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ARTICLE in UROLOGIC ONCOLOGY · NOVEMBER 2011

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Prostate-specific antigen: An evolving role in diagnosis, monitoring, and treatment evaluation in prostate cancer

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Received 1 October 2009; received in revised form 29 October 2009; accepted 4 November 2009

Abstract

Prostate specific antigen (PSA) was introduced as a prostate cancer screening tool more than 20 years ago. However, there is continuing debate regarding its utility in screening for prostate cancer. Mass screening is costly, may result in the diagnosis and treatment of prostate cancers that never become clinically significant, and the evidence of a subsequent reduction in mortality is inconclusive. In addition to its role in screening, PSA is also used to monitor the progression of the disease, both localized and metastatic. Although the evidence is contradictory, PSA is still an important tool for monitoring patient progression following treatment of definitive localized prostate cancer. However, its use in monitoring castrate-resistant prostate cancer (CRPC) is more controversial, particularly in the context of novel targeted treatments, which may have little impact on PSA levels. These issues highlight the urgent need to identify prostate cancer biomarkers that will improve early disease detection, increase accuracy of diagnosis, determine the aggressiveness of disease, and monitor treatment efficacy, particularly in late-stage disease. This review discusses the key issues associated with the use of PSA as an early screening tool for prostate cancer, as a prognostic marker to measure disease progression in both early- and late-stage prostate cancer, and as a surrogate endpoint in clinical trials with new agents. © 2011 Elsevier Inc. All rights reserved.

Keywords: PSA; Prostate; Cancer; Screening; Prognostic; Biomarker

1. Introduction

Prostate specific antigen (PSA) is a kallikrein-related serine protease that is produced almost exclusively by prostate epithelial cells [1]. In normal, healthy prostate tissues, PSA is released at high concentrations into the seminal fluid to liquefy it [2]. PSA was identified in seminal fluid in the 1960s [3], and its use as a prostate cancer tumor marker was postulated in the 1970s when it was isolated from normal, benign hypertrophic, and malignant prostate tissues, but not from other human tissues [4]. In the mid 1980s, PSA was introduced into clinical medicine as an accurate serum marker of prostate cancer [5]. Although prostate cancer cells produce less PSA than normal cells, it is thought that the disruption of the prostate architecture in tumors results in the leakage of PSA into the blood, which causes serum PSA levels to rise up to 105-fold [1]. However, it should be noted that serum PSA levels are raised not only in prostate cancer, but also in a number of nonmalignant conditions such as benign prostatic hyperplasia, infection, or chronic inflammation [3]. Moreover, other factors such as ejaculation, prostatic manipulation, body weight, carbohydrate intake, and insulin resistance can all influence serum PSA levels [6]. In addition, because PSA production is itself androgen-dependent, PSA level is a less reliable indicator of disease status in androgen-deficient states.

2. PSA as a screening tool

Prostate cancer is the second leading cause of cancer-related death in men in the Western world, and this disease will account for an estimated 25% of newly diagnosed male cancers in the US in 2009 [7,8]. Therefore, an accurate screening test for prostate cancer would be invaluable to help reduce deaths from this disease.

A series of 10 criteria for appraising the validity of a screening program were developed by Wilson and Jungner in the 1960s (Table 1) [9]. In summary, the criteria state that...
the target disease process should be a common problem, which has a better outcome when treated at an early stage, and that the screening test employed should be acceptable to the patient, sufficiently sensitive, specific, and cost effective. Sensitivity (true-positive ratio) is defined as the proportion of individuals with the target condition in a population who are correctly identified by a screening test, and specificity (true-negative ratio) is defined as the proportion of individuals free of the target condition in a population who are correctly identified by a screening test [9].

PSA screening has been deployed in the detection of prostate cancer for many years. Previously, the majority of men with prostate cancer would have presented with metastatic disease. PSA screening has, therefore, resulted in a greater detection of prostate cancers at an early, localized and, therefore, more curable stage of the disease [10]. Furthermore, the use of PSA monitoring to better identify men who are at increased risk of developing prostate cancer may also facilitate the employment of chemopreventive strategies. However, PSA screening is controversial, due to the cost of mass screening, verification bias, the overdiagnosis, and overtreatment of cancers that may never assume clinical significance during a patient’s lifetime, and the conflicting evidence of a subsequent reduction in prostate cancer mortality [1,3,11]. Overdiagnosis and overtreatment of the disease can incur increased costs, involve unnecessary treatment of nonaggressive cancers, and reduce quality of life due to treatment side effects and increased anxiety [3].

