Published in final edited form as:

Curr Opin Urol. 2009 May ; 19(3): 221–226. doi:10.1097/MOU.0b013e32832a2d10.

Early prostate-specific antigen changes and the diagnosis and prognosis of prostate cancer

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Abstract

Purpose of review—To delineate how recent findings on prostate-specific antigen (PSA) can improve prediction of risk, detection, and prediction of clinical endpoints of prostate cancer (PCa).

Recent findings—The widely used PSA cut-point of 4.0 ng/ml increasingly appears arbitrary, but no cut-point achieves both high sensitivity and high specificity. The accuracy of detecting PCa can be increased by additional predictive factors and combinations of markers. Evidence implies that a panel of kallikrein markers improves the specificity and reduces costs by eliminating unnecessary biopsies. Large, population-based studies have provided evidence that PSA can be used to predict PCa risk many years in advance, improve treatment selection and patient care, and predict the risk of complications and disease recurrence. However, definitive evidence is currently lacking as to whether PSA screening lowers PCa -specific mortality.

Summary—PSA is still the main tool for early detection, risk stratification, and monitoring of PCa. However, PSA values are affected by many technical and biological factors. Instead of using a fixed PSA cut-point, using statistical prediction models and considering the integration additional markers may be able to improve and individualize PCa diagnostics. A single PSA measurement at early middle age can predict risk of advanced PCa decades in advance and stratify patients for intensity of subsequent screening.

Keywords

diagnosis; mortality reduction; prostate cancer; prostate-specific antigen; risk stratification

Introduction

Prostate cancer (PCa) is the most common malignancy among men worldwide and the second leading cause of cancer-specific death in men in United States [1]. Prostate-specific antigen (PSA) has revolutionized PCa detection [2•], risk stratification [3••], and monitoring of treatment outcomes [3••,4]. PCa-specific mortality in the United States has decreased by almost 33% [5,6], which some have attributed to PSA screening [7]. However, almost 50% of screen-detected cancers may be indolent [1], and overdiagnosis and overtreatment of PCa have become

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common. Here, we review recent discoveries on PSA, its subforms, and the homologous kallikrein-related peptidase 2 (hK2).

Specificity of prostate-specific antigen

PSA is highly abundant in the prostate epithelium, and it is virtually organ specific. Because, though, it is expressed in both normal, cancerous, and hyperplastic tissue, it suffers from poor specificity in discriminating cancer from benign prostate conditions, especially benign prostatic hyperplasia (BPH), which also results in increased release of all PSA forms and hK2. The specificity of PSA is most problematic in the range of 2–3 up to 10–15 ng/ml, resulting in a negative biopsy rate of 70–80% [8,9].

Prostate-specific antigen cut-off

Despite numerous proposed values, no single cut-off for total PSA (tPSA) has been shown to reliably separate the men at high risk for PCa from men at low risk, or men with ‘significant’ from those with ‘insignificant’ cancer. This point was clearly illustrated by analyses of the placebo arm of the Prostate Cancer Prevention Trial (PCPT) [10], a large randomized trial of finasteride for chemoprevention of PCa. At enrollment, the 18 882 participants were aged 55 years or older and had PSA less than 3 ng/ml and normal digital rectal examination (DRE). All participants underwent prostate biopsy at the end of the study, permitting assessment of the true risk of PCa in the placebo arm. Among the 2950 men (aged 61–92 years) with PSA level of 4 ng/ml or less and normal DRE, 15.2% had PCa [11]. Although nominally small PSA elevations were strongly associated with increased PCa risk, no PSA range was free from risk of PCs (even PSA level of 0.5 ng/ml or less was associated with a PCa risk of 6.6%). Moreover, no cut-point achieved both high sensitivity and high specificity [12].

The PCPT and other studies have demonstrated that the PSA cut-off of 4 ng/ml is arbitrary [13•], and lowering the tPSA threshold may be beneficial for the identification of men at high long-term risk of PCa of unquestionable significance. In general, however, we should consider not only clinical and epidemiologic features, but also the social and psychological implications of possible PCa detection. The laboratory report, instead of stating whether tPSA and percentage of fPSA (%fPSA) are in the reference interval, should give a probability of PCa based on a statistical model including age, DRE, and, as described below, a kallikrein panel [13•,14•,15].

