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Serum markers in prostate cancer detection

Ola Bratt^{1,2} and Hans Lilja^{1,3,4}

¹Nuffield Department of Surgical Sciences, University of Oxford, United Kingdom

²Department of Clinical Sciences, Lund University, Sweden

³Department of Laboratory Medicine in Malmö, Lund University, Sweden

⁴Departments of Laboratory Medicine, Surgery (Urology), and Medicine (GU-Oncology), Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Abstract

Purpose of review—Prostate-specific antigen (PSA) testing provides significant benefits by reducing prostate cancer mortality, but also leads to important harms by detecting clinically insignificant cancers. Hence, there are urgent needs for complementary tools for middle-age men with modest PSA elevations in blood. This review includes research on prostate cancer biomarkers in blood published from March 2013 through August 2014.

Recent findings—Research progress has been made mainly on PSA as a predictive marker and in the field of kallikrein-based tests: [–2] proPSA, the Prostate Health index, and a panel of four kallikrein markers. As men with PSA levels below age-median are at very low 20-year risk of metastatic prostate cancer, individualized screening intervals, based on PSA levels, may help reducing screening costs, prostate biopsies and detection of insignificant cancer. Statistical models based on kallikrein-markers in blood improve the specificity at modestly elevated PSA (2–10 ng/mL), eliminate unnecessary biopsies, and help selecting men at risk of significant prostate cancer for biopsy or imaging.

Summary—Individualized, risk adapted PSA testing intervals and reflex-testing of kallikrein-markers for men with modestly increased PSA values may decrease the harms of screening. However, the clinical value of the proposed testing algorithms and additional tests await definitive confirmation in prospective trials.

Keywords

Prostatic neoplasms; diagnosis; biomarkers; kallikreins; prostate-specific antigen

Correspondence to: Professor Hans Lilja, M.D., Ph.D., Nuffield Department of Surgical Sciences, University of Oxford, John Radcliffe Hospital, Headley Way, Headington, Oxford, United Kingdom, OX3 9DU., Tel +44-1865617123; Mob +44-7771531732; Fax +44-1865617125, hans.lilja@nds.ox.ac.uk.

Conflict of interest

Hans Lilja holds patents for free PSA, kallikrein related peptidase 2, and intact PSA assays, and along with AV, is named as co-inventor on a patent application for intact/nicked PSA assays and for a statistical method for predicting the result of a prostate biopsy. Ola Bratt has no conflicts of interest.

Introduction

No biomarker has affected the clinical management of cancer more than prostate-specific antigen (PSA). Since its introduction in clinical practice in the late 1980s and early 1990s, PSA testing has led to a doubling of the incidence of prostate cancer and a marked migration to earlier stages at diagnosis in most Western countries (1, 2). In addition to changing the epidemiology of prostate cancer, PSA testing of men without clinical signs of prostate cancer has created a new “disease entity”: men with increased PSA but no prostate cancer diagnosis. Managing these men occupies large healthcare resources. The increased use of PSA has been followed by decreasing prostate cancer mortality (1–3). However, PSA testing has also led to over-diagnosis of many indolent cancers that would not have caused clinical disease (4). Autopsy studies have consistently shown that the prevalence of clinically undetected prostate cancer increases with age from at least 20% among men aged 50–70 years to 70% among men in their nineties (5). Since moderately increased PSA values are more often caused by benign prostatic hyperplasia than by cancer, systematic prostate biopsies in men with clinically benign prostates will inevitably sometimes detect clinically insignificant cancer. The Prostate Cancer Prevention Trial, in which all men underwent prostate biopsy regardless of the PSA value, may be used to illustrate the detection of clinically insignificant prostate approximately (6). After 7 years 24% of the men in the placebo arm were diagnosed with prostate cancer, which is almost ten times the percentage of deaths in US men that were contributed to prostate cancer at that time (7). Also the European Randomised study of Screening for Prostate Cancer (ERSPC) has reported considerable over-diagnosis of prostate cancer resulting from systematic PSA testing (8, 9). The harms caused by over-diagnosis and overtreatment were the main reason for the United States Preventive Services Task Force’s decision in 2012 to recommend against PSA testing in the absence of clinical signs or symptoms suggestive of prostate cancer (10). However, this recommendation has been criticized (11). The ERSPC showed a 27% decrease in prostate cancer mortality among screened men after 13 years follow-up (9). That no benefit of screening was reported from the American screening study (12) is most likely explained by wide-spread PSA testing before inclusion in the control arm and by low biopsy-compliance among screen-positive men (11). Although the utility of PSA as a diagnostic biomarker has been questioned (13), it is clear that it is an extremely powerful clinical tool in the low and high ranges. Low PSA levels (< 0.5 – 1 ng/mL) almost entirely exclude clinically significant prostate cancer and predict a very low risk of advanced prostate cancer up to 25 years ahead (14–20). Almost all men with PSA values > 50 ng/mL have advanced prostate cancer, unless they have an acute urinary infection (21). The challenge is how to manage men with intermediate PSA values, where the specificity of PSA is poor. There are urgent needs for complementary tools for these men. Since there is increasing evidence for that Gleason grade 3 prostate cancer rarely progresses to metastatic disease (22, 23), the review focuses on the detection of Gleason grade 4–5 cancer and the prediction of metastatic and lethal prostate cancer. It includes research published from March 2013 through August 2014.