Before 2009, significant variation existed in PSA screening guidelines, both between the UK and the US, and within the US [12–15]. While the 2001 American Cancer Society (ACS) guidelines recommended that a PSA test should be offered annually, beginning at the age of 50 years, to men who have a life expectancy of greater than 10 years [13]. Following the publication of ongoing PSA screening clinical trials in 2009 [16,17], the ACS [18] and other US societies, including the American Urology Association (AUA) [19], National Comprehensive Cancer Network (NCCN) [20], American College of Preventative Medicine (ACPM) [21], and the US Department of Health and Human Services [14] have aligned their guidelines to highlight that the benefits of screening for prostate cancer are uncertain and that the balance of benefits and harms cannot be determined. These organizations, therefore, recommend that men should be informed and educated on the benefits and risks before deciding to undergo PSA testing. The UK National Screening Committee recently initiated a Prostate Cancer Risk Management Program to enable men to make informed choices about PSA testing rather than recommend a prostate cancer screening program [15].

2.1. Evaluation of PSA screening in clinical trials

The value of PSA screening for detection of prostate cancer has been questioned following variable outcomes from clinical trials evaluating its utility. Some studies have demonstrated a reduction in prostate cancer mortality as a result of PSA screening [22,23], whereas others have shown no significant benefit [24,25]. Many of these trials had methodological flaws, limiting their ability to impact on current practice. Two ongoing large scale, randomized, controlled trials are investigating the value of PSA screening for prostate cancer; the European Randomized Study of Screening for Prostate Cancer (ERSPC) [16] and the Prostate, Lung, Colorectal, and Ovarian (PLCO) [17] cancer screening trial in the US. Initial results from these trials added to the uncertainty over the value of PSA screening for the detection of prostate cancer [11]. The PLCO study reported no mortality benefit from combined screening with PSA testing and digital rectal examination (DRE) after 7 to 10 years of follow-up [17]. It has been argued that this is because the majority of men enrolled had previously undergone PSA testing. In contrast, the ERSPC trial reported that PSA screening was associated with a 20% relative reduction in prostate cancer mortality at a median follow-up of 9 years, resulting in the reduction of about 7 prostate cancer deaths per 10,000 men screened [16]. However, the mortality benefit came at a cost of overdiagnosis, as the incidence of prostate cancer in the screened population was significantly higher than the incidence of men presenting with clinically significant disease. This was compounded as PSA screening was associated with approximately 76% false positive result (i.e., the test was elevated although there was no evidence of cancer on the biopsy) [17]. The reduction in mortality reported in the ERSPC study is comparable to that observed in screening programs for other cancer types but the risk of false positives appears to be much greater. The high rate of negative biopsy and false positive results indicates that PSA alone is clearly not an effective screening technique. A recent review of the effectiveness of breast cancer screening reported that mortality reductions range from 24% to 48% in women who have attended at least 1 screen [26]. The risk of a false positive result in breast cancer screening has been assessed in a Scandinavian study, which reported that the risk of a false positive result over 10 screens was up to 22% [27]. Ongoing analyses on quality of

<table>
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<th>Table 1</th>
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<tr>
<td>Wilson and Jungner disease screening criteria</td>
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<tr>
<td>1. The disease should be an important public health problem</td>
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<td>2. There should be an effective treatment for patients with the disease</td>
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<tr>
<td>3. Facilities for diagnosis and treatment should be available</td>
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<td>4. There should be a recognized latent or early symptomatic stage of the disease</td>
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<td>5. There should be an effective screening technique for the disease</td>
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<td>6. The screening tests should be acceptable to the population</td>
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<td>7. The natural history of the condition, including the development from latent to declared disease, should be adequately understood</td>
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<td>8. A strategy for determining which patients should and should not be treated must exist</td>
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<td>9. The cost of screening and treating of patients should be economically acceptable</td>
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<td>10. Screening should be a continuous process</td>
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life and cost effectiveness from the ERSPC and PLCO screening trials, along with other large trials, such as the Prostate Testing for Cancer and Treatment (PROTECT) trial in the UK [28], are needed to help settle the ongoing PSA screening debate (Table 2). These findings highlight that not all of the criteria for an effective screening tool, outlined by Wilson and Jungner, are fulfilled by PSA alone as a marker of prostate cancer.

