Prostate cancer

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Biomarkers and screening for prostate cancer

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Introduction

Biomarkers in prostate cancer (PC) are subject to intensive research efforts worldwide. Research concentrates on the improvement of diagnostic markers in serum and urine, and marker substances that can be applied to serum and tissue allowing the differentiation between aggressive and less-aggressive (indolent) prostate cancer. In spite of many limitations to be outlined in this chapter, prostate-specific antigen (PSA) and its molecular isoforms remain the cornerstone of diagnosing prostate cancer. Limitations of its usefulness mainly come from the fact that PSA is not a marker for prostate cancer but a marker for prostatic tissue. As a consequence, elevations of PSA due to prostate cancer and those due to benign prostatic hyperplasia, the age-dependent benign enlargement of the prostate occurring in more than 25% of all men above the age of 50, show a strong overlap. This obviously has an impact on the performance characteristics of PSA in terms of its relative sensitivity and specificity. Still, in terms of the volume of its use and its qualities, PSA and its derivatives can still be considered the best marker in human oncology. Chances of new markers to enter the clinical field within a short period of time are small if one considers that it took from 1979 [1] when PSA was purified and identified as prostate-specific antigen until 1991 when its diagnostic value in the setting of screening was first recognised [2].

This review will concentrate on biomarkers, which are in current clinical use in diagnosing prostate cancer. The field of prognostic markers and tissue markers as well as the initial results of recent approaches to identify new markers by differential gene expression analysis will not be covered. Very recent comprehensive reviews of these subjects are available [3, 4]. This review will therefore concentrate on PSA and its molecular subforms as far as they have reached the clinic. The adjunct value of rectal examination will also be dealt with.

Biomarkers and the Diagnosis of Prostate Cancer

In spite of severe limitations of PSA, the lack of specificity and the difficulty in identifying a normal cut-off value, this marker still plays a major role in diagnosing prostate cancer. PSA is a protease belonging to the kallikrein family. It comprises 15 serine proteases encoded by a cluster of genes on chromosome 19q13 [5]. The genes are numbered KLK1-15 and the corresponding proteins hK1-15. PSA is identical with hK3. It shares 80% homology with hH2, another prostate-specific protease [4].

PSA in the prostate is secreted by the epithelial cells and is also present in prostate cancer cells. In the normal prostate, PSA is secreted into acini and subsequently prostatic ducts from where it is added to sperm and functions to digest the gel formed by seminogelins after ejaculation. The mechanism by which PSA leaks into the serum is unclear. Current thinking is that leakage occurs as a result of the disturbance of the normal structure of the prostate, which is associated with the obstruction of prostatic acini and ducts. The elevation of PSA in the serum with conditions like prostatitis, benign prostatic hyperplasia (BPH) and prostate cancer (PC) fits this hypothesis. Still, only a small fraction of PSA escapes into the circulation. This also explains why serum concentrations of PSA may be higher in prostate cancer than with the presence of benign enlargement of the prostate [6].

PSA Isoforms and Clinical Use

The largest portion of PSA detected in serum is bound to α1-antichymotrypsine (PSA–ACT). Up to 35% of PSA is free. Assays for both total PSA and free PSA are readily available for clinical use and are introduced in the automated analysers of most clinical laboratories. Considerable variations between assays have been reported and analysed in the past [7, 8]. Much of this variability was eliminated by calibrating assays to the Tandem® assay system, which was developed and is marketed by Beckman Coulter Hybridtech. More recently, an international standard was introduced, which leads to recalibration of most assays and to considerably lower values when compared with the Tandem®/Access system [9–10]. The clinical community is still struggling with this problem. Many clinicians and investigators have elected to continue using and reporting data based on the Tandem®/Access system. This is also true for all reports coming from the European Randomised Study of Screening for Prostate Cancer (ERSPC) and the only other randomised study of screening for prostate cancer, the Prostate, Lung, Colon and Ovary (PCLO) screening trial of the National Cancer Institute in the USA [11–12].