PSA as a predictor of future advanced prostate cancer

The evidence is accumulating for the predictive value of low PSA values. In a Swiss study, only 0.2% of 5,000 men with an initial PSA value below 1 ng/mL were diagnosed with aggressive prostate cancer within 8 years (24). Similar results were reported in a smaller, American study (25). In a study based on frozen blood plasma only 0.1% of 10,000 Swedish 45–49 years old men with PSA values below the median (0.7 ng/mL) developed metastatic prostate cancer within 15 years (26). A Danish case-control study reported a more than doubled risk of aggressive prostate cancer within 14 years for men aged 50–64 years with an initial PSA of 0.8–1.5 ng/mL and a six-fold increased risk for men with an initial PSA of 1.5–2.7 ng/mL, compared with the men whose initial PSA value was below 0.8 ng/mL (27). A population-based Swedish study, based on frozen blood samples from 17,837 men, showed an only 0.4% risk of metastatic prostate cancer within 20 years for the two thirds of men aged 50 years who had a PSA < 1 ng/mL (28). The corresponding risk for men aged 60 years was 0.7%. The prospective Olmsted County study has reported a similarly high negative predictive value of a PSA < 1 ng/mL for men in their forties (25). Using the US Surveillance, Epidemiology and End Results (SEER) database, Vickers and co-workers demonstrated that most of the over-diagnosis of clinically insignificant prostate cancer is caused by systematic prostate biopsies in men older than 60 years with PSA values above 1 ng/mL (29).

These findings is used to create screening algorithms that test almost half of the male population only 3 times, *e.g.* at age 50, 55 and 60 years (30). Although such individualized, risk-based screening would decrease screening costs, the low specificity of any reasonable PSA cut-off remains a cause of over-diagnosis of clinically insignificant cancer.

PSA velocity

In a study based on more than 200,000 Californian men aged more than 45 years with at least three PSA values during 10 years of follow-up, the median annual PSA increase was 8–11% in the men who were diagnosed with prostate cancer and only 2.5% in those who were not (31). A Danish study including 121 prostate cancer cases and 382 control subjects showed highly significant differences in PSA velocity between cases and controls during the 20 years that preceded the cases' diagnosis (19). The age-adjusted prostate cancer mortality was 3.4 times higher for men with a PSA velocity > 0.35 ng/mL/year than for those with lower PSA velocity. However, despite these positive results, a recent review concluded that PSA velocity adds little or no clinically useful information compared to the absolute PSA value alone (32) and that the negative conclusion in an earlier systematic review of PSA velocity is still valid (33).

