Table 1. Recent practice and the proportion of men with cancer according to PSA and DRE examination

	PSA (ng/ml)							
	0-2		2-4		4-10		>10	
DRE result	Biopsy	% of PC	Biopsy	% of PC	Biopsy	% of PC	Biopsy	% of PC
Normal	No	approx. 1	No	15	Yes	25	Yes	>50
Suspected PC	Yes	5	Yes	20	Yes	45	Yes	>75

Reproduced from Catalona (2000).

value too high, the specificity significantly increases, but at the expense of sensitivity. The threshold value has been set at the internationally accepted value of 4 ng/ml. At present, however, we know that about 20% of patients with PC has a PSA level lower than 4 ng/ml and, on the contrary, that PC is diagnosed in only 25% of patients with PSA levels in the range 4–10 ng/ml (Table 1).

The increased level of total PSA in the serum can be observed in PC, but also in other diseases, such as benign prostatic hyperplasia (BPH), prostatitis, acute urinary retention, after some urological interventions, and even after sexual intercourse. Tchetgen et al. (1996) have studied the influence of ejaculation on the PSA level and they have found that 1 h after ejaculation, the level of PSA increased by 41%. After 24 h, however, in 92% of cases the PSA level returned to the original value. At present, we do not routinely ask patients before PSA testing about their last ejaculation, but in the cases of unexpectedly increased PSA levels this question should be asked.

Semjonow et al. (1996), while evaluating the increased PSA levels in acute urinary retention, have shown that during 24–48 h after detection and treatment of the retention, the PSA levels decreased by 50%. The increased PSA levels in acute prostatitis return, after adequate therapy, to the normal value within 6–8 weeks. After prostate biopsy, it is necessary to wait for an objective result approximately 6 weeks. The higher occurrence of PSA is probably connected with impairment of the basal membrane of epithelial prostatic cells and with the contact of the content of prostatic tubules with blood. Despite that the half-life of PSA in the serum is 1.9–3.2 days, the inflammatory reaction accompanying biopsy maintains the PSA value at a higher level for several following weeks. After transurethral prostate resection, the concentration of serum PSA increases and returns to the basal level approximately 20 days later (Oesterling et al., 1993a).

At present, the rectal examination is no more considered to be a source of elevated PSA (Wojno et al., 1996). The majority of authors also believe that current catheterization, cystoscopy, or transrectal sonography do not significantly increase the PSA values (Oesterling et al., 1993a; Deliveliotis et al., 1994).

With growing use of medicaments, the therapeutic approaches to BPH have been focused on the possibility to influence the PSA values by medicaments. After 6-month therapy with Finasteride (in men without PC), the serum concentration of PSA decreased by an average of 50%. On the other hand, alpha-blocking medicaments did not significantly influence the PSA values (Polascik et al., 1999).

Finally, it is necessary to point out that PSA values may vary depending on utilization of different methods of examination and diagnostic kits provided by different producers.

PSA and screening

PC diagnosed clinically, based on the symptoms, usually exceeds the boundaries of the prostatic capsule and invades distant organs, most often lymph nodes and bones. Treatment of patients with progressive PC is thus only palliative and their prognosis is bad.

There are four approaches to decreasing the mortality of PC: 1. prevention, 2. improvement of early diagnostics, 3. improvement of effective treatment of localized disease, 4. discovery of new therapeutic approaches in advanced disease. The prevention is not easy, since the etiology of PC is not yet totally clear. Recently, chemoprevention with selen, vitamins A, E, D, retinoids, etc., is more and more frequently mentioned. The most promising way seems to be as early as possible diagnosis, which can be achieved by screening of men after a certain age limit.

According to the World Health Organization, the screening is defined in the following way: case-finding examination, selective test to find diseased persons and differentiate them from healthy persons. The persons who probably have disease are further examined to determine their final diagnosis and start adequate therapy. The aim of screening is to decrease the mortality of the disease. From screening of asymptomatic population, it is indispensable to clearly differentiate the so-called case-finding (e.g. of PC) in men who have visited a general practicioner or a urologist, or who have been hospitalized with symptoms not connected with the investigated disease.

Among others, the problem remains in PC screening of standardization of the PSA threshold, because in about 20% of PC patients the level of PSA is lower than 4 ng/ml. If the detection of PC is based only on longitudinal, sensitive case-finding tests such as determination of PSA, the level of detection, based on the initial examination, is relatively high, but it decreases after repeated examination as a consequence of elimination

of histologically verified carcinomas in defined groups of men. Longitudinal follow-up lasting several years has shown that, after an initial increase in new cases of PC by 10–20% in a selected population, in the following years the annual increase of newly diagnosed cases has stabilized at 2–4% (Catalona et al., 1991; Labrie et al., 1992).

