Screening for Prostatic Cancer: the Case For

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The worldwide incidence of prostatic cancer derived from data published by the Union Internationale Contre le Cancer and the International Red Cross Committee has been estimated to be 200,000 new cases each year. Cases occur predominantly in the USA (75 per 100,000) and in northern Europe (40 per 100,000), whereas the incidence is low in Asia. Comparison of clinical series and autopsies confirms the high incidence of cancer in older age groups, although not all cases are seen clinically. Mortality increases more slowly than the incidence of the disease, indicating that diagnosis and treatment are increasingly effective[1].

Considering the variable biological potential of prostatic cancer, it becomes obvious that the diagnosis of malignancy does not necessarily reflect the individual clinical significance. The frequency of prostatic cancer found incidentally at post-mortem examinations varies between 15% and 46%; the more thorough the histological examination and the older the patient the higher the frequency[2]. Furthermore, the discrepancy between the incidence and mortality of prostatic cancer illustrates the variable and unpredictable biological potential of this disease. It becomes obvious that a large number of patients suffer from latent disease and will rarely develop during their lifetime any clinical manifestation requiring therapeutic intervention. These patients might be exposed, if their tumours were detected, to the risks of unnecessary treatment.

In a population-based regionally well-defined study of 223 patients (mean age 72 years) with early-stage (T0-2, Nx, M0) initially untreated prostatic cancer, the 10-year, disease-specific survival rate was 86.8%, and this was equally high (87.9%) in a subgroup of 58 patients who met current indications for radical prostatectomy[3].

However, approximately one third to one quarter of the men in whom clinical prostatic cancer develops will die of the disease. These considerations underline the need to recognize those patients who require intervention. In carefully selected series, 40% of men who undergo radical prostatectomy have extra-prostatic disease[4]. For low-stage disease, curative treatment modalities are available; survival rates after radical prostatectomy equal those of the normal male age-matched population. Comparing the 10-year survival rates of patients with stage pT1 and pT2pN0M0 after radical prostatectomy of 95% and 70%, respectively, to the corresponding rate of 60% in cases with tumours extending through the capsule, a stage-related prognostic difference is evident[5].

McNeal has proposed that biologically aggressive behaviour in adenocarcinoma of the prostate may be a direct function of cancer volume. In a study of over 200 radical prostatectomy specimens, the morphological variables such as capsule penetration, seminal vesicle invasion and positive surgical margins strongly correlated with cancer volume. Metastatic potential was most strongly predicted by a combination of tumour volume plus the percentage of high-grade tumour (quantified by Gleason grading); cancers with more than 3.2 cm^3 of a grade 4 and/or 5 component showed a 100-fold increase in the proportion of cases with nodal spread[6]. Furthermore, carcinomas of the prostate with a volume $< 1\ cm^3$ were usually well differentiated and subsequently dedifferentiate into moderately and poorly differentiated carcinomas as they increase in size. With increasing size and dedifferentiation they were increasingly likely to mestastasize[7].

These findings might suggest that detection of prostatic cancer by screening at an early and—by definition—more treatable stage, could result in a decrease of mortality by at least preserving the option for curative therapy. However, early detection would reveal a proportion of cancers not destined to impact on prostatic cancer mortality rates. Detection of such clinically 'unimportant' cancers would lead to therapeutic overkill, and one form of bias—whereby the apparent benefit from screening was reflected in a diminished mortality rate in the screened population—would be a consequence of the diagnosis (and treatment) of clinically irrelevant cancers[8].

For screening in general reasonably high specificity of a test is required if an unmanageable number of false-positive cases is to be avoided. However, the properties of the screening test, no matter how good they are, reveal nothing about the impact that screening might have on the consequences of a cancer[9].

Another important prerequisite for a screening programme is a reliable method for assessing the progression capability (growth rate and metastatic potential) of a detected tumour. The occurrence of rapidly progressing cancers, which escape detection at the initial examination but which progress beyond potential curability in the interval between screenings, would reflect adversely on a screening programme[8].

