Original Paper

Urologia Internationalis

Urol Int 1998;60:25–27

Received: July 24, 1997
Accepted: September 11, 1997

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Diagnostic Significance of Prostate-Specific Antigen Velocity at Intermediate PSA Serum Levels in Relation to the Standard Deviation of Different Test Systems

Key Words
Prostate specific antigen
Digital rectal examination
Benign prostatic hyperplasia
Carcinoma, prostate
Prostate specific antigen, assay reliability

Abstract
Serial prostate-specific antigen (PSA) measurements (PSA velocity) as an additional instrument to detect prostatic cancer was introduced in 1992. It has previously been reported that PSA increase per year differed in the last 5 years prior to diagnosis in patients with benign prostatic hyperplasia (0.18 ng/ml/year), locally confined (0.75 ng/ml/year) and metastasized (4.4 ng/ml/year) cancer of the prostate (CaP) in contrast to healthy men (0.04 ng/ml/year). The ability of PSA velocity to detect organ-confined CaP in patients with intermediate PSA serum values depends therefore on a reliable and reproducible PSA result. The present study comprised 85 men with PSA values between 3 and 8 ng/ml (Abbott IMx). PSA measurements were repeated with Abbott IMx (n = 85 patients) and Hybritech Tandem-E (n = 59 patients) assays. The PSA serum values differed from one examination to the other from 0.02 to 2.74 ng/ml with the Abbott IMx. Standard deviation amounted to 0.35 ng/ml with the Abbott IMx PSA assay. Using the Hybritech Tandem-E assay, mean standard deviation was 1.15 ng/ml and therefore higher than with the Abbott IMx assay. The difference from one test to the other ranged from 0.05 to 4.05 ng/ml with the Hybritech Tandem-E. Using the Abbott IMx assay, 10.6% of all repeat measurements exceeded 1 ng/ml whereas in the Hybritech Tandem-E assay 62.7% of the second measurements differed >1 ng/ml from the first PSA result. An increase in PSA serum values may therefore be due to intratest variation, physiological day-to-day variation as well as prostatic disease. It is important to notice that the intra-assay variation may be greater than the PSA increase per year in a patient with CaP. Therefore, PSA velocity seems to be of limited value.

Introduction

Within the last 10 years, prostate specific antigen (PSA) has been shown to be the most important tumor marker for the diagnosis of carcinoma of the prostate (CaP). Catalona et al. [1] could show that in the recognition of CaP, PSA determination is superior to the rectal palpation of the prostatic gland. PSA screening particularly increased the discovery of more organ-confined and thus curable tumors compared to digital rectal examination (DRE). Especially in patients with an unsuspicious finding on DRE, PSA elevation alone may indicate the

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0042–1138/98/0601–0025$15.00/0

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Table 1. Intermediate PSA values and results of control measurements obtained with two different PSA test systems from the same serum sample

PSA	Abbott IMx		Hybritech Tandem-E	
	1	2	3	4
Range, ng/ml	3–8	2.86–10.49	1.46–15.69	0.71–11.2
Minimal difference, ng/ml	–	0.02	–	0.05
Maximal difference, ng/ml	–	2.74	–	4.05
Standard deviation, ng/ml		0.35		1.15

presence of a significant but – in the majority of cases – organ-confined tumor mass [2].

However, there is no cutoff level to differentiate between healthy men and patients with benign prostatic hyperplasia (BPH) or CaP. At intermediate PSA serum levels (between 4 and 10 ng/ml), the risk of having CaP is 20.2–27%, and 58.1–67% at serum PSA levels exceeding 10 ng/ml [1, 3]. With the intermediate PSA range, prediction of the presence of CaP is particularly difficult as serum PSA levels overlap in patients with BPH and CaP. Furthermore, PSA concentration was shown to be age dependent, and in 1993 Oesterling et al. [4] were able to establish age-specific PSA reference ranges for healthy men on a community-based population.

Searching for an additional instrument to distinguish between BPH and CaP, Carter et al. [5] introduced serial PSA measurements (so-called PSA velocity). They evaluated serum PSA levels of patients with histologically proven BPH or CaP over an 8- to 26-year period prior to diagnosis. As a result of their studies, they could demonstrate differences in PSA increases per year for healthy men, patients with BPH as well as local or metastasized CaP. Physiological annual PSA increase for healthy 60-year-old patients was calculated to be 0.04 ng/ml/year. In contrast to healthy men, in patients with BPH or locally confined CaP the increase in PSA can be estimated to be 0.18 and 0.75 ng/ml/year, respectively. Carter et al. [5] concluded that prostate disease is the factor most affecting serum PSA levels with age. The following study was therefore designed to test the ability of PSA velocity to diagnose CaP in patients with intermediate PSA levels (between 3 and 8 ng/ml) regarding standard deviation of different PSA assays.