Other kallikrein markers

%fPSA and hK2 are promising for detection, staging, prognosis, and monitoring of PCa [14•,16,17,18•]. Both markers are associated more specifically with malignancy than is tPSA [16]. Among men with tPSA of 4–10 ng/ml, evidence has been reported that hK2 and pPSA (various truncated isoforms of proPSA) improve PCa diagnosis compared with tPSA and fPSA [19]. It has been suggested that hK2 adds statistically and clinically important information for PCa detection and especially prognostics [20,21]. This information is particularly important for the many men with PCa at tPSA levels less than 10 ng/ml, the range in which tPSA does not stratify risk well. However, we await evidence from large prospective trials to assess the role of other kallikreins in PCa diagnosis and prognosis [3••].

The value of a panel of four kallikrein markers (tPSA, fPSA, intact PSA, and hK2) was investigated in the Göteborg arm of the European Randomized Study of Screening for Prostate Cancer (ERSPC). For predicting the outcomes of prostate biopsy in previously unscreened men with elevated tPSA, the accuracy of a base model including age and PSA significantly increased after incorporating the other three kallikreins into the model [14•]. A similar increment in predictive accuracy was seen if DRE result was added to the base model. With

the threshold for biopsy set at a 20% risk of cancer, the four-kallikrein panel compared to tPSA alone would have permitted the number of biopsies to be reduced by 573 per 1000 men with elevated PSA, whereas only 42 men with PCa would have been advised against immediate biopsy [14•]. Results of the Göteborg study are currently being independently validated using the ERSPC-study cohort from Rotterdam [A. Vickers *et al.*, in preparation].

The more elaborate detection and screening strategies can be cost-effective compared with, for example, the costs of unnecessary biopsies [2•,3•,14•,15,22,23•,24,25], (A. Vickers *et al.*, personal communication).

Challenges of prostate-specific antigen detection

PSA levels vary with age, race, and weight [3•,22,26]. Additional biases can be caused by the assays and calibrators used, lack of specificity of assay antibodies, sample handling, freezing and thawing of the sample, or excess fat, debris, or fibrin-threads in the sample [3•,27].

The currently used PSA assays are not 100% interchangeable. Moreover, comparability of the values depends strongly on whether the assay was standardized to the WHO calibrator or to the older Hybritech calibrator, which yield values differing by about 20% [3•,28•,29,30]. For these reasons, caution is required when comparing results from different commercial tPSA assays and from the same commercial assay standardized to different calibrators [2•,28•,29,30]. Different assays and different calibrators may explain some differences in reported PCa detection rates and clinical outcomes [28•,29–32].

The different forms of PSA have different stability properties *in vitro*, which complicates data interpretation in studies using archival samples [14•,24,33]. Concentrations of tPSA and complexed PSA are highly stable in plasma or serum stored at –20°C for many years; fPSA appears stable in plasma but unstable in serum at –20°C and is degraded in repeated freeze thaw cycles [24,33,34]. Proper handling of blood with rapid separation of serum from blood cells, direct freezing at –80°C, and analysis of samples immediately after thawing are essential to minimize degradation [24,34].

Even with valid measurement methods, the interpretation of PSA values is still challenging. Eastham *et al.* [35] demonstrated that more than 40% of men with an abnormal PSA finding had one or more normal PSA findings during 4-year follow-up, and they suggested that isolated elevation of PSA should be confirmed before prostate biopsy.