In the presence of limited financial and medical resources a further important component of screening

evaluation is cost. Screening costs include the cost of the test, the cost of side effects of the test, and the cost of biopsy and treatment; while screening benefit can be measured in terms of lives saved, life years saved, or quality-adjusted life years[9]. In the United States a mass screening programme using transrectal ultrasound (TRUS), and the anticipated treatment of men aged 50–70 years for carcinoma of the prostate arising therefrom, would change spending allocation from 0.06% of the total US health care budget to more than 5%, and if prostate-specific antigen (PSA) determination were included even to 6%. Adoption of such a programme would obviously require significant cutbacks in other services or a significant increase in federal or private health care spending[10].

Modalities for diagnosis of prostatic cancer

Since there is no characteristic symptom that occurs at an early stage of prostatic cancer, the diagnosis is usually established incidentally by discovering a nodule on rectal examination as part of a routine physical examination, or by histology after operation for ostensibly benign disease, or at autopsy. Only a decade ago transurethral resection was still the most common way of establishing the diagnosis of prostatic cancer (56.6% in 1983), followed by digital rectal examination (DRE) (45%)[11]. In recent years transrectal ultrasound (TRUS) and the determination of serum levels of PSA have enlarged the diagnostic armamentarium; their impact for screening has been evaluated both as single measures and in combination.

Digital rectal examination (DRE)

Palpation of the prostate is hampered by its subjectivity, since 32% of carcinomas will be missed even by experienced examiners[12]. A review of the results of routine urological screening of 2005 men aged 40–70 years for adenocarcinoma of the prostate demonstrated that DRE is an insensitive screening device with poor predictive value[13].

Friedman *et al.*[14] conducted a case-control study comparing, in 139 men with metastatic carcinoma of the prostate and an equal number of matched men free of this condition, the history of rectal examinations before prostatic cancer was diagnosed. In the 10 years before initial diagnosis the average number of examinations for routine screening (2.45 v. 2.52) or to evaluate intestinal or rectal symptoms (0.44 in both) were similar in cases and controls. After adjustment for racial differences, the relative risk of metastatic prostatic cancer for men with one or more screening rectal examinations compared with men with none was 0.9, with a 95% confidence interval of 0.5–1.7. The authors concluded that screening by routine digital examination appears to have little if any effect in preventing metastatic prostatic cancer. Thus, if there is a small benefit, it will be difficult to demonstrate by a conventional epidemiological study.

Phillips & Thompson[15], reviewing 96 patients who died from prostatic cancer, found that, as a minimum, any attempt at early detection using annual DRE within this population of men could not have prevented 25% of the deaths from prostatic cancer, since these patients exhibited a palpably normal gland at the time of diagnosis. On the other hand, several studies have revealed that approximately 50% of cancers detected through DRE screening had already spread beyond the prostate[16].

However, even recognizing the limitations of this clinical test, it remains the cheapest and simplest evaluation of the prostate gland and no test has yet been proved to be better. At this time, DRE remains the principal method for early detection and staging of prostatic carcinoma[15].

The key to demonstrating an overall benefit from prostatic screening is a diminished disease-specific mortality rate. To date, this has not been shown. Lower mortality rates from prostatic cancer can be demonstrated only through a randomized study comparing screened and unscreened populations[16]. In 166 patients with a palpable abnormality within the prostate suspicious for carcinoma, the echotexture was correlated with the histopathological report[15]. In 47 cases prostatic cancer was diagnosed whereas in 119 patients a benign condition only was proved. The ultrasound finding with the highest predictive value for carcinoma was that of a hypoechoic lesion. Nevertheless, it is noteworthy that 49% of palpable prostatic cancers had TRUS findings other than those of hypoechoic lesions. Indeed, fully 43% of all tumours were isoechoic. However, 36% of the benign lesions also appeared hypoechoic and 55% isoechoic. Thus, it is unclear how TRUS will interface with DRE because of the multiple echo patterns that prostatic diseases, regardless of diagnosis, can exhibit[15].