Patients and Methods

85 men were included in the study. Patients' age ranged from 30 and 87 years (mean 65.9 years). There were 14 healthy men, 57 patients with histologically proven BPH and 14 patients with histologically proven CaP. In all cases, blood samples were obtained prior to DRE and any form of treatment. All patients had serum PSA levels between 3 and 8 ng/ml in the first measurement (Abbott IMx). Using the same serum sample, PSA measurements were repeated in 85 patients with the Abbott IMx and in 59 patients with the Hybritech Tandem-E assay.

Results

Serum PSA levels ranged from 3 to 8 ng/ml in the first Abbott IMx and from 2.86 to 10.49 ng/ml in the second evaluation (table 1). Processing of the same serum samples with the Hybritech Tandem-E resulted in 59 of the 85 patients in serum PSA levels of 1.46–15.69 ng/ml in the first measurement and 0.71 and 11.2 ng/ml in the second test, respectively. Standard deviation amounted to 0.35 ng/ml with the Abbott IMx PSA assay. The serum PSA value differed between both examinations by 0.02–2.74 ng/ml. In the Hybritech Tandem-E assay, mean standard deviation was 1.15 ng/ml and therefore higher than in the Abbott IMx assay. The intertest difference ranged from 0.05 to 4.05 ng/ml. 10.6% of all serum PSA repeat measurements with the Abbott IMx assay exceeded 1 ng/ml whereas in the Hybritech Tandem-E assay 62.7% of the second measurements differed >1 ng/ml compared to the first PSA result. In 83 of the 85 patients, serum PSA values were higher with the Hybritech Tandem-E than with the Abbott IMx. Hybritech Tandem-E PSA values exceeded Abbott IMx results on average by 2.08 ng/ml.

Discussion

The probability of recognizing organ-confined and thus curable CaP is highest in patients with serum PSA values <10 ng/ml. In patients with PSA results >10 ng/ml, the risk of having an advanced tumor with tumor extension beyond the prostatic capsule or positive lymph nodes increases to 34.9 and 41.3% [6]. PSA values

<10 ng/ml are therefore especially interesting for the detection of curable CaP. At unsuspicious DRE findings and a PSA value within the normal age-specific PSA range, there is no necessity to perform prostate biopsy except that an abnormal PSA increase over time is recorded. Indication for prostatic biopsy depends therefore on reliable and reproducible PSA measurements. As the aforementioned results demonstrate, a PSA difference of up to 2.74 ng/ml with the Abbott IMx PSA assay and 4.05 ng/ml with the Hybritech Tandem-E assay may be present in the same serum sample. In addition, it must be kept in mind that a physiological day-to-day variation exists for PSA. Stamey et al. [7] repeated serum PSA measurement in 91 patients within an interval of 38 days with the Hybritech Tandem-R assay. The first PSA value ranged from 4 to 10 ng/ml. They concluded that a PSA increase is not significant as it does not exceed 30% of the original value. Stamey et al. [7] judged this PSA difference as physiological PSA difference from day to day. However, they did not take into consideration the intratest variation that is even admitted by test manufacturers. For the Abbott IMx PSA assay at a given PSA concentration of 4 ng/ml, the PSA value may range from 3 to 5 ng/ml in further examinations. Thus, part of the described 'physiological' PSA range from day to day described by Stamey et al. [7] may be due to intratest variation.

Regarding the study by Carter et al. [5] who could show a PSA velocity of 0.04 ng/ml/year in healthy 60-year-old men [1], it has to be considered that a PSA elevation of 1 ng/ml/year may be due to CaP on the one hand and to the PSA intratest variation on the other hand.

Furthermore, PSA results from different test systems cannot be directly compared. Therefore, standardization of PSA assays is warranted.

Conclusions

PSA velocity depends on reproducible PSA measurements. Our results indicate the limited reproducibility in the same serum sample. Therefore, differences in PSA values may be due to test variation, physiological day-to-day variation as well as prostatic disease. In addition, the determination of PSA velocity requires more than two measurements. In case of an increased PSA value, control measurements should be performed to ascertain a real PSA increase. In the intermediate PSA range, changes in this tumor marker have to be regarded very carefully.

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