Additional kallikrein-based tests for screening

Much of the over-diagnosis of indolent cancers is caused by the current practice of performing systematic prostate biopsies in men with PSA values of 2–10 ng/mL and no suspicion of cancer on digital rectal examination (29). The purpose of introducing new serum markers for prostate cancer screening would mainly be to complement PSA as a

primary screening test, using the additional test(s) to identify which men with PSA 2–10 ng/mL that need further investigations.

Recent research has focused on the development, analytical, and clinical validation of different kallikrein-marker assays, such as distinct variants of the heterogeneous free, unbound PSA forms in blood: proPSA and intact PSA. ProPSA is an inactive precursor of PSA, which can be cleaved *in vitro* by the kallikrein-related peptidase 2 (hK2) and other kallikreins proteases, resulting in the “mature” form of PSA. Several truncated forms of proPSA (*e.g.* [–2] proPSA) may be detected at higher levels in the circulation in men with prostate cancer than in men with benign prostates. Intact PSA is the non-catalytic single-chain form of free PSA as opposed to the nicked, internally cleaved forms of free PSA.

A panel of four kallikrein markers in blood

The panel of four kallikrein markers in blood (4KRK) comprises of free PSA (fPSA), single-chain intact PSA (iPSA), total PSA (tPSA), and hK2 (34). The previously mentioned study by Stattin and co-workers showed that the 4KRK panel could identify a large group (59%) of 1,692 men aged 50 years with a PSA value of > 2 ng/mL who had only a 1% risk of metastatic prostate cancer within 20 years (28). It seems reasonable not to immediately apply further investigations to men with such a low risk, but to instead continue screening and act only on increasing PSA values or 4KRK risk category. The risk of metastases for the remaining 41% of the men was 7.6%. The corresponding figures for men aged 60 years with a PSA value > 2 ng/mL were 1.4% risk of metastatic disease for 28% of the men and 15% risk for the remaining 72%. In 202 men with PSA > 3 ng/mL on repeat screening in the Rotterdam section of the ERSPC, the 4KRK panel performed equivalently to PCA3 in a multivariable model (35).

Also %fPSA alone has been shown to predict aggressive prostate cancer. Men aged 50 to 58 years with %fPSA below the median value 20% had a 2.4-fold increased risk of aggressive prostate cancer within 14 years, compared with men with > 20 %fPSA (27). One third of the men younger than 58 years had < 15 %fPSA; their risk was increased 11-fold (27).

The interaction between PSA and genetic markers

More than 70 single nucleotide polymorphisms (SNPs) that may be used to complement PSA as a screening test have been identified (36). Some of these polymorphisms affect the expression of the PSA gene, causing an inter-individual variation in the effects of benign hyperplasia and cancer on serum PSA. In a report from the ProtecT study 7 SNPs were associated with prostate cancer among men with low but not among men with high PSA values, suggesting that these SNPs affect PSA expression (37). Correction for the effects of 4 SNPs resulted in a 18% to 22% reduction of men meeting biopsy thresholds in a population of men of Caucasian ethnicity (38). A later study showed similar results in African-American men (39).

Kallikrein based tests in clinical practice

Evaluating men with increased PSA levels in clinical practice is different to the population-based screening setting since additional information can be obtained by digital rectal examination, transrectal ultrasound, magnetic resonance imaging and the family history (40). Men with increased PSA levels that have a prostatic nodule or a high PSA density are usually recommended prostate biopsies. The potential value of additional serum markers in the clinical setting would thus be greatest for men with a total PSA of 2–10 ng/mL and a benign prostatic enlargement on digital rectal examination (*i.e.* a low PSA density).

The Prostate Health Index (PHI) and proPSA

The Prostate Health Index (PHI) combines total PSA, %fPSA and [–2] proPSA (41). According to a meta-analysis of 8 studies, comprising 2,969 men, PHI is superior to %fPSA alone for prostate cancer detection at first biopsy in men with total PSA values of 2–10 ng/mL (42). The AUC was 0.74 for PHI and 0.63 for %fPSA. It is, however, unclear whether PHI is superior to [–2] proPSA alone in men with PSA in this “gray zone” (43–45). The value of PHI has been confirmed in an Asian population (46). PHI and [–2] proPSA alone both discriminate between high and low grade cancer (47–51) and between organ confined and extraprostatic prostate cancer (51).

