

Cancer cell invasion into surrounding tissue is an early and crucial step of carcinogenesis and several recent studies emphasized the role of a biologic approach to identify the genes and expression of their corresponding products that might have a role in local and metastatic progression, including the von Hippel-Lindau/hypoxia-inducible factor (VHL/HIF-1 α) gene pathway, matrix metalloproteinases, and adhesion molecules of the integrin family, and therefore prognostic and therapeutic significance, especially for the clear cell RCC subtype [8–11].

In conclusion, this study from UCLA represents an important advance in the development of an accurate staging system for patients with intracapsular RCC and shows that the TNM classification might also be improved through the careful examination of the pathologic specimen. Nevertheless, the incorporation of molecular factors into current prognostic algorithms will surely result in better prognostic tools that might eventually guide the choice of different adjuvant treatments and appropriate follow-up schemes.

Conflicts of interest

The authors have nothing to disclose.

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(I) Re: Prostate Specific Antigen Velocity in Men with Total Prostate Specific Antigen Less than 4 ng/ml

Loeb S, Roehl KA, Nadler RB, Yu X, Catalona WJ

J Urol 2007;178:2348–53

Expert's summary:

This study analyses the prostate-specific antigen (PSA) determinations of 11,709 men with two or more PSA measurements within approximately 12 mo, an initial PSA of <4 ng/ml, and using biopsy indications of PSA ≥ 2.5 ng/ml or ≥ 4.0 ng/ml. The authors found that PSA velocity (PSAV) thresholds in the range of 0.4 ng/ml/yr should be used to help guide the need for biopsy in men with a total PSA level <4 ng/ml. Receiver operating characteristic (ROC) analysis showed that the area under the curve (AUC) was 0.68 for PSAV and 0.87 when total PSA was included in addition to PSAV.

Expert's comments:

This is the third time that a paper, which deals with the value of PSAV in the early detection of prostate cancer, is commented on and once more the conclusion is that inadequate methodology leads to incorrect results.

In both the earlier commented studies of Berger et al and Sun et al [1,2] the following statements were made: "Correctly assessing the discriminating value of a biomarker for having a particular disease, yes or no, requires a similar method of verification of the disease status in all men".

In the current study, the cohort consisted of 11,792 men with a total PSA <4.0 ng/ml and two or more PSA measurements within about 12 mo, which allowed determination of PSAV. In these men 501 cases of prostate cancer were diagnosed. Several multivariate analyses showed that a PSAV threshold of 0.4 ng/ml/yr is most useful in recommending biopsy in men with total PSA values <4.0 ng/ml.

The method of verification in this case would have been to biopsy all 11,792 men. This was not done because the indication for biopsy was a serum PSA value of ≥ 4.0 ng/ml or ≥ 2.5 ng/ml (after May 1995). Next to this the predictive ability of the different predictors entered into the multivariate model are valued suboptimally. It is regrettable that studies like the one dealt with here are published without a proper discussion on the effect of these issues on the outcome.

Two attempts are made here to clarify the effect of misinterpreting the value of the different predictors for biopsy outcome and verification bias with

simple examples, based on the screening data of the Rotterdam part of the European Randomized Study of Screening for Prostate Cancer (ERSPC).

The study cohort used for this example consists of 10,752 men screened two times (4-yr interval, biopsy indication PSA ≥ 3.0 ng/ml). Their PSA at initial screening was, as in the study by Loeb et al, < 4.0 ng/ml and they were not biopsied at initial screening. The two available PSA measurements (thus over a period of 4 yr) were used to calculate the PSAV. This was done with the simple formula: (PSA2-PSA1)/time in years between visits 1 and 2.

Although it is known that linear regression should be the method of choice for calculating PSAV, using first and last PSA values only may be adequate for everyday clinical use, as long as measurements are separated by a sufficiently long time period [3].

We used this definition of PSAV to create the dichotomous variable PSAV ≤ 0.4 ng/ml/yr or > 0.4 ng/ml/yr. First, we copied the multivariate analyses model 1 (variables used: dichotomous PSAV, age, and family history) and model 2 (identical to model 1 but with addition of the PSA value at time of detection). The calculated probabilities of these models were used for ROC analyses.

Because men within ERSPC are all white the effect of race was not evaluated. It is important to realize that the fact that men with PSA values < 3.0 ng/ml may have a biopsy-detectable prostate cancer is completely ignored here.

In this setting (Table 1) the predictive value of PSAV is impressive. However, when we add the last known PSA value (ie, at second screening) to the model we see that the odds ratio of PSAV suddenly becomes much lower (Table 2). These results are comparable to the study of Loeb et al.

PSAV still is a significant predictor for biopsy outcome although its odds ratio is considerably decreased. The absolute PSA level at second screening is also a predictor for biopsy outcome. This is easily explained since the men with prostate cancer have a PSA level of ≥ 3.0 ng/ml (the cut-off level for biopsy), so automatically PSA will be a significant predictor for biopsy outcome simply because the existence of the verification bias resulting from the assumption that all men with PSA < 3.0 ng/ml do not have cancer!