3. PSA as a marker of prostate cancer disease progression

In addition to the controversy surrounding PSA-based screening, there is an ongoing debate on the role of PSA as a prognostic factor in men who have been diagnosed with prostate cancer.

3.1. PSA as a prognostic factor in early-stage prostate cancer

Early-stage prostate cancer tumors are known to secrete PSA, which can be used as a biomarker to monitor response to therapy and disease progression, and can aid treatment decisions. PSA levels can be used preoperatively to predict outcomes after radical prostatectomy. Freedland et al. [29] demonstrated that preoperative PSA levels were significantly related to advanced, high-grade disease and biochemical progression. Other groups have shown PSA to be an independent predictor of all pathologic stages of prostate cancer over time [30]. Following therapy for localized prostate cancer, PSA levels can be monitored to detect recurrent cancer before the tumor would be detectable by any other means. In particular, the PSA doubling time (PSA-DT) has been shown to stratify the risk of clinical progression for those men with a rising PSA after radical treatment [31,32]. These studies demonstrate the predictive value of PSA following treatment for early-stage prostate cancer.

Although PSA is useful for monitoring early-stage prostate cancer, the treatments administered for this disease can impact PSA levels. For example, although a steady decline in PSA occurs following radiotherapy, an initial ‘PSA bounce’ is often observed, especially with brachytherapy, which can affect disease monitoring. This transient increase in PSA levels is benign and subsequently drops to ‘pre-bounce’ levels [33]. This phenomenon is thought to occur through a combination of the release of PSA as a result of cell death and/or through the increased release of PSA into the serum because of altered vascular permeability as a consequence of inflammation and/or radiation [33].

The majority of men diagnosed with prostate cancer who elect to be treated with definitive radiotherapy or brachytherapy will also receive additional neoadjuvant hormone therapy. Those men with high risk disease will continue with hormone manipulation in an adjuvant setting for up to 2–3 years. PSA levels are usually suppressed by the time

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of participants</th>
<th>Age of participants (years)</th>
<th>No. of participating countries/states</th>
<th>Recruitment times</th>
<th>.Screening interval</th>
<th>Study design</th>
<th>PSA cut-off value for biopsy (ng/ml)</th>
<th>Recruitments</th>
<th>Reported results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERSPC</td>
<td>&gt;200,000</td>
<td>55–74</td>
<td>8 European countries</td>
<td>1993–present</td>
<td>3 4 years</td>
<td>Randomized to prostate cancer screening with PSA and DRE or standard of care</td>
<td>3</td>
<td>20% relative reduction in prostate cancer mortality (median 9 years follow-up) [16]</td>
<td></td>
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<tr>
<td>PLCO</td>
<td>77,000</td>
<td>55–74</td>
<td>10 US states</td>
<td>1992–2001</td>
<td>4 Annual for 6 years</td>
<td>Randomized to prostate cancer screening with PSA and DRE or standard of care</td>
<td>4</td>
<td>No mortality benefit (7–10 years follow-up) [17]</td>
<td></td>
</tr>
<tr>
<td>PROTECT</td>
<td>460,000</td>
<td>50–69</td>
<td>9 UK cities</td>
<td>2001–2008</td>
<td>NS</td>
<td>Randomized to prostate cancer screening with PSA or standard of care</td>
<td>NS</td>
<td>Not yet reported</td>
<td></td>
</tr>
</tbody>
</table>

DRE = digital rectal examination; NS = not stated.

a European Randomized Study of Screening for Prostate Cancer (ERSPC).

b Prostate, Lung, Colorectal, and Ovarian cancer screening trial (PLCO).

c Prostate Testing for Cancer and Treatment (PROTECT) trial.
radiotherapy commences. However, once hormone therapy is halted, PSA levels will rise due to recovery of the residual normal prostate tissue. The Phoenix definition of biochemical failure following radiotherapy (with or without hormone therapy) was developed to determine whether radiotherapy continues to be effective in suppressing the prostate cancer, with biochemical failure determined to be a rise of 2 ng/ml above an initial PSA nadir [34].