Transrectal ultrasound (TRUS)

Advances in technology, especially the improved resolution since the introduction of high-frequency transducers, have allowed for a more precise visualization of the infrastructure of the prostate. However, the quality of the equipment employed as well as the investigator's expertise will influence the sonographic diagnosis. Lee *et al.*[17] found that the overall detection rate for prostatic cancer with TRUS was twice as high as with DRE (2.6 versus 1.3%). The sensitivity of TRUS was also twice as high as DRE, which prompted the authors to advocate broader implementation and evaluation of TRUS as a tool for early detection. In a study of 2400 randomly selected men (age 55–70 years) for early detection of prostate cancer, Norming *et al.*[18] found that TRUS added significantly to the detection rate of 3.5%. If radical

Table 1. Statistical characteristics of PSA, DRE and TRUS as single modalities in the detection of prostatic cancer

	Sensitivity (%)			Specificity (%)			PPV (%)		
PSA (ng/ml)	*>2.7*	*>4*	*>10*	*>2.7*	*>4*	*>10*	*>2.7*	*>4*	*>10*
Allhoff *et al.*[19]	90	—	70	50	—	90	70	—	90
Allhoff *et al.*[20]	93	88	64	39	50	76	45	49	59
Babaian *et al.*[21]	—	81	—	—	82	—	—	—	—
Brawer[22]	—	65	—	—	69	—	—	50	—
Catalona *et al.*[23]	—	79	—	—	59	—	—	40	—
Delaere *et al.*[24]	80	—	57	58	—	88	—	—	—
Powell *et al.*[25]	—	—	89	—	—	90	—	—	47
TRUS									
Allhoff *et al.*[20]		77			62			52	
Babaian *et al.*[21]		84			82			—	
Carter *et al.*[26]		52			68			54	
Catalona *et al.*[23]		92			27			28	
Palken *et al.*[27]		61			36			27	
DRE									
Allhoff *et al.*[20]		80			70			59	
Babaian *et al.*[21]		89			84			—	
Catalona *et al.*[23]		86			44			33	
Palken *et al.*[27]		74			53			38	
Predicted PSA (TRUS gland volume × 0.2 ng/ml/g)									
Lee *et al.*[28]					23→88			37→72	

PPV = positive predictive value; PSA = prostate-specific antigen; TRUS = transrectal ultrasound; DRE = digital rectal examination

surgery is restricted to stages T1 and T2a, the combined use of DRE and TRUS detected twice as many cases fit for this treatment as DRE alone.

On the other hand, due to its low specificity, ranging between 27% and 82%, TRUS cannot be considered a first-line screening test for prostatic cancer (Table 1). Only 60% of tumours are hypoechoic, and hyper- or isoechoic malignancies are difficult or impossible to detect, which also applies to the 25% of cancers arising in the poorly echogenic transitional zone. In addition, tumours < 0.5 mm in diameter escape the spatial resolution of TRUS[29].

A prostatic cancer screening study of 315 asymptomatic men by Palken *et al.*[30] comparing DRE and TRUS identified 23 cancers, a detection rate of 7.3%. Seventeen (5.4%) were diagnosed by DRE. Contrary to the experience of others, this was a higher rate than that achieved by TRUS (14 cases or 4.4%). DRE and TRUS identified the same number of patients with small (< 1.5 cm^3) cancers, contrary to other reports that found TRUS to be superior. The authors consider DRE an effective screening examination, equivalent to TRUS and preferable because of lower cost.