Total PSA is composed of complexed PSA and free PSA. The majority of PSA occurring in serum is bound to α1-antichymotrypsine (PSA–ACT). Up to 35% of PSA is unbound and is named free PSA (fPSA). For unexplained reasons the level of PSA–ACT in serum is higher in prostate cancer than in benign prostatic conditions or in men with normal prostates in...
relation to the level of free PSA. It therefore seems sensible to develop complexed PSA (cPSA) as a more sensitive and hopefully more specific marker for prostate cancer. The development of immuno-assays for PSA is, however, a late development due to technical difficulties. Complexed PSA contains two other isoforms in concentrations of 1%–2% and 5%–10%, the complexes with α-1-protease inhibitor (API) and with α-2-microglobulin (A2M). In spite of all technical difficulties an assay for cPSA has become available [13]. The value of cPSA in diagnosing prostate cancer is still under debate. However, evidence is accumulating that cPSA improves the performance of tPSA in terms of a higher relative specificity but that it is equivalent to the value of the ratio of free and total PSA in this respect [9, 14].

Free PSA contains several PSA isoforms specifically the −2, 4, −5 and −7 proPSA. Mature PSA contains several cleaved forms of mature PSA and 'BPSA'. BPSA and cleaved forms of mature PSA are thought to be derived from the benign prostatic tissue while proPSA might be more specific for prostate cancer. This working hypothesis is, however, still under investigation. The issue has been subject to an extensive recent review [3, 4].

One urine test has become available in the US and is in the process of being marketed in Europe. PCA3–D3 is the most prostate cancer specific gene found to date. It is over expressed in more than 95% of primary prostate cancer specimens and in prostate cancer metastasis. It is upregulated to six-fold in prostate cancer tissue compared with normal tissue. Using a specialised real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay to identify PCA3–D3 RNA in urine, the test showed a 90% negative predictive value in a population of men admitted for prostate biopsy based on serum PSA >3 ng/ml. PCA3 has the potential to improve to specificity of PSA and is at present used for this purpose in the US [16].

**how to use PSA in diagnosing prostate cancer?**

As mentioned above, the usefulness of PSA in diagnosing prostate cancer has been challenged by recent studies resulting from the Prostate Cancer Prevention Trial (PCPT) in which 5754 men, aged above 55, were biopsied, either by indication of developing a PSA level of ≥4 ng/ml or an abnormal rectal examination during a 7-year follow-up period with yearly screen. A total of 1934 participants in the placebo control arm underwent 308 biopsies and in whom 67 prostate cancers were found [21]. The findings are summarised in Table 1. It is evident that in comparison to the standard, a biopsy indication with PSA ≥4 ng/ml and a positive rectal examination, every variation of the biopsy indication leads to a reduction of the proportion of men to be biopsied (again in relative specificity) which is associated with a loss of sensitivity. It is a clinical question and a question of judgment whether it is acceptable to miss 3%–12% of prostate cancers that could otherwise be diagnosed. Obviously, since biopsies have only been carried out on the basis of the regimen PSA, DRE and transrectal ultrasound (TRUS), true sensitivities cannot be calculated. The relative sensitivities reported here are subject to attribution bias which also governs all other studies in the literature with the exception of those which used the diagnostic strategies under study as a biopsy indication.

**Table 1. Simulated case selection, first screen ERSPC Rotterdam, 172 men, age 55–74, 308 biopsies, 67 prostate cancers (PC) [21]**

<table>
<thead>
<tr>
<th>Biopsy indicator</th>
<th>Reduction of biopsies % (SE)</th>
<th>Loss of PC % (SE)</th>
<th>Biopsies/PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA &gt;=4, DRE, TRUS</td>
<td>–</td>
<td>–</td>
<td>4.6</td>
</tr>
<tr>
<td>PSA &gt;=4, DRE</td>
<td>17 (2.1)</td>
<td>3 (2.1)</td>
<td>3.9</td>
</tr>
<tr>
<td>PSA age, DRE</td>
<td>37 (2.8)</td>
<td>12 (4.0)</td>
<td>3.3</td>
</tr>
<tr>
<td>PSAD, DRE</td>
<td>28 (2.4)</td>
<td>11 (3.8)</td>
<td>3.6</td>
</tr>
<tr>
<td>F/T ratio, DRE</td>
<td>37 (2.8)</td>
<td>11 (3.8)</td>
<td>3.3</td>
</tr>
</tbody>
</table>

DRE, digital rectal exam; F/T ratio, free to total PSA ratio; PC, prostate cancer; PSA, prostate-specific antigen; TRUS, transrectal ultrasound.