This effect confirms the earlier remark made by the same group: "There is a significant direct association between the total PSA level and the PSAV. Men with higher total PSA levels are more likely to have a high PSA velocity" [4]. If thus the disease status is only verified in men with relatively higher PSA values (ie, higher PSAV values), it is not

Table 1 – Results of multivariate regression model 1 on the ERSPC data

Variables under study	Odds ratio for prostate cancer at second screen	95%CI	p
PSAV > 0.4	16.4	12.–20.8	< 0.001
Age	1.0	1.0–1.01	0.01
Family history of prostate cancer	1.4	0.9–2.2	0.08

ERSPC = European Randomized Study of Screening for Prostate Cancer; CI = confidence interval; PSAV = prostate-specific antigen velocity.

Table 2 – Results of multivariate regression model 2 on the ERSPC data

Variables under study	Odds ratio for prostate cancer at second screen	95%CI	p
PSAV > 0.4	2.2	1.5–3.3	< 0.0001
PSA at second screen	1.7	1.5–1.8	< 0.0001
Age	1.0	0.9–1.1	0.244
Family history of prostate cancer	1.5	0.9–2.3	0.066

ERSPC = European Randomized Study of Screening for Prostate Cancer; CI = confidence interval; PSAV = prostate-specific antigen velocity.

surprising that PSAV is positively correlated with the presence of prostate cancer.

The AUC of the calculated probabilities of models 1 and 2 are displayed in Table 3.

Similar to the study under review the AUC with the PSA at second screening in the model is considerably higher than the AUC without this PSA value. Calculating the AUC of a model where the following variables are entered: age, family history, and PSA at second screening (ie, without PSAV) results in an AUC of 0.95, comparable to the one with PSAV. Obviously, although PSAV is a significant predictor in the multivariate analysis it does not add much to the predictive power. The information of the PSA at second screening completely overwhelms the information of the PSAV (ie,

Table 3 – AUC of the calculated probabilities of model 1 and model 2

Model	AUC	95%CI
1	0.75	0.72–0.78
2	0.95	0.94–0.95

Variable is prostate cancer detected at second screening. AUC = area under the curve; CI = confidence interval

a PSAV $<$ or ≥ 0.4 ng/ml/yr). This last AUC calculation is absent in the paper of Loeb et al.

An AUC of 0.95 for PSA alone (or in the range of 0.87 as in the study of Loeb et al) is already an indication that something is ignored here. If indeed PSA is capable of predicting biopsy outcome in such an excellent way, it is unnecessary to continue the search for other more specific markers.

Conflicts of interest

The author has nothing to disclose.

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Analyzing the prostate-specific antigen (PSA) determinations of 11,709 men with two or more PSA measurements within approximately 12 mo and an initial PSA of < 4 ng/ml, Loeb et al found that PSA (PSAV) thresholds in the range of 0.4 ng/ml/yr should be used to help guide the need for biopsy in men with a total PSA level < 4 ng/ml. Despite the acceptance of the presence of a verification bias, the conclusion of the study is left unchanged: PSAV is significantly associated with detection of prostate cancer in men with a total PSA < 4.0 ng/ml.

Expert's comments:

As mentioned in the discussion, only 1669 of the 11,291 men (14.8%) labeled as having no prostate cancer actually underwent biopsy. This implies that the assumption is made that men without a biopsy (ie, men with a PSA value < 2.5 ng/ml) have no prostate cancer. As already pointed out in their discussion the data from the Prostate Cancer Prevention Trial (PCPT) showed that this is a wrong assumption [1].

In this second comment on the study of Loeb et al, an attempt is made clarify the effect of verification bias with a simple example, based on the screening data of the Rotterdam part of the European Randomized Study of Screening for Prostate Cancer (ERSPC).

The study cohort used for this example consists, similar to the previous comment, of 10,752 men, screened two times (4-yr interval, biopsy indication PSA ≥ 3.0 ng/ml). Their PSA at initial screening was, as in the study by Loeb et al, < 4.0 ng/ml and they were not biopsied at initial screening. The two available PSA measurements (thus over a period of 4 yr) were used to calculate the PSAV. This was done with the simple formula:

(PSA2–PSA1)/time in years between visits 1 and 2.

We used this definition PSAV to create the dichotomous variable PSAV ≤ 0.4 ng/ml/yr or > 0.4 ng/ml/yr. Again we copied the multivariate analyses model 1 (variables used: dichotomous PSAV, age, and family history) and model 2 (identical to model 1 but with addition of the PSA value at time of detection). Because men within ERSPC are all white the effect of race was not evaluated.

It is important to note the fact that only men actually biopsied at the second screen were entered into the model ($n = 1232$; 11.5%).

In the setting displayed in Table 1, the predictive value of PSAV is not significant and just above the value of 1. However, when we add the last known

Table 1 – Results of multivariate regression model 1 on the ERSPC data (only men actually biopsied)

Variables under study	Odds ratio for prostate cancer at second screen	95%CI	p
PSAV > 0.4	1.02	0.79–1.32	0.855
Age	1.0	0.97–1.03	0.850
Family history of prostate cancer	1.4	0.88–2.20	0.157

ERSPC = European Randomized Study for the Screening of Prostate Cancer; CI = confidence interval; PSAV = prostate-specific antigen velocity.