Coffield *et al.*[31] correlated the TRUS detection of prostatic adenocarcinoma with 63 histological whole-mount step-sectioned prostatic specimens harvested from 148 consecutive autopsies. No patient had known or palpably-suspected prostatic adenocarcinoma on pre-mortem DRE. Prostate specific antigen (PSA) was assayed in each case from pre-mortem serum samples. Of 19 cancers, 32% were detected by TRUS and all were hypoechoic. Of the 13 non-detected cancers, 7 were isoechoic, 3 were mixed hypoisoechoic, 2 were hypoechoic and one was mixed hyperisoechoic. PSA > 4 ng/ml would have aided in cancer detection by suggesting the need for biopsy or further biopsy in 5 cancers with significant volume which were missed by TRUS. The sensitivity (32%) and specificity (64%) of TRUS appeared to be too low for use in clinical screening for prostatic adenocarcinoma. In this series PSA and TRUS together appeared to be more effective than sonography alone in the detection of prostatic adenocarcinoma.

TRUS seems more appropriate as an adjunct to biopsy. Rifkin *et al.*[32] compared the accuracy of digitally guided biopsy versus ultrasound-guided biopsy of the prostate in 112 consecutive men with palpable prostatic lesions. In 44 patients (39.3%) with negative results on conventional biopsy, the results of ultrasound-guided biopsy revealed cancer.

Prostate-specific antigen (PSA)

The detection of prostatic cancer by DRE and TRUS is not infallible, since malignancies may be neither palpable nor visible on ultrasound. Thus, the introduction of PSA by Wang and associates in 1979 opened a new era in the diagnosis of prostatic disease, enabling intrinsic glandular alterations to be monitored[33].

PSA is a 34 kd-240-amino acid glycoprotein, synthesized exclusively by the epithelial cells of the ducts and acini of the mature prostate and secreted into the seminal fluid. Its function is assumed to be the digestion of the seminal vesical-specific antigen and liquefaction of the semen coagulum[34]. Entry into the circulation therefore demonstrates only inappropriate secretion, characterizing PSA as a 'reactive' marker, a fact which should always be considered when results are interpreted. A variety of causes is known for PSA-elevation in benign conditions (Table 2). Most

Table 2. Non-cancerous causes of PSA elevation[35-39]

Benign prostatic hyperplasia
Infarction
Prostatitis
Mechanical alteration:
Instrumentation (biopsy, TURP)
Massage
Palpation (not immediately)
Urinary retention
Interferences (drugs, metabolic disorders)
Alteration of PSA metabolism

important is its possible role as an indicator of prostatic malignancy, with a sensitivity ranging between 65% and 88% when the titres exceed the normal ranges of the employed test kits. However, in cases of moderate PSA elevation, the lack of specificity with respect to malignant disease and the poor positive predictive value of the test, as well as the fact that a PSA within the normal range does not exclude prostatic cancer, limits the use of this serum marker as single measure for early detection (Table 1). This is due to the critical overlap with non-cancerous causes as well as to multiple biological factors in cases of malignancy which might impact on the marker's level (Table 3).

In our own series[19] PSA levels were within the normal range in approximately 10% despite the presence of prostatic cancer. Looking at the various PSA levels within the intermediate range (4.0–10 ng/ml, monoclonal assay) with respect to the diagnosis of the underlying disease, a shifting of the statistical characteristics could be observed. With increasing values an increasing specificity indicating malignancy was associated with a loss in sensitivity and vice versa (Table 1). This was mainly caused by approximately 25% of patients with malignant disease exhibiting PSA titres within the intermediate range[19]. Whilst not overlooking PSA's indicative potential, serial determinations are therefore mandatory not only to confirm the previous value but also to obtain the individual's PSA kinetics longitudinally. Carter *et al.*[45] found the rate of change in PSA levels to be significantly greater in subjects with prostatic cancer compared with control subjects and subjects with benign prostatic hyperplasia (BPH). Also, the rate of change in PSA levels distinguished subjects with prostatic cancer from those with BPH and controls with a specificity of 90% and 100%, respectively[45].