Hormonal manipulations including androgen deprivation therapy (ADT) result in a lowering of PSA levels, both through tumor regression and via direct suppression of androgen-dependent PSA gene transcription [35]. Following this initial decrease, PSA levels then stabilize on continued treatment. The PSA nadir on ADT is thought to be an important prognostic parameter and has been associated with time to androgen-independent progression, clinical progression, and death [1]. An increase in PSA levels indicates renewed tumor growth as well as reactivation of the androgen receptor, a common feature of CRPC [1]. CRPC is confirmed once there is evidence of cancer progression following initial hormone therapy (indicated by PSA or imaging) despite castrate levels of testosterone.

In summary, although concerns exist over the use of PSA as a prognostic marker, and consideration needs to be given to the impact of prostate cancer treatments, PSA is still an important tool for monitoring patient progression following treatment of definitive localized prostate cancer.

3.2. PSA as a prognostic factor in advanced prostate cancer

As prostate cancer progresses, the utility of PSA as a prognostic factor decreases. The tumor may expand without a concomitant increase in PSA levels, either because little PSA is being produced (due to tumor cell dedifferentiation for example) or because PSA production is being suppressed by treatment with antiandrogens. Prostate cancer tumors become much more heterogeneous as the disease progresses, both between patients and, importantly, within the same patient, leading to variability in tumor PSA expression that could result in false positive or false negative PSA test results [36].

4. PSA as a surrogate marker of prostate cancer disease progression in clinical trials

Surrogate endpoints are commonly used in clinical trials evaluating the efficacy of new developmental therapies. A surrogate endpoint should be associated with a clinically meaningful outcome, completely encompassing the net effect of any treatment on that outcome. To confirm surrogacy in patients treated with new vs. standard interventions, there must be strong correlation between the relative effect of the treatment on the surrogate and on the true endpoint [37]. In patients with early-stage prostate cancer, a post-treatment PSA-DT within 3 months of radical prostatectomy or radiation therapy has been suggested to be a surrogate marker for prostate cancer-specific mortality [38]. In patients with a PSA-DT of less than 3 months following such treatments, it has been recommended that ADT or alternative novel approaches should be initiated to delay the imminent sequelae of metastatic disease [38]. In contrast, despite extensive investigation of PSA as a surrogate endpoint in a range of clinical trials in patients with CRPC, the use of a PSA-based endpoint for overall survival in these patients is currently under scrutiny [39].

4.1. PSA as a surrogate endpoint for survival following chemotherapy

PSA levels have been measured in studies evaluating cytotoxic chemotherapy in patients with CRPC with conflicting results [1,40–43]. For example, in the SWOG 99–16 study that compared docetaxel and estramustine with mitoxantrone and prednisone for treatment of advanced CRPC, PSA was demonstrated to be a good surrogate marker for overall survival as the decline in PSA levels correlated with a significant improvement in overall survival [41]. In contrast, other studies of chemotherapeutic agents have reported PSA to be a poor surrogate marker for overall survival in patients with CRPC. The phase II ASCENT study comparing DN-101 plus docetaxel vs. docetaxel alone demonstrated that PSA levels were a poor surrogate endpoint for survival in patients with CRPC. DN-101 treatment was associated with a significant improvement in overall survival (median overall survival: DN-101 plus docetaxel, 24.5 months [estimated]; placebo plus docetaxel, 16.4 months; HR 0.67; 95% CI 0.45, 0.97; P = 0.04), but not a significant decline of ≥50% PSA levels (≥50% PSA decline; DN-101 plus docetaxel, 58%; placebo plus docetaxel, 49%; P = 0.16), suggesting no relationship between PSA levels and survival [43]. Furthermore, in the TAX-327 study comparing weekly and 3-weekly schedules of docetaxel plus prednisone vs. mitoxantrone plus prednisone, a similar decline of ≥50% PSA was observed with both docetaxel regimens, however, this did not translate into an improvement in overall survival in the weekly docetaxel group [42]. A re-analysis of the TAX-327 study did, however, report that a ≥30% decline in PSA (as opposed to the previous analysis of ≥50%) within 3 months of chemotherapy initiation was a moderate surrogate marker for overall survival [40].

4.2. PSA as a surrogate endpoint for survival following treatment with targeted agents

PSA response to therapy is dependent on the mechanism of action of the treatment modality. Cytotoxic agents such as docetaxel directly kill cancer cells, whereas targeted therapies can exert their effect via cytostatic, antiproliferative, or other nontoxic mechanisms, which may have less impact on PSA levels [44]. Clinical trials of novel targeted agents in which PSA has been used as a surrogate marker for disease progression and overall survival have reported...
inconsistent PSA responses, even across trials of the same drug [45,46]. Learnings from a number of recent studies of targeted agents that have evaluated PSA in patients with CRPC (discussed below) highlight some of these issues.