By applying the PHI test to 646 men with PSA values between 2 and 10 ng/mL who had no previous prostate biopsies, 16% of the biopsies could have been avoided at the cost of missing 3 of 139 cancers with Gleason score 7 and no Gleason score 8–10 cancer (43). The performance of the PHI test among the men with clinically benign prostate was not reported. The same group of researchers used data from 5 European tertiary care centers to validate a nomogram, based on age, previous prostate biopsy, findings on digital rectal examination, prostate volume and PHI, in patients scheduled for a prostate biopsy (52). With a cut-off set so that 20% of the men would have avoided a 12 core biopsy, only 2 of 204 Gleason score 7–10 cancers would have been missed among 883 men.

Inflammation decreases the %fPSA, making the discrimination between prostate cancer and prostate inflammation difficult. However, [–2] proPSA and PHI may discriminate chronic histologic prostatic inflammation from cancer in men with total PSA values of 4–10 ng/mL and a normal digital rectal examination (53).

PHI performed similarly to the urinary prostate cancer markers PCA3 and TMPRSS2:ERG (47, 54, 55). The combination of PHI with any of these urinary markers was not better than using PHI alone (47, 54, 55).

The 4 kallikrein panel

In a recent study of 531 men with PSA 3–15 ng/ml undergoing first-time prostate biopsy, the 4KRK panel performed similar to PHI (56). A cut-off for biopsy at 10% predicted risk of high-grade cancer by the 4KRK panel or at PHI 39 would reduce the number of men undergoing biopsy with 29% at the cost of delaying diagnosis for 10% of the men with high-grade cancers. A report from the ProtecT study showed that the 4KRK panel significantly increased the area under the receiver operating curve for detection of high risk prostate

cancer in 6,606 men who underwent 10 core prostate biopsies because of PSA ≥ 3 ng/mL (57). Almost half (43%) of the biopsies could have been avoided if the 4 KRK panel had been used, at the cost of reducing the detection rate of high risk cancer from 13% to 12%. Since the 4KRK panel discriminates between low and high risk prostate cancer it may be useful also for selecting prostate cancer patients for active surveillance (58).

Serum kallikreins in hypogonadal men

The expression of the prostate-specific kallikreins genes is androgen dependent. Prostate cancer may therefore not increase PSA values in hypogonadal men as much as in men with normal plasma testosterone values (59). Correcting total PSA values and PHI for bioavailable testosterone enhances the detection of prostate cancer (59, 60).

Conclusion

The recent advances in clinical research on serum biomarkers for prostate cancer detection have been in the kallikrein field. Low PSA levels have proved to be a powerful predictor of future risk of advanced prostate cancer. Individualized, risk differentiated screening algorithms based on PSA values may decrease the costs of PSA based screening. A trial testing this concept was started recently. The PHI, proPSA and the 4KRK panel may identify which men with PSA values of 2–10 ng/mL that should be recommended imaging or prostate biopsies. However, prospective studies are needed to establish their role in prostate cancer screening. Important areas of uncertainty include the performance of the different kallikrein tests in men treated with 5-alpha-reductase inhibitors and in men at a genetically defined increased risk of prostate cancer.

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Key points

Recent advances in the research on serum biomarkers for prostate cancer have been made in the field of kallikrein-based tests.

Men with a very low PSA value are at an extremely low risk for metastatic prostate cancer within 20 years' time. These men require repeat screening only after several years, if at all.

A screening algorithm with individualized test intervals, based on the PSA values would reduce the screening costs.

A more selective approach to prostate biopsy would decrease over-diagnosis of indolent, clinically insignificant prostate cancer in men with moderately increased PSA values.

Kallikrein-based tests (the Prostate Health index (PHI), the 4 kallikrein panel and [-2] proPSA) may select men with PSA values of 2–10 ng/mL for further investigations.