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PSA in prostate cancer screening

WHILE THE MEASUREMENT OF TOTAL PSA IS DECISIVE, ASSESSMENT OF THE FREE PSA/TOTAL PSA RATIO PROVIDES BETTER DIAGNOSTIC GUIDANCE FOR PROSTATE CANCER SCREENING

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Abstract

Prostate cancer detection is mainly based on serum PSA levels and digital rectal examination. The widespread use of PSA over time has led to an increase in the incidence of prostate cancer in the higher-resource countries, with a lower mortality rate compared with the less developed regions of the world. Prostate cancer screening is one of the most controversial subjects in the field of urology. The scientific societies have drawn up their recommendations in favour of shared decision-making after informing patients who have a life expectancy of at least 10 to 15 years. Given the imprecision of the two diagnostic examinations, strategies to reduce overdiagnosis and overtreatment are necessary. Research is focusing on biomarkers able to improve the detection of prostate cancer, such as the prostate health index (phi) and the PCA3 score. In patients with a total PSA of 2–10 ng/ml, measurement of the fPSA/tPSA ratio appears to be the best indicator of prostate cancer.

Ultimately, in the setting of early individual diagnosis, measurement of the free PSA level appears to offer a certain benefit by increasing the positive predictive value of the tPSA assay while reducing the indications for prostate biopsy.

A little pathophysiology

PSA (Prostatic Specific Antigen) is a glycoprotein belonging to the kallikrein group (human kallikrein 3: hK3), a family of 14 proteins identified to date. It is secreted almost exclusively by the secretory epithelial cells of the prostatic acini, and in smaller amounts by the epithelial cells of the periurethral glands. PSA is specific to the secretory epithelium of the prostate and not to a disease of the prostate.

PSA is a serine protease, secreted in large quantities into the seminal fluid, and its proteolytic enzymatic activity is involved in the fluidity of the ejaculate (fragmentation of the semenogelins) and is thought to facilitate the migration of spermatozoa. PSA is normally present in the serum of men at a level of the order of one nanogram/ml. In women, it may be detected at levels below one picogram/ml.

In blood, PSA circulates either in a free form (fPSA) (10 to 40% of total PSA) or complexed to protease inhibitors, essentially to the serine protease inhibitor ACT or alpha-1 antichymotrypsin (60 to 90% of tPSA), to alpha-1 antitrypsin or API (3 to 5% of tPSA) and to alpha-2 macroglobulin (< 1% of tPSA).

Variation in the serum PSA level related to assay methods

The serum tPSA assay is performed on serum or plasma from a simple blood sample.

Immunoassay methods may differ in sensitivity as regards the measurement of total PSA (free and bound) depending on the epitopes they detect. It is very important to have successive PSA assays performed in the same laboratory, because measurement techniques may vary and give the impression of discordance between two assays. Sexual abstinence is recommended for 3 days before the assay, failing which the free PSA level may rise.

Laboratoire Sion performs total and free PSA assays by immunoenzymatic assay.

Variations in the serum PSA level related to hormonal status, drugs and prostatic manipulation

The PSA level is dependent on the androgen level. It is low in hypogonadism. Apart from the drugs used in the hormonal treatment of prostate cancer, 5-alpha reductase inhibitors (finasteride INN) indicated in the treatment of benign prostatic hypertrophy or in the chemoprevention of baldness reduce the serum PSA concentration but do not influence the free PSA level.

Digital rectal examination, prostatic massage, endorectal ultrasound or ejaculation cause non-significant variations in the tPSA level (less than 1 ng/ml). By contrast, endo-urethral manoeuvres (bladder catheterisation, cystoscopy) and, a fortiori, prostate biopsy or prostate surgery cause a significant rise in the serum tPSA concentration. Under these conditions, a minimum interval corresponding to at least 21 days must be observed before performing a serum tPSA assay.

Variations in serum PSA levels related to non-cancerous conditions

Acute prostatitis and acute urinary retention may cause a marked rise in the serum PSA level. The same applies, though sporadically, to certain acute conditions such as acute renal failure, acute hepatitis or myocardial infarction. Prostatic hypertrophy and prostatic inflammation (chronic prostatitis), for their part, increase tPSA levels to a variable degree and may be the source of false positives in the early diagnosis of prostate cancer (PSA levels between 4 and 10 ng/ml).