Prostate-specific antigen kinetics

Posttreatment PSA dynamics (PSA velocity at the time of recurrence and PSA doubling time) has been shown to have predictive value [36–38]. In addition, pretreatment PSA dynamics has been suggested as prognostic tools in PCa diagnostics and follow-up [39–43]. However, pretreatment and posttreatment PSA dynamics differs in one important respect. Pretreatment PSA levels depend on both malignant and nonmalignant processes in the untreated prostate [44]. PSA dynamics is therefore only partly determined by cancer growth. In posttreatment patients, PSA levels derive mainly (and after radical prostatectomy completely) from cancer, and therefore PSA dynamics would be expected to match cancer growth more closely [45–47]. Two recent studies of PSA dynamics before treatment [25,48] yielded no evidence that the rate of change of PSA was of value. In addition, a recent systematic review analyzed 87 studies investigating pretreatment PSA velocity or doubling time in early-stage PCa [49•]. Only two of the studies compared the accuracy of a statistical model incorporating both PSA and the PSA dynamic with the accuracy of PSA alone. Only one of the studies showed improved accuracy, and the improvements were minor and the study was subject to verification biases. Furthermore, studies comparing accuracy of PSA with PSA dynamics failed to show clear

evidence in favor of PSA dynamics. The use of pretreatment PSA dynamics in clinical practice therefore appears not to be supported by any clear or strong clinical evidence.

Long-term prediction of prostate cancer risk

PCa can be predicted many years before its manifestation. The data from early studies of the long-term predictive value of PSA suggested that an elevated PSA may be found 5–13 years before diagnosis [33,50,51]. Later, baseline tPSA of 0.7–2.5 ng/ml at age 40–50 years compared with a level below the median (<0.7 ng/ml) was associated with 14.6-fold higher risk of subsequent PCa diagnosis [52]. So far, the largest cohort ($n = 21\,277$) used to investigate long-term prediction is the Malmö Preventive Project (MPP) [3•,15,22,23•,24,25]. PSA levels in archived plasma taken from men aged 40–50 years were analyzed retrospectively. Men who were later diagnosed with PCa had higher PSA and hK2, and lower %fPSA, than did controls [23•]. However, combining %fPSA or hK2 with tPSA did not importantly aid the accuracy of long-term prediction. A single PSA test at age 44–50 year was found to be a significant predictor of PCa diagnosed 25 or more years later. In a follow-up, the authors further showed that tPSA at age 44–50 years predicted the likelihood of developing PCa that was locally advanced or metastatic at the time of diagnosis [15]. In another MPP-based analysis, the prognostic accuracy of tPSA decreased with age, presumably resulting from the greater prevalence of BPH among older men, whereas the predictive accuracy was significantly enhanced when tPSA was combined with both %fPSA and hK2 in the older, albeit not the younger men [22].

The MPP-based analyses have several strengths because of high accuracy of case ascertainment through the excellent coverage of the Swedish National Cancer Registry [53]. In addition, the participation rate was high (74%), and verification bias was minimal as participants were enrolled before PSA assays became available, and the frequency of PSA testing has remained low in this region [15].

The above studies clearly indicate that men who will eventually develop PCa have increased tPSA levels years or decades before the cancer is diagnosed. It is currently unclear whether the early PSA elevations reflect a premalignant state or presence of malignant cells in the prostate [15,22]. In addition, the early elevations presumably reflect, at least in part, the long duration of prostate carcinogenesis, but an intriguing possibility is that they could reflect a causal role of PSA in the development or progression of PCa or both [2•].

The time between PSA reaching 3.0 ng/ml and cancer diagnosis was estimated as 4.5 years among men in the Swedish randomized study who participated in an early detection program for PCa, compared with 10.7 years among men who did not participate in the early detection program [54]. These long intervals have implications for PSA-based screening. A randomized study of the ERSPC demonstrated that the many men with PSA levels of less than 1 ng/ml could safely be tested at 3-year intervals [55]. Furthermore, only 3–5% of Western men with PCa have lethal disease. Consequently, diagnosis should possibly be made not as early as possible, but instead as late as possible while the cancer is still curable.

Prostate-specific antigen in prostate cancer screening

Both the American Urological Association and American Cancer Society advise men to obtain annual DRE and serum PSA tests beginning at age 50 years. In contrast, the US Preventive Services Task Force and American College of Physicians do not support routine PSA testing [3••]. In many European countries, screening is still not recommended [56].