A phase II trial of the selective endothelin A (ET\_A) receptor antagonist atrasentan in patients defined as having hormone-refractory prostate cancer reported no reduction in the primary endpoint of time to disease progression relative to placebo. However, a significant improvement in the secondary endpoint of median time to PSA progression was observed [45]. Two subsequent phase III trials in the metastatic and nonmetastatic hormone-refractory prostate cancer setting failed to meet their primary endpoint of time to disease progression or time to PSA progression [46,47], despite evidence of biological effects on PSA and bone alkaline phosphatase as markers of disease burden [46]. Differences were observed, however, between US and non-US patients in time to disease progression in the nonmetastatic hormone-refractory prostate cancer trial, likely due to premature treatment discontinuation [47]. Although PSA levels were not formally considered indicative of disease progression, the discontinuation rate based on PSA was four times higher in US patients [47], thus skewing any true beneficial effect of the drug. This study also highlights the importance of patient and physician education on the role of PSA during the progression of prostate cancer [48].

A phase II study of zibotentan (ZD4054), a specific ET\_A receptor antagonist, in patients with metastatic hormone-resistant prostate cancer (HRPC) showed no significant decline in PSA levels despite promising improvement in overall survival compared with placebo [49]. Based on these results and the findings from the atrasentan trials, PSA levels were not selected as a primary endpoint in the ongoing phase III ENTHUSE clinical program investigating zibotentan in patients with metastatic and non-metastatic HRPC [50].

Discordance between PSA progression and improvements in bone scans in the initial part of a 2-stage phase II study of the oral multikinase inhibitor sorafenib led to a protocol amendment to remove PSA-defined progression as a criterion in the second part of the study [51].

These and other studies with novel agents indicate that PSA is not consistently useful as a surrogate endpoint in clinical trials of treatments for CRPC. In particular, PSA should not be regarded as the standard measure to assess the potential of novel targeted agents for the treatment of CRPC. This has been discussed by the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) [52], who have recently updated the outcome measures for clinical trials that evaluate systemic treatment for patients with CRPC. The PCWG2 highlighted that PSA response should not be the sole criterion for clinical decisions, and in the absence of other clinical indicators of disease progression, early changes in PSA levels are not sufficient to justify discontinuation of a study drug. In addition, they recommended that drug evaluation pathways specific to the mechanism of action of the drug should be developed; cytotoxic drug trials should include assessments of both control/relieve/eliminate or prevent/delay endpoints, and trials for nontoxic agents should be designed with prevent/delay endpoints [52]. Indeed, potential benefits of this approach were demonstrated when the use of clinical progression (radiographic or symptomatic) measures safely extended treatment despite PSA progression in a recent exploratory analysis of data from a phase II trial of docetaxel, bevacizumab, and thalidomide in patients with metastatic CRPC. Furthermore, the continuation of treatment in this study was associated with improved survival compared with discontinuation based solely on PSA progression [53].

5. Novel biomarkers for prostate cancer detection, prognosis, and progression

The limitations of PSA presented in this review demonstrate the need for new biomarkers that are more selective and specific for the detection and progression of prostate cancer. Other kallikrein markers such as percentage-free PSA and human glandular kallikrein 2 (hK2) are promising for the detection and prognosis of prostate cancer as they are more specifically associated with malignancy than total PSA [54]. In addition, a number of novel biomarkers are currently being investigated to more accurately diagnose and predict clinical response in prostate cancer (Table 3). These include serum markers (e.g., circulating tumor cells [CTC] and early prostate cancer antigen [EPCA1]), tissue markers (e.g., α-methylacyl coenzyme A racemase [AMACR]), and urine markers (e.g., prostate cancer antigen 3 [PCA3]), which are briefly described below. An in-depth explanation of these novel biomarkers lies beyond the scope of this review; for a more detailed description of these biomarkers, refer to Lin 2009 [55] and Makarov et al. 2009 [56]. Ultimately, combined analysis of PSA along with novel serum and genetic markers that are currently being investigated may offer a more effective and individualized method of prostate cancer diagnosis and prognosis [39].