To distinguish further between benign and malignant prostatic conditions in cases of moderate PSA elevations, volume-adjusted upper limits of normal PSA can be determined for the different levels of specificity desired. Kane *et al.*[46] found a direct relationship between serum PSA levels and estimated prostatic volume for both the currently available monoclonal and polyclonal PSA assays. Benson *et al.*[47] used TRUS-determined prostatic volumes in a well-defined population of 535 men to form a serum PSA/prostatic volume ratio called prostate-specific antigen density (PSAD) (monoclonal assay). Discriminant analysis according to negative or positive outcome allowed for the construction of nomograms, which resulted in a PSAD-defined cancer risk ranging from 3% to 100%, thus allowing for a more individualized interpretation of PSA. A similar approach by Lee and coworkers[28] employing a predicted PSA value (TRUS gland volume × 0.2 ng/ml/g = polyclonal PSA), resulted in an improvement of the TRUS-positive predictive value (PPV) from 52% to 86% when serum PSA exceeded the predicted value (Table 1).

A study performed by Babaian & Camps[48] confirmed the proportional relationship between PSA level and the risk for prostatic cancer, indicated in Table 1, showing the increasing specificity of the marker at an extended range. They advocated that, regardless of other findings, all patients with an initial PSA value >10 ng/ml (monoclonal assay) require biopsy because of the high likelihood of cancer (83.3%). This is supported by the results of Catalona *et al.*[23] who found a 67% rate of prostatic cancer in such patients.

Table 3. Biological factors impacting on PSA titre in malignant disease[40-44]

Intra-individual variation
Variation in the relative amount of epithelium
Unpredictable BPH component
Variable PSA synthesis due to tumour heterogeneity
Genetic instability during tumour growth

Combined approach

The limited capacity of DRE, TRUS and PSA reliably to detect prostatic cancer prompted numerous efforts to develop a multi-modality approach which might help to promote cancer control by early diagnosis.

Lee and coworkers[17], comparing the clinical usefulness of TRUS and DRE in a screening programme examining 784 men over age 60 years, achieved a positive predictive value (PPV) that was higher (50%) than for TRUS alone (31%) or DRE alone (34%), when the results from both DRE and TRUS were positive (Table 4).

Catalona *et al.*[23], presenting a study based on PSA-determination as a first-line test in 1653 healthy men aged over 50 years, found that of the two-test combinations, PSA measurement plus DRE gave the lowest error rate. In their series 22% of the men with PSA levels of 4–9.9 μg/l and 67% with PSA levels ⩾10 μg/l had prostatic cancer on biopsy. If DRE alone had been used to screen the men who had biopsies, 32% would have been missed. If TRUS had been used to screen these men, 43% would have been missed. The authors concluded that the combination of DRE and PSA, with TRUS performed in patients with

Table 4. PPVs (%) employing the various modalities as single measures or in combination

	DRE	TRUS	PSA	DRE + TRUS	DRE + PSA	DRE + PSA + TRUS
Allhoff *et al.*[20]	59	52	49	62	74	78
Babaian *et al.*[49]	6	5	—	15	27	62
Cooner *et al.*[50]	43	—	48	—	62	—
Lee *et al.*[17]	34	31	—	50	—	—
Perrin *et al.*[51]	51	6	—	58	—	—

PPV = positive predictive value; DRE = digital rectal examination; TRUS = transrectal ultrasound; PSA = prostate-specific antigen

abnormal findings, provided a better method of detecting prostatic cancer than DRE alone.

Superiority of the combination 'DRE and PSA > 4 ng/ml' was also demonstrated recently by our own group in a prospective study of 1230 patients over 40 years of age, in which DRE, TRUS and PSA were correlated in all possible combinations under various conditions (requiring at least one of the parameters or all to be positive for reliable diagnosis). As a first-line approach, DRE plus PSA > 4 ng/ml enabled the detection of prostatic cancer with a specificity of 86.5% and PPV of 74%. TRUS did not contribute significantly to the final diagnosis[20] (Table 4).