Advocates of PSA screening have pointed to a decline in the incidence of metastatic disease, reduction in cancer-related mortality, and increasing number of patients with cancer of low volume, grade, and stage [57–60]. For example, data from the Tyrol study have found evidence

of increased cancer detection rate and simultaneously decreased cancer-specific mortality rate after initiation of PSA screening [61]. Similar outcomes have been reported from Asia [62, 63]. However, these observational studies are subject to lead-time bias, and therefore whether screening decreases mortality is still controversial [64–69]. The gold standard is randomized trials of PSA screening such as the upcoming North American and European randomized screening trials [59,70], results of which are expected to be reported in 2010.

Screening focused on those at highest risk of PCa morbidity or mortality might have a superior benefit-to-harm ratio compared with the current approach of screening all men. Screening may be inappropriate for most men of 75 years or older [71].

The characteristics of cancers at diagnosis change with repeated screening. A recent prospective study [69] demonstrated that cancer diagnosed at an initial screening (prevalent cancer) versus cancer diagnosed at later screenings (incident cancer) was associated with shorter time to PSA failure after radical prostatectomy. Similarly, prevalent compared with incident cancers have been associated with higher PSA, larger tumor volume, more advanced clinical stage, and higher Gleason scores [58,67,72].

Risk stratification

A primary goal for PSA testing is risk stratification for subsequent intervention. One recommendation based on the long-term predictive value of PSA could be that all men should obtain a PSA test in their mid-40s to late 40s. The few men (~1–2%) with PSA above the threshold for biopsy (e.g. 3 ng/ml) could be referred for immediate biopsy. The primary purpose, however, would be to determine which men should be invited back for regular screening at age 50 years and which men advised that PSA screening is unlikely to benefit them [15].

For men with a diagnosis of PCa, PSA results can be especially important for decisions on active surveillance [73,74]. Nevertheless, baseline PSA and the rate of PSA changes are poor predictors of lethal PCa among patients managed by watchful waiting [75].

Prostate-specific antigen to predict disease characteristics and treatment outcome

PSA before treatment predicts both tumor characteristics and risk of recurrence after treatment [3•,15,21,23•,41,49•]. A model including tPSA, fPSA, and hK2 has been shown to be superior to tPSA in older, but not in younger, men. tPSA levels of 1.01–2 ng/ml and 2.01–3 ng/ml are associated with odds of advanced PSA elevated by seven- fold and 22-fold, respectively. The majority (66%) of advanced cancers occur in the 20% of the population with the highest PSA levels [15].

Future studies

Numerous potential markers of PCa are under investigation. These include ‘benign’ PSA (BPSA), proPSA, nicked PSA, other subfractions of fPSA, and several non-PSA markers [2•,3•,76]. New markers must be evaluated by adding them to established prediction models and assessing whether accuracy is improved [77]. In addition, new markers should undergo independent replication in a large, population-based cohort of men who have elevated PSA and are considering biopsy [78•] (A. Vickers *et al.*, unpublished data). Several markers, such as MRP-14, have already revealed low specificity compared with tPSA [79]. Other markers are in an early stage of evaluation [80–90]. Evidence has been reported from prospective studies suggesting that PCA3 may contribute predictive value [80,83,87,90,91]. Two markers, plasma

transforming growth factor (TGF- β 1), and interleukin-6 soluble receptor, have undergone some replication but still require further validation. In addition, combined analysis of serum and genetic markers may offer a way to enhance and individualize PCa diagnostics.

Conclusion

PSA is still one of the few markers used for detection, risk stratification, and monitoring for PCa and its recurrence after treatment. Before age of 50 years, it is a strong indicator of cancer appearing in subsequent decades. A PSA value is not, however, a simple statement of biological status but is affected by many technical and biological factors. The optimal use of PSA in diagnostics will require that a binary PSA cut-point be replaced by a statistical prediction model, ideally with integration of additional markers.

Acknowledgments

The work was sponsored by Fulbright Grant 68431998, 1R21CA127768-01A1 phased innovation research in cancer prognosis and prediction grant from the National Cancer Institute, The Sidney Kimmel Center for Prostate and Urologic Cancers, Finnish Medical Foundation, and Sigrid Juselius Foundation.

H.L. holds patents for free PSA and hK2 assays.

We thank Janet Novak of Helix Editing for the substantial contribution in editing this manuscript. Dr Novak was paid for her work by MSKCC.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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