**ways out of the PSA dilemma**

One obvious possibility is the use of adjuvant measures such as the application of PSA isoforms, the additional use of digital rectal examination (DRE), the use of PSA corrected for prostatic volume (PSA density), age-specific reference ranges and a change of cut-off points. Unfortunately, only limited information on the value of such procedures is available for PSA ranges <4 ng/ml. With the use of the traditional cut-off point of PSA ≥4 ng/ml, Bangma et al. analysed the relative sensitivity and specificity in 1726 first-round ERSPC participants who underwent 308 biopsies and in whom 67 prostate cancers were found [21]. The findings are summarised in Table 1. It is evident that in comparison to the standard, a biopsy indication with PSA ≥4 ng/ml and a positive rectal examination, every variation of the biopsy indication leads to a reduction of the proportion of men to be biopsied (again in relative specificity) which is associated with a loss of sensitivity. It is a clinical question and a question of judgment whether it is acceptable to miss 3%–12% of prostate cancers that could otherwise be diagnosed. Obviously, since biopsies have only been carried out on the basis of the regimen PSA, DRE and transrectal ultrasound (TRUS), true sensitivities cannot be calculated. The relative sensitivities reported here are subject to attribution bias which also governs all other studies in the literature with the exception of those which used the diagnostic strategies under study as a biopsy indication.
Several studies have addressed the additional value of DRE. Catalona et al. in a large multicentre study found that the positive predicted value of DRE (the proportion of positive rectal examinations associated with cancer) in the PSA range <4 ng/ml is about 10% [22]. This means that of 10 biopsies indicated by DRE, only one is correctly positive. Within the European Randomised Study of Screening for Prostate Cancer (ERSPC) the issue has also been studied. It was found that the positive predictive value (PPV) and the parameters of aggressiveness of cancers diagnosed decreased with decreasing PSA values [23].

**PSA isoforms**

The isoforms of PSA that are in clinical use have been studied for the PSA ranges 2–4 and >4.0 ng/mL. The value of the free/total PSA ratio has first been established by Catalona et al. [24]. The study showed that a PSA cut-off of 25% improved relative specificity saving 25% of biopsies and still maintaining cancer detection at a 95% level. This is not at variance with the findings of Bangma reported in Table 1. Recently, a meta-analysis was conducted of eligible reports using the free/total (f/t) PSA ratio and the Beckman Coulter Hybritech Tandem E or R assays [9]. Representative data are summarised in Table 2. The data indicate that in terms of improving relative specificity the f/t ratio is more effective in the PSA range 4–10 ng/mL than with lower PSA values, F/t ratios have never been studied with PSA values below 2 ng/mL. Again, the use of the f/t ratio to improve specificity will lead to missing cancers that can otherwise be diagnosed. This may not be the case if the ratio had been studied as a primary biopsy indication. All data presented are subject to attribution bias and attempts to correct for this problem have not been made.

The report by Roddam et al. [9] (Table 2) presents a similar overview meta-analysis for complexed PSA. This analysis is based on 14 studies in which 4984 and 595 men were biopsied for tPSA values between 4–10 and 2–4 ng/mL. The authors conclude a better test performance of cPSA with respect to tPSA but could not find a diagnostic advantage of cPSA above f/t PSA. Again, none of the isoforms have been studied as a biopsy indication; the relative sensitivities reported and used in receiver operating characteristic (ROC) analyses are subject to attribution bias, which may change the reported data substantially. A simple example is given in [25].

Two other parameters of potential usefulness in improving test performance of PSA, age-specific reference ranges and PSA density will not be further discussed. It has been shown that in the screening setting, the correlation between PSA and age is weak. Prostate volume, however, plays an important role specifically with second round screening applications. This has been subject to a recent extensive analysis [26].

**should we lower PSA cut-off levels?**

It has been suggested to reduce the PSA cut-off level for prostate cancer detection to 2.5 ng/ml. The effect of this procedure has been subject to an analysis with an attempt of correction for attribution bias. The issue is subject to heavy debate [27, 28]. Within the European Randomised Study of Screening for Prostate Cancer (ERSPC), an ongoing experiment, a PSA cut-off value of 3.0 ng/ml is used as the only biopsy indication. This approach has been validated against PSA ≥4.0 ng/ml plus rectal examination as a biopsy indicator [29]. About 80% of all men age 55–74 have PSA values ≤3 ng/ml. The PPV of a PSA ≥2 ng/ml amounted to 29.2% with a detection rate of 5.3% [30]. The detection rate in two subsequent rounds of screening of the same population 4 years apart was about 9%, modest in comparison with the 24.2% of PCPT control arm.