Elevated serum tPSA level and symptoms suggestive of prostate cancer

A rise in the tPSA level, generally above 10 ng/ml, in a patient presenting with symptoms suggestive of prostate cancer often reflects locally advanced or metastatic disease. The presenting features may then be voiding disorders, initial haematuria or bone pain. Digital rectal examination will find a prostatic induration, and prostate biopsies will be performed to confirm the diagnosis and to give the degree of differentiation (Gleason score) of the tumour. The probability of having a cancer confined to the prostate decreases as the serum tPSA concentration rises. But the positive predictive value of tPSA is too low to predict, in a given subject, the tumour volume or to distinguish whether or not the tumour is confined. The free PSA level could statistically be associated with the pathological stage, but there is considerable overlap of values, so that, compared with total PSA, measurement of the free PSA level does not appear to provide prognostic information. Among other parameters, a tPSA threshold of 16 ng/ml would make it possible to diagnose 97.8% of patients with a cancer confined to the prostate. The probability of lymph node or bone metastases increases as the serum tPSA concentration rises.

Circumstances of prostate cancer screening

It is usually accepted that, when the early diagnosis strategy is adopted, the age range for candidates for PSA testing is 50–70 years. The upper limit depends on life expectancy. Early diagnosis is considered to apply only to subjects with a life expectancy of at least 10 years. It should be remembered that mean life expectancy varies between 12 and 9 years respectively for subjects aged 70 to 75 years. Where there is a family history of prostate cancer (an affected first-degree relative, or second-degree relative (maternal and paternal uncles, nephews)), the precautionary principle might be to offer screening from the age of 45 years or, if one refers to the approach adopted for the other cancers with a hereditary component, screening should be offered at an age 10 years below that of the relative affected earliest in the family.

Normality threshold and PSA uncertainty zone for prostate cancer screening

Usually, the threshold of 4 ng/ml is used for total PSA as the normal value. However, two recent studies, in which biopsies were performed for tPSA values between 2.5 and 4 ng/ml in patients with a normal digital rectal examination, show that between 12 and 23% of prostate cancers are found. These thresholds have led some experts to recommend lowering the PSA threshold value for performing biopsies. Conversely, the high prevalence of benign prostatic hypertrophy in the male population over 50 years of age, and the changes in PSA level associated with it, burden the tPSA assay with a low predictive value for cancer for tPSA values below 10 ng/ml. Indeed, nearly 25% of men over 50 years of age have a total PSA above 2 ng/ml. As a result, the 4–10 ng/ml range (and a fortiori 2.5–10 ng/ml) for total PSA values is considered an uncertainty zone (grey zone) for deciding whether or not to perform prostate biopsies. It is nevertheless the range of PSA values in which the greatest number of curable cancers can be diagnosed.

PSA tests that improve the performance of the total PSA assay

The insufficient performance of the serum total PSA assay in the diagnosis of prostate cancer justifies modifications in the use of the serum tPSA assay in order to reduce false negatives and improve the positive predictive value. The aim is thus to reduce the number of unnecessary (negative) prostate biopsies while avoiding missing cancers.

The usual clinical situation addressed by these optimisations of the test is that of a patient whose digital rectal examination is normal and whose serum tPSA concentration lies between 4 and 10 ng/ml (for tPSA tests whose normal value is equal to 4 ng/ml, which corresponds to the most frequent situation). Several methods of PSA optimisation have been proposed (indexation to age, PSA density, PSA kinetics, free/total PSA ratio).

Of these different methods, the free/total PSA ratio would be the method that most increases the positive predictive value of the test at constant sensitivity for tPSA values between 4 and 10 ng/ml. The free PSA level (ratio of the free PSA concentration to the total PSA concentration) is on average higher in benign prostatic hypertrophy than in prostate cancer. Assaying the free and macromolecule-complexed forms of PSA increases the specificity of the PSA assay, particularly between 4 or 2.5 and 10 ng/ml. For reasons still unknown, prostate cancer is associated with a decrease in the percentage of the free PSA to total PSA ratio, whereas this level is not modified by benign prostatic hypertrophy.

By contrast, chronic inflammation of the prostate is thought to be associated with a low free PSA level. Recently, an assay kit for PSA complexed (cPSA) to alpha-1 antitrypsin and alpha-1 antichymotrypsin has been made available, but is not yet commercially marketed. The cPSA assay is proposed to replace total PSA or the free/total PSA ratio. It appears from several studies that cPSA has the same clinical significance as the free/total PSA ratio, with, however, the advantage of bringing the cost of the assay down to one instead of two for the study of the free/total PSA ratio, and of having better stability than free PSA.

How should monitoring be carried out?

There is little information available on the optimal interval between two tPSA assays. If the first tPSA assay is normal and there is no clinical suspicion of prostate cancer, force of habit is to propose PSA testing once a year. It has however been proposed to perform the PSA assay only every two years, stopping it at 75 years of age, or from 65 years of age for men with low tPSA levels, below 0.5 or 1 ng/ml.

Age ranges ([40 – 79])	Normal PSA values
40 – 49 years	<2.5 ng/ml
50 – 59 years	<3.5 ng/ml
60 – 69 years	<4.5 ng/ml
70 – 79 years	<6.5 ng/ml

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