The proportion of men with clinically developed PC detected by repeated screening was significantly lower. The repeated screening detected a higher proportion of clinically low stage, well differentiated PC (Smith et al., 1996a). Recent preliminary results of a randomized study of prostate screening (ERSPC) have also shown a significant decrease of PC stage and grade in the screened group compared to the control group (Schröder et al., 1999).

It is obvious that screening helps to diagnose higher numbers of PC and higher numbers of localized disease but its contribution to decreasing PC mortality has not yet been proved. The possibility to diagnose localized PC (and at the same time higher incidence of latent PC) raises fears of how many clinically non-significant PC can be diagnosed by a screening program. Clinically non-significant PC is defined as a carcinoma that does not threaten the patient's health for the rest of his life. In some patients we thus diagnose clinically non-significant carcinoma, which does not need to be treated. Another possible goal of the screening program is therefore to differentiate clinically significant PC from non-significant cases.

It thus seems that Chodak's evaluation of today's view on PC screening is still valid, stating that the resulting effect of general PC screening is dependent on so many subjective and objective aspects that the detection of the disease by itself does not enable us to select the optimal therapy, if any.

PSA and detection of PC

The success of oncological therapy almost always depends on early detection of the malignant tumor and on precise diagnosis. Examination of the serum PSA concentration is currently the method of choice in PC diagnostics. PSA determination combined with rectal examination has improved PC detection and enabled earlier diagnosis; however, more than 40% of newly diagnosed tumors are already locally advanced or metastasizing (Pound et al., 1997).

The sensitivity of PSA is, in relation to PC detection, stated to be between 68–80%, and the specificity between 49–90%. The problem still remains of low specificity of PSA at the values 4–10 ng/ml, the so-called gray zone, where only 25% of patients are affected by PC.

PSA density (PSAD)

In 1990, Babaian pointed out the importance of the serum PSA level in relation to the prostate volume for the first time and introduced the term PSA density (Babaian et al., 1990). PSAD is a relative number calculated by dividing the serum value of total PSA (ng/ml) by the prostate volume (cm^3) measured by ultrasound. Sensitivity of this calculation is not very high with regard to a high variability of results obtained by ultrasound measurement of prostate volume, which can differ as much as by 30% (Bates et al., 1996).

Seaman et al. (1993) have observed that PSAD was significantly elevated in patients with PC (0.285) as compared to control patients without detected PC (0.181), $P < 0.05$. To differentiate between BPH and PC they have suggested the threshold of 0.15, which improves PSA sensitivity by 50% (Seaman et al., 1993). A large multicentric study has later shown, however, that such threshold would decrease the number of biopsies by more than 50%, while as much as 50% of PC would go undetected (Catalona et al., 1994). These results led some authors to move the PSAD threshold to 0.1, reducing the number of biopsies to 24–42% and the number of undetected PC to 20% (Catalona et al., 1994; Cookson et al., 1995).

In 107 men with intermediate PSA levels Brawer et al. could not demonstrate any statistical or clinical difference between those with positive and negative prostate needle biopsies using PSA density (Brawer et al., 1993).

Some authors consider PSAD relevant when the detected PSA level is higher than 10 ng/ml and peripheral prostate biopsy is negative. They state that in half of the cases the patients are affected by adenocarcinoma originating from the transition zone and the threshold PSAD value of 0.15 and higher should be considered as an alarming signal in this case (Fowler et al., 1996).

It thus seems that PSA density does not represent a suitable diagnostic test that would make PC detection more precise and would avoid unnecessary biopsy in patients with serum PSA levels in the range 4–10 ng/ml, normal digital rectal examination and without prostate cancer.

PSA density of the transition zone (PSA-TZ)

Similarly as PSAD, it is possible to also determine the parameter PSA-TZ (ratio between PSA and transition zone volume). Transition zone PSA density attempts to improve the specificity of prostate cancer detection by accounting for the proportion of PSA produced by the transition zone. This concept is based on the histological localization of hyperplasia almost exclusively to the transition zone, while rare BPH tissue within the central and peripheral zones is assumed to be a constant and less significant producer of PSA (Kalish et al., 1994).

The threshold value 0.3 has been suggested, which would avoid 51% of biopsies while only 12% of carcinomas (Maeda et al., 1997) would not be detected.