5.1. CTCs

CTCs are cells that have detached from the developing tumor into the circulation. Increased numbers of serum CTCs have been detected in patients with CRPC, and CTC levels have been reported to predict survival in these patients [57]. A study by Okegawa et al. demonstrated that overall survival was significantly increased (P < 0.001) in patients who had less than 5 CTCs per 7.5 ml of blood compared with those patients who had greater than 5 CTCs [57]. In another study investigating the effect of chemotherapy in patients with CRPC, CTCs were used to monitor treatment response and predict patient outcome. This study reported that elevated pretreatment CTCs were associated with decreased overall survival [58]. The po-
### Table 3

<table>
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<th>Potential marker</th>
<th>Description</th>
<th>Method of detection</th>
<th>Potential type of marker</th>
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<tr>
<td>Circulating tumor cells (CTC)</td>
<td>Circulating prostate cancer cells</td>
<td>Serum marker</td>
<td>Diagnostic and prognostic</td>
</tr>
<tr>
<td>Early prostate cancer antigen (EPICA)</td>
<td>Nuclear matrix protein</td>
<td>Serum marker</td>
<td>Diagnostic</td>
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<tr>
<td>Prostate-specific membrane antigen (PSMA)</td>
<td>Type II membrane glycoprotein</td>
<td>Serum marker</td>
<td>Diagnostic</td>
</tr>
<tr>
<td>Human glandular kallikrein 2 (hK2)</td>
<td>Prostatic secretory protein</td>
<td>Serum marker</td>
<td>Diagnostic and prognostic</td>
</tr>
<tr>
<td>Muc7</td>
<td>Unknown protein</td>
<td>Serum marker</td>
<td>Diagnostic</td>
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<tr>
<td>Transforming growth factor-β1 (TGF-β1)</td>
<td>Multifunctional cytokine</td>
<td>Serum marker</td>
<td>Diagnostic</td>
</tr>
<tr>
<td>Interleukin-6 (IL-6) and IL-6 receptors (IL-6R)</td>
<td>Multifunctional cytokine</td>
<td>Serum marker</td>
<td>Diagnostic and prognostic</td>
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<tr>
<td>Vascular cell adhesion molecule (VCAM)</td>
<td>Cell adhesion molecule</td>
<td>Serum marker</td>
<td>Prognostic</td>
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<tr>
<td>Matrix metalloproteinase-2 (MMP-2)</td>
<td>Cell adhesion molecule</td>
<td>Serum marker</td>
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<tr>
<td>Bone-specific alkaline phosphatase (bALP)</td>
<td>Marker of bone turnover</td>
<td>Serum marker</td>
<td>Prognostic</td>
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<tr>
<td>Total alkaline phosphatase (tALP)</td>
<td>Marker of bone turnover</td>
<td>Serum marker</td>
<td>Prognostic</td>
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<td>Cross-linked C-terminal of type 1 collagen (CTx)</td>
<td>Marker of bone turnover</td>
<td>Serum marker</td>
<td>Prognostic</td>
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<td>C-terminal telopeptides of type 1 collagen (ICTP)</td>
<td>Marker of bone turnover</td>
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<td>Amino-terminal procollagen propeptides of type 1 collagen (PINP)</td>
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<td>Serum marker</td>
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<td>Soluble ErbB3 (sErbB3)</td>
<td>Fat metabolism enzyme</td>
<td>Tissue marker</td>
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<td>α-methylacyl coenzyme A racemase (AMACR)</td>
<td>Negative regulator of p53 tumor suppressor</td>
<td>Tissue marker</td>
<td>Prognostic</td>
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<tr>
<td>MDM2</td>
<td>Marker of cellular proliferation</td>
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<td>Ki-67</td>
<td>Genetic marker</td>
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<td>N-methyl derivative of glycine</td>
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<td>Calgranulin B</td>
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<td>TMPRSS2:ER gene fusions</td>
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5.2. EPCA

The EPCA series of proteins identified in prostate cancer tissue, but not in benign tissues or benign prostatic hyperplasia tissues [60], are a promising group of biomarkers for the early detection of prostate cancer. Immunostaining of EPCA in human prostate needle cores can differentiate men with and without prostate cancer by evaluating histologically normal tissues adjacent to areas of benign glands of prostate cancer tissues [56]. Although it is detected in benign tissues, EPCA is potentially more cancer-specific than PSA. The sensitivity and specificity of EPCA for detecting prostate cancer have been reported to be 84% and 85%, respectively [61]. EPCA-2 is a nuclear structural protein associated with prostate cancer. In a study of 385 patients with a wide variety of cancer (organ confined and non-organ defined prostate cancer, in addition to patients with other cancers) and normal controls, an EPCA-2 serum ELISA was shown to have 92% specificity and 94% sensitivity for detecting prostate cancer, whereas in the same group of patients the specificity of PSA was only 65%. Furthermore, this study demonstrated promise for this biomarker due to the high accuracy in differentiating between localized and extracapsular disease \( (P < 0.0001) \), which was in contrast to PSA \( (P = 0.05) \) [62].

