, 24.4)	24.3 (19.6, 30.6)	20.5 (15.0, 27.0)
Intact PSA	0.39 (0.28, 0.52)	0.40 (0.25, 0.52)	0.47 (0.36, 0.62)	0.49 (0.37, 0.67)
Human kallikrein 2	0.046 (0.029, 0.066)	0.055 (0.038, 0.081)	0.059 (0.041, 0.082)	0.073 (0.051, 0.101)
Nicked PSA	0.36 (0.25, 0.51)	0.27 (0.18, 0.39)	0.35 (0.25, 0.51)	0.24 (0.16, 0.40)
Total PSA dynamics****				
Velocity, ng/ml per year	0.29 (0.18, 0.53)	0.29 (0.19, 0.47)	0.36 (0.22, 0.56)	0.37 (0.27, 0.58)
Doubling time, mo	66.8 (38.8, 113)	66.4 (47.1, 109)	63 (40.6, 101)	63.8 (45, 96.1)
Biopsy Gleason score				
≤6	[en]	269 (84%)	[en]	297 (77%)
7	[en]	45 (14%)	[en]	78 (20%)
≥8	[en]	8 (2%)	[en]	13 (3%)
Clinical stage				
T1C	[en]	252 (78%)	[en]	236 (61%)
T2A	[en]	48 (15%)	[en]	90 (23%)
T2B	[en]	9 (3%)	[en]	31 (8%)
T2C	[en]	4 (1%)	[en]	17 (4%)
T3	[en]	8 (2%)	[en]	14 (4%)
Unknown	[en]	1 (0.3%)	[en]	0 (0%)

PSA = prostate-specific antigen.

* Shown are participants who were biopsied for the first time after round 1. Data are given as number (%) or median (interquartile range).

** All are given in nanogram per milliliter, except for percentage free PSA

*** Free PSA was measured using clinical/unfrozen (Göteborg) or previously frozen (Rotterdam) samples.

**** The number of PSA measurements used to calculate PSA dynamics can be determined by the round of biopsy. For example, participants with a biopsy in round 2 generally had two PSA measurements, and participants with a biopsy in round 3 generally had three PSA measurements. The exact numbers varied slightly (in the single digits) because a few participants had a repeat PSA in the same screening round.

Table 2

[en] Predictive accuracy*

	Any cancer		High-grade cancer (Gleason sum ≥ 7)			
	AUC		p value	AUC		p value
	Base	Base + PSAV		Base	Base + PSAV	
Göteborg and Rotterdam ($n = 2742$)						
Total PSA, age	0.531	0.569	<0.001	0.683	0.689	0.023
Total PSA, age, %fPSA	0.609	0.626	<0.001	0.746	0.747	0.053
Göteborg ($n = 1241$)						
Total PSA, age	0.559	0.579	0.0032	0.675	0.671	0.2
Total PSA, age, %fPSA	0.597	0.613	0.0027	0.736	0.734	0.174
Rotterdam ($n = 1501$)						
Total PSA, age	0.539	0.571	0.002	0.692	0.701	0.11
Total PSA, age, %fPSA	0.623	0.635	0.002	0.760	0.753	0.4

AUC = area under the curve; PSA = prostate-specific antigen; PSAV= PSA velocity; %fPSA = free-to-total prostate-specific antigen ratio.

* Accuracy is given as the AUC and has been corrected for overfit using repeated 10-fold cross-validation. The base model includes total PSA, age, and free-to-total PSA ratio. The p values are for PSAV in the multivariable model.

Table 3
[en] Predictive accuracy of velocity for other kallikrein markers*

Base model		Base plus velocity model		
Variables	AUC	Variables	AUC	<i>p</i> value
Total PSA, age, free PSA	0.600	Total PSA, age, free PSA plus free PSAV	0.608	0.004
Total PSA, age, %fPSA	0.609	Total PSA, age, %fPSA plus %fPSAV	0.623	<0.001
Total PSA, age, intact PSA	0.540	Total PSA, age, intact PSA plus intact PSAV	0.538	<0.001
Total PSA, age, nicked PSA	0.666	Total PSA, age, nicked PSA plus nicked PSAV	0.669	0.3
Total PSA, age, hK2	0.576	Total PSA, age, hK2 plus hK2 velocity	0.578	0.15

AUC = area under the curve; hK2 = human kallikrein-related peptidase 2; PSA = prostate-specific antigen; PSAV = prostate-specific antigen velocity; %fPSA = free-to-total prostate-specific antigen ratio; %fPSAV = free-to-total prostate-specific antigen velocity ratio.

* AUC given for the base model (consisting of total PSA and age) combined with each additional kallikrein marker without or with velocity of the respective marker. Data combined from both cohorts.

Table 4
[en] Incidence of cancer according to prostate-specific antigen velocity (PSAV) cut points

PSAV cut point	Patients, no. (%), above cut point	Patients, no. (%), below cut point	Cancers, no. (%), in patients above cut point	Cancers, no. (%), in patients below cut point
0.35 ng/ml per year **	820 (78)	225 (22)	224 (27)	71 (32)
0.5 ng/ml per year	601 (58)	444 (42)	163 (27)	132 (30)
0.75 ng/ml per year ***	305 (29)	740 (71)	72 (24)	223 (30)

* The analysis was limited to participants with a prostate-specific antigen level 4[en]10 ng/ml.

** Data from Thompson et al [2] and Vickers et al [14].

*** Data from Thompson et al [2].

Table 5
[en] Sensitivity analyses

Base model (total PSA and age)	n	Base AUC	Base + PSAV AUC	p value
Main analysis	2742	0.531	0.569	<0.001
Velocity calculated only using two most recent PSA measurements	2742	0.531	0.545	0.0053
Velocity calculated from at least four prior PSA measurements over 6 yr (Göteborg only)	284	0.571	0.559	0.034
PSA variability (residual sum of the squares)	1115	0.532	0.548	0.15
Log-transformed PSA values	2742	0.531	0.580	<0.001
PSA doubling time	2742	0.531	0.544	0.017
PSA doubling time plus %fPSA	2742	0.609	0.618	0.003
Prostate volume included in the base model	2460	0.654	0.676	<0.001
Prostate volume included in the base model, prediction of high-grade disease	2460	0.754	0.754	0.053
Velocity modeled without nonlinear terms	2742	0.531	0.545	0.0011
Velocity modeled without nonlinear terms plus %fPSA	2742	0.609	0.618	<0.001

AUC = area under the curve; PSA = prostate-specific antigen; PSAV = prostate-specific antigen velocity; %fPSA = free-to-total prostate-specific antigen ratio.