Finally, the findings of a similar project by the American Cancer Society exposed the influence of the diagnostic triad on the prostatic cancer detection rate. Amongst the men found to have cancer ($n = 88/2425$), TRUS was abnormal in 80.6% and the PSA level and DRE were abnormal in 67% and 50%, respectively. The influence of PSA levels on cancer detection increased as the serum level increased above 4 ng/ml. The PPVs of both DRE and TRUS were influenced significantly by the presence of an elevated PSA level ($P = 0.044$ and $P < 0.001$, respectively). The results of this ongoing multi-centre study support the statement that the detection rate of organ-confined disease can be improved substantially by early detection programmes[49]. Nevertheless, the optimal diagnostic algorithm still remains to be defined and its validity prospectively confirmed.

Perspectives

Despite these promising results, no study has proved that routine screening reduces mortality from prostatic cancer. Therefore the European Programme against Cancer is supporting a study of the feasibility of screening for prostatic diseases. Two slightly different studies, both randomized and prospective, were launched in Rotterdam (October 1991, Director F Schröder) and Antwerp (November 1990, Director L Denis) comparing the overall mortality in the screened populations with that in the control groups. It will take about eight years before valid data with respect to mortality are available[52]. Hopefully these studies will confirm that screening will detect greater numbers of potentially morbid or lethal cancers, so that treatment will become possible in more patients for whom it is necessary.

However, our research should focus on the development of prognostic features that accurately predict the potential of an individual tumour and thus also enable selection of those patients in whom unnecessary treatment can be avoided.

Meanwhile, in equivocal selected cases, our current knowledge of the characteristics and potential of the various diagnostic techniques may be an advantage in the differential diagnosis of prostatic cancer.

References

1 Debré B, Geraud M, Steg A. Epidemiology of prostatic cancer. *J Intern Med Res* 1990; **18** (Suppl. 1): 3-7

2 Rosai J. Male reproductive system: Prostate and seminal vesicles. In: Rosai J, ed. *Ackerman's Surgical Pathology*, Vol 1. 1981: 848-70

3 Johansson J-E, Adami H-O, Andersson S-O, Bergström R, Holmberg L, Krusemo UB. High 10-year survival rate in patients with early, untreated prostate cancer. *JAMA* 1992; **267**: 2191-6

4 Walsh PC. Why make an early diagnosis of prostate cancer. *J Urol* 1992; **147**: 853-4

5 Frohmüller H. Screening for prostate cancer. *Acta Oncol* 1991; **30**: 269-72

6 McNeal JE. Cancer volume and site of origin of adenocarcinoma in the prostate: relationship to local and distant spread. *Hum Pathol* 1992; **23**: 258-66

7 Brawn PN. The dedifferentiation of prostate carcinoma. *Cancer* 1983; **52**: 236-51

8 Whitmore WF jr. Natural history of low-stage prostatic cancer and the impact of early detection. *Urol Clin North Am* 1990; **17**: 689-97

9 Prorok PC, Connor RJ, Baker SG. Statistical consideration in cancer screening programs. *Urol Clin North Am* 1990; **17**: 699-708

10 Optenberg SA, Thompson IM. Economics of screening for carcinoma of the prostate. *Urol Clin North Am* 1990; **17(4)**: 719-37

11 Schmidt JD, Mettlin CJ, Natarajan N, Peace BB, Beart RW jr, Winchester DP, Murphy GP. Trends in patterns of care for prostatic cancer, 1974-1983: results of surveys by the American College of Surgeons. *J Urol* 1986; **136**: 416-21

12 Krauss DJ, Lilien OM. The benign killer: carcinoma of the prostate. *J Urol* 1975; **113**: 820-3

13 Thompson IM, Ernst JJ, Gangai MP, Spence CR. Adenocarcinoma of the prostate: results of routine urological screening. *J Urol* 1984; **132**: 690-2

14 Friedman GD, Hiatt RA, Quesenberry CP, Selby JV. Case-control study of screening for prostatic cancer by digital rectal examinations. *Lancet* 1991; **337**: 1526-9

15 Phillips TH, Thompson IM. Digital rectal examination and carcinoma of the prostate. *Urol Clin North Am* 1991; **18**: 459-66