Should the PSA cut-off be lowered for routine screening to 3.0 or 2.5 ng/ml or even lower PSA values? Recent publications consider the effect on a population basis. Welch et al. [31] used the access to a large serum repository and database of a nutritional study carried out in the US in men aged 55–69 to determine PSA and to calculate that in the US in a given year about 2.74 million men would present with a PSA value >2.5 ng/ml and be classified as having an abnormal PSA. Data reported by Thompson et al. [18, 19] allowed them to calculate that PSA in the range of 2.1–4 ng/ml is associated with a PSA of 24.7% if all men undergo biopsy. It is important to realise that the PPV becomes identical with the detection rate in a setting where all men undergo the decisive test, a biopsy. These data allowed the effect of using a PSA cut-off of ≥2.5 ng/ml to be calculated during the year of 2005 on prostate cancer detection and the incidence mortality ratio. Schröder and Roobol [32] figured that in a given year 775 000 men would be diagnosed with prostate cancer in the USA. This is 542 910 more than expected and 26.5 times more than 30.50 men expected to die of prostate cancer in 2005 [34]. At present, the incidence mortality ratio in the US is in the range of 7:1 [34].

**PSA kinetics**

The increase of PSA over time can be expressed in PSA velocity (PSAV), the increase of PSA in ng/ml/year or as PSA doubling time (PSADT). Both tests require the discontinuation of the use of cut-off points and serial observations, which take account of the individual variation of PSA which is in the range of 20%–40% and may have various causes [4]. Both PSAV and PSADT are likely to be predictors of outcome in
terms of aggressiveness of prostate cancer associated with high PSAV and short PSADTs. With respect to the diagnosis of prostate cancer, the issue is still heavily debated. All analyses of the value of PSA kinetics with respect to the diagnosis of prostate cancer are subject to attribution bias. As the recent discussion shows, however, again as with other derivatives of PSA and adjuvant clinical parameters, the use of PSAV is associated with an improvement of relative specificity but with a heavy loss of the proportion of cancers diagnosed [35, 36].

**overdiagnosis**

By definition, the routine application of diagnostic tests to the general population is associated with overdiagnosis. Zappa et al. [37] estimated that screening for prostate cancer with a cut-off value of 4 ng/ml and the use of rectal examination would lead to overdiagnosis of 51% and 93% at age 60 and above 65, respectively. Ettzioni et al. [38] estimated overdiagnosis based on the assumption of leadtimes of 3, 5 and 7 years to be in the range of 15%, 25% and 35%, respectively. McGregor et al. [39] calculated that 84 of 100 screen detected cancers may not kill by the age of 85 and that 16 of 100 cancer cases detected by screening may be saved from dying of prostate cancer. Draisma et al. used data from ERSPC, Rotterdam to estimate overdiagnosis and leadtime using the MISCAN model [40]. Some of the resulting data are summarised in Table 3. With the screening regimen used in ERSPC, overdiagnosis is in the range of 54% and leads to a 105% increase of lifetime risk of being diagnosed with prostate cancer.

**how to avoid overtreatment?**

It seems that at present markers that would allow the differentiation between aggressive and non-aggressive prostate cancer before taking a biopsy are not available and will not be available, if at all, for a very long period of time. If all overdiagnosed cases translate in overtreatment, it seems from a medical ethical point and probably also from a point of cost-effectiveness in a public health setting, that screening for prostate cancer may be unacceptable even if a mortality reduction is shown. While the natural history of screen detected cases per PSA range is not understood, tumour characteristics seem more favourable with lower PSA ranges, if radical prostatectomy and biopsy specimens are considered. Table 4 gives an example from ERSPC. Is it possible to identify ‘minimal’ or ‘indolent’ cancers prior to treatment? Kattan et al. [42] have developed a nomogram for identifying what may be called ‘indolent’ or ‘minimal’ cancer (volume less than 0.5 ml, tumour confined to the prostate, no Gleason score 4 or 5 pattern) in whole mount radical prostatectomy sections. Eighty of 409 clinical cases included showed such features. The precision of predictions is obviously dependent on input characteristics but amounted to 73%–80%. The same decision analysis strategy was applied to ERSPC data. The crucial difference was that 49% of 247 eligible radical prostatectomy specimens could be classified as minimal disease. The precision of the predictions was very similar [43]. While the classification of prostate cancers as ‘minimal’ or ‘indolent’ or ‘insignificant’ is arbitrary, they clearly are recruited at the most favourable prognostic spectrum of cancers identified clinically and by screening. Table 5 gives an overview showing the percentage of insignificant cancers diagnosed in various clinical and screen-detected series. Obviously, their prevalence will depend on clinical selection, evaluation technique and, as