5.3. AMACR

AMACR is an enzyme involved in fat metabolism, which is strongly expressed in prostate cancer tissues. AMACR mRNA levels have been shown to be up-regulated 9-fold in 88% of prostate cancer tissues compared with normal prostate tissues, and the up-regulation of AMACR protein has been demonstrated to be localized to the peroxisome [63]. A study reported that immunohistochemical staining of AMACR had 97% sensitivity and 100% specificity for prostate cancer detection from 94 needle biopsy specimens [64]. A small study used PCR to detect AMACR from mRNA isolated from urine samples following prostatic massage. The normalization of AMACR levels to cellular PSA mRNA levels with a diagnostic cut-off value of 2 standard deviations above the mean demonstrated 100% specificity (correctly identifying 9/9 noncancerous controls) and 70% sensitivity (correctly identifying 7/10 patients with prostate cancer) for prostate cancer detection [65]. A recent study of 92 patients (43 with and 49 without prostate cancer) used quantitative RT-PCR to detect AMACR in urine samples, which demonstrated 70% sensitivity and 71% specificity, and was significantly superior \( (P = 0.006) \) to PSA \( (P = 0.306) \) in detecting prostate cancer [66].

5.4. PCA3

The PCA3 gene, a noncoding segment of mRNA located on chromosome 9, is overexpressed in prostate cancer cells compared with normal cells. The PCA3 urine diagnostic test was recently developed into an ‘easy-to-use’ standard assay. PCA3 and PSA were compared in men who had a prostate...
biopsy based on pre-existing risk factors (n = 70) and healthy men with no known risk factors (n = 52). This study demonstrated that PCA3 had 69% and 79% sensitivity and specificity, respectively, whereas serum PSA demonstrated the same sensitivity however, it was only 60% specific [67]. More recently, a multicenter study of 586 men with a serum PSA level of 3–15 ng/mL used a time-resolved fluorescence-based variant of the PCA3 test. This study confirmed the greater specificity of PCA3 compared with PSA, with AUC values of 0.66 and 0.57 for PCA3 and PSA, respectively, for predicting a positive biopsy [68].

These biomarkers offer improved sensitivity and specificity for prostate cancer screening. However, the heterogeneous nature of prostate cancer suggests that a combination of markers is likely to provide the most accurate, predictive value. For example, in one recent study, the combined analysis of urinary AMACR and PCA3 improved sensitivity and specificity compared with either test alone [66]. Currently, the cost of screening with novel biomarkers compares disadvantageously with the cost of screening with PSA. For example, in the UK a PSA test costs up to £30 [69] whereas tests for PCA3 and CTCs can cost as much as £400 [70] and £150 [71], respectively. However, if the use of novel biomarkers can increase the sensitivity and specificity of prostate cancer detection, the need for costly biopsies and unnecessary treatments could be reduced.

6. Conclusions

Controversy persists regarding the use of PSA as a screening tool to detect prostate cancer. Given the uncertain risk: benefit outcomes of early PSA testing, many guidelines now highlight the need for men to be well informed and well educated on the benefits and risks of the PSA test before deciding to undergo screening. Further analysis of the ERSPC and PLCO trials, along with the results of other ongoing large trials such as PROTECT should help clarify the utility of PSA as a large scale screening tool for the detection of prostate cancer. PSA does currently play a role as a prognostic tool for early-stage prostate cancer, but is less reliable in late-stage disease where it should be employed with other prognostic tests. The highly variable PSA responses in clinical trials of novel targeted agents for the treatment of CRPC suggest that PSA levels are not a reliable surrogate endpoint in this setting. New biomarkers are being identified although more research is needed to validate these as markers for use in the diagnosis and monitoring of disease progression, and as surrogate endpoints in clinical trials.

Acknowledgments

The authors thank Dr. Claire Routley, from Mudskipper, who provided editorial assistance funded by AstraZeneca.

References


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