16 Gerber GS, Chodak GW. Digital rectal examination in the early detection of prostate cancer. *Urol Clin North Am* 1990; **17**: 739-44

17 Lee F, Littrup PJ, Torp-Pedersen ST, Mettlin C, McHugh TA, Gray JM, Kumasaka GH *et al.* Prostate cancer: comparison of transrectal US and digital rectal examination for screening. *Radiology* 1988; **168**: 389-94

18 Norming U, Gustafsson O, Nyman CR, Almgard LE, Fredriksson A, Gustaffon G, *et al.* Digital rectal examination versus transrectal ultrasound in detection of prostate cancer. Preliminary results from a study of a randomly selected population. *Acta Oncol* 1991; **30**: 277-9

19 Allhoff EP, De Riese W, Eifinger M, Pethke J, Jonas U. Prostate-specific antigen—comparative clinical appreciation of a sero-diagnostic measure after 8 years experience. *World J Urol* 1989; **7**: 12-16

20 Allhoff EP, De Riese W, Gonnermann O, Liedke SG, Schlick R, Höfner K *et al.* Successful, costeffective algorithm in early detection of prostate cancer (pCa). *J Urol* 1992; **147**: 291A

21 Babaian RJ, Miyashita H, Evans RB, v. Eschenbach AC, Ramirez EI. Early detection program for prostate cancer: results and identification of high risk patient population. *Urology* 1991; **37**: 193-7

22 Brawer MK. Prostate specific antigen. A review. *Acta Oncol* 1991; **30**: 161-8

23 Catalona WJ, Smith DS, Ratliff TL, Dodds KM, Coplen DE, Yuan JJ *et al.* Measurement of prostate specific antigen in serum as a screening test for prostate cancer. *N Engl J Med* 1991; **324**: 1156-61

24 Delaere KP, Van Dieijen-Visser MP, Gijzen AH, Brombacher PJ. Is prostate-specific antigen the most useful marker for screening in prostate cancer? *Am J Clin Oncol* 1988; **11** (Suppl. 2): S65-7

25 Powell CS, Fielding AM, Rosser K, Ames AC, Vaughton KC. Prostate specific antigen—a screening test for prostatic cancer? *Br J Urol* 1989; **64**: 504-6

26 Carter HB, Hamper UM, Sheth S, Sanders RC, Epstein JI, Walsh PC. Evaluation of transrectal ultrasound in the early detection of prostate cancer. *J Urol* 1989; **142**: 1008-10

27 Palken M, Cobb OE, Warren BH, Hoak DC. Prostate cancer: correlation of digital rectal examination, transrectal ultrasound and prostate specific antigen levels with tumor volumes in radical prostatectoma specimens. *J Urol* 1990; **143**: 1155-62

28 Lee F, Littrup PJ, Loft-Christensen L, Kelly BS, McHugh TA, Siders DB *et al.* Predicted prostate specific antigen results using transrectal ultrasound gland volume. *Cancer* 1992; **70**: 211-20

29 Perrin P. Transrectal ultrasound for the diagnosis and staging of prostate cancer. *Current Opinion in Urology* 1992; **2**: 344-7

30 Palken M, Cobb OE, Simons CE, Warren BH, Aldape HC. Prostate cancer: comparison of digital rectal examination and transrectal ultrasound for screening. *J Urol* 1991; **145**: 86-92

31 Coffield KS, Speights VO, Brawn PN, Riggs MW. Ultrasound detection of prostate cancer in postmortem specimens with histological correlation. *J Urol* 1992; **147**: 822-6

32 Rifkin MD, Alexander AA, Pisarchick J, Matteucci T. Palpable masses in the prostate: superior accuracy of US-guided biopsy compared with accuracy of digitally guided biopsy. *Radiology* 1991; **179**: 41-2

33 Wang MC, Valenzuela LA, Murphy GP, Chu TM. Purification of a human prostate specific antigen. *Invest Urol* 1979; **17**: 159-63