<table>
<thead>
<tr>
<th>Screening</th>
<th>Age (y)</th>
<th>Overdiagnosis</th>
<th>% of detection</th>
<th>% increase in lifetime risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td>55</td>
<td>27%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>38%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>47%</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>53%</td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>56%</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>Interval</td>
<td>Every y, 55–67</td>
<td>50%</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Every y, 55–75</td>
<td>56%</td>
<td>124%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Every 4y, 55–67</td>
<td>48%</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Every 4y, 55–75</td>
<td>54%</td>
<td>105%</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Estimates of prostate cancer overdiagnosis from PSA screening from the ERSPC [40]

<table>
<thead>
<tr>
<th>PSA range (ng/mL)**</th>
<th>Median, mean tumor volume in ml (range)</th>
<th>% minimal tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.0</td>
<td>0.28, 0.32 (0.00–1.09)</td>
<td>67</td>
</tr>
<tr>
<td>3.0–3.9</td>
<td>0.58, 0.72 (0.00–3.10)</td>
<td>45</td>
</tr>
<tr>
<td>4.0–9.9</td>
<td>0.77, 1.08 (0.00–13.48)</td>
<td>27</td>
</tr>
<tr>
<td>&gt;10</td>
<td>1.82, 2.16 (0.00–7.99)</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>0.65, 1.06 (0.00–13.48)*</td>
<td>33</td>
</tr>
</tbody>
</table>

*Significant, p<0.001.
**Correlation tumor volume/PSA level. round 1: R² = 0.15, round 2: R² = 0.12 (p=0.0001).

Table 4. Tumor volumes in 550 radical prostatectomy specimens per PSA range detected in round 1 (ERSPC Rotterdam) [41]

<table>
<thead>
<tr>
<th>Reference</th>
<th>Detection mode</th>
<th>Rad. prostatectomies (N)</th>
<th>Insignificant PC %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein et al. (1998) [44]</td>
<td>Clinical T1c</td>
<td>163</td>
<td>30.7</td>
</tr>
<tr>
<td>Krumholz et al. (2002) [45]</td>
<td>Clinical T1c</td>
<td>94</td>
<td>11.5</td>
</tr>
<tr>
<td>Augustin et al. (2003) [46]</td>
<td>Clinical T1–T3</td>
<td>1254</td>
<td>5.8</td>
</tr>
<tr>
<td>Kattan et al. (2003) [42]</td>
<td>Clinical T1–T2a</td>
<td>409</td>
<td>20.0</td>
</tr>
<tr>
<td>Sokoloff et al. (2005) [47]</td>
<td>Clinical</td>
<td>79</td>
<td>48.0</td>
</tr>
<tr>
<td>Postma et al. (2005) [41]</td>
<td>Screen det.</td>
<td>386</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>2nd round</td>
<td>164</td>
<td>43</td>
</tr>
</tbody>
</table>

Table 5. Minimal (‘‘insignificant’’, ‘‘indolent’’) PC in reported series of radical prostatectomies
pointed out, on the mode of detection, by screening or in a clinical setting.

**active surveillance**

The only way out of the problem of overtreatment of PSA detected cancers is the assignment of apparently favourable prognostic cases to active surveillance strategies. Such strategies have been applied and shown favourable results, which are comparable to those of active treatment in similar populations [48, 49]. In order to resolve the problem in a more definite fashion, the European Randomised Study of Screening for Prostate Cancer’s European study group has designed a retrospective and prospective protocol, which will be reported in the near future.

**references**


42. Kattan MW. Comparison of Cox regression with other methods for determining prediction models and nomograms. J Urol 2003; 170: S6–9;