34 Lee C, Keefer M, Zhao ZQ, Kroes R, Berg L, Liu XX *et al.* Demonstration of the role of prostate-specific antigen in semen liquefaction. *J Androl* 1989; **10**: 432-8

35 Breul J, Binder K, Block T, Hartung R. The effect of digital rectal examination on serum concentration of prostate-specific antigen. *Eur J Urol* 1992; **21**: 195-9

36 Garvin TJ. Re: Prostate infarction associated with aortic and iliac aneurism repair. *J Urol* 1990; **144**: 1485

37 Kramer W, Oremek G, Schuldes H, Boeckmann W, Jonas D. Medikamente interferieren mit der PSA-Bestimmung. *Urologe A* 1990; **29** (Suppl.): A11

38 Liu S, Miller PD, Holmes SA, Christmas TJ, Kirby RS. Eosinophilic prostatistis and prostatic specific antigen. *Br J Urol* 1992; **69**: 61-3

39 Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine BA. Prostate specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med* 1987; **317**: 909-16

40 Baylin SB, Mendelsohn G. Time-dependent changes in human tumors: Implications for diagnosis and clinical behaviour. *Semin Oncol* 1982; **9**: 504-12

41 Cohen RJ, Glezerson G, Haffejee Z. Prostate-specific antigen and prostate-specific acid phosphatase in neuroendocrine cells of prostate cancer. *Arch Pathol Lab Med* 1992; **116**: 65-6

42 Deijter SW, Martin JS, McPherson RA, Lynch JH. Daily variability in human serum prostate-specific antigen and prostatic acid phosphatase: a comparative evaluation. *Urology* 1988; **32**: 288-92

43 Partin AW, Carter HB, Chan DW, Epstein JI, Oesterling JE, Rock RC, Weber JP, Walsh PC. Prostate specific antigen in the staging of localized prostate cancer: influence of tumor differentiation, tumor volume and benign hyperplasia. *J Urol* 1990; **143**: 747-52

44 Weber JP, Oesterling JE, Peters CA, Partin AW, Chan DW, Walsh PC. The influence of reversible androgen deprivation on serum prostate-specific antigen levels in men with benign prostatic hyperplasia. *J Urol* 1989; **141**: 987-92

45 Carter HB, Pearson JD, Metter EJ, Brant LJ, Chan DW, Andres R *et al.* Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. *JAMA* 1992; **267**: 2215-20

46 Kane RA, Littrup PJ, Babaian R, Drago JR, Lee F, Chesley A *et al.* Prostate-specific antigen levels in 1695 men without evidence of prostate cancer. *Cancer* 1992; **69**: 1201-7

47 Benson MC, Wang IS, Pantuck A, Ring K, Kaplan SA, Olsson CA, Cooner WH. Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate cancer. *J Urol* 1992; **147**: 815-16

48 Babaian RJ, Camps JL. The role of prostate-specific antigen as part of the diagnostic triad and as a guide when to perform a biopsy. *Cancer* 1991; **68**: 2060-3

49 Babaian RJ, Mettlin C, Kane R, Murphy GP, Lee F, Drago JR *et al.* The relationship of prostate-specific antigen to digital rectal examination and transrectal ultrasonography. *Cancer* 1992; **69**: 1195-1200

50 Cooner WH, Mosley BR, Rutherford CL, Beard JH, Pond HS, Terry WJ, Igel TC, Kidd DD. Prostate cancer detection in a clinical urological practice by ultrasonography, digital rectal examination and prostate specific antigen. *J Urol* 1990; **143**: 1146-54

51 Perrin P, Maquet JH, Bringeon G, Devonec M. Screening for prostate cancer. Comparison of transrectal ultrasound, prostate specific antigen and rectal examination. *Br J Urol* 1991; **68**: 263-5

52 Denis LJ. To screen or not to screen? *Prostate* 1992; Suppl 4: 63-70