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# Innovative biomarkers for prostate cancer early diagnosis and progression

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## Contents



## Abstract

The marker currently used for prostate cancer (CaP) detection is an increase in serum prostate-specific antigen (PSA). However, the PSA test which may give false positive or negative information, is not reliable and does not allow the differentiation of benign prostate hyperplasia

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(BPH), non-aggressive CaP and aggressive CaP. There is thus an urgent need to search for novel CaP biomarkers to improve the early detection and accuracy of diagnosis, determine the aggressiveness of CaP and to monitor the efficacy of treatment. Proteomic techniques allow for a high-throughput analysis of bio-fluids with the visualization and quantification of thousands of potential protein markers and represent very promising tools in the search for new, improved molecular markers of CaP. In this review, we will summarize conventional CaP biomarkers and focus on novel identified biomarkers for CaP early diagnosis and progression that might be used in the future.


*Keywords:* Prostate cancer; Biomarkers; Proteomics; SELDI-TOF-MS; Diagnosis; Prognosis

## 1. Introduction

Prostate cancer (CaP) is the second most prevalent type of cancer in males particularly in Northern America and Australia/New Zealand, and results in the sixth highest mortality rate in men worldwide in 2002 [1]. In New South Wales, Australia, CaP has the highest incidence rate in all persons and in men in 2004, resulting in 5477 new cases (28.6% of all cancers in men) and 905 deaths which accounts for 12.7% of all cancer deaths in men [2]. It has been reported that approximately 1 in 8 men will develop CaP by 75 years of age and 1 in 5 by the age of 85 years [2].

In order to cure CaP patients successfully, it is important to detect the disease at an early stage as well as to monitor its progress accurately. Currently available diagnostic techniques include pathohistology of prostate biopsies, digital rectal examination (DRE), transrectal ultrasonography (TRUS), and assaying prostate-specific antigen (PSA). DRE and TRUS are widely employed by diagnosticians but are very limited in their ability to diagnose CaP and do not provide the ability to distinguish between benign prostate hyperplasia (BPH) and CaP.

Pathohistology of prostate tissue can definitively identify CaP in most cases. This method is the most commonly used prognostic indicator for CaP and results in a grading called the Gleason score which is based on the architecture of cancer tissue observed under a microscope [3]. The lower the Gleason score is, the better the prognostic outcome [3]. However, there are limitations to this method of screening. First of all, a biopsy or similar operation must be performed in order to obtain the cancer tissue for testing. Second, the Gleason's grading scale used by pathologists is at least semiquantitive since it may be difficult to search every cell of every tissue slice. Third, there is a lack of concordance between the threshold of scoring by different pathologists [4]. For these reasons Gleason scores themselves have limited quantitative value. Using biomarkers overcomes the problem of quantification, and thus can provide a more accurate way for early diagnosis of CaP and for monitoring its progression.

Gleason score is the most used prognostic factor for CaP, with high scores particularly from 7 to 10 presenting a higher risk of death from CaP than low Gleason score (Gleason score $< 4$) cancers when patients aged 74 were treated conservatively [5]. However patients aged from 55 to 74 with Gleason score between 5 and 6 subjected to treatments are likely die from competing medical conditions and patients with Gleason score greater than 6 are likely to die from CaP despite treatment [6]. After age 75 years average life expectancy in men is less than 10 years and there is general agreement that men older than 75 years are unlikely to benefit from CaP screening [7,8]. However, despite the apparent lack of benefit from screening for CaP in men older than 75 years indirect evidence suggests that PSA testing in elderly men is a fairly common occurrence [9,10]. Selection of CaP treatment is difficult with CaP identified by PSA test as it does not differentiate the clinical significant CaPs [11]. A recent investigation of this question using patient reported data documented a CaP screening rate of over 30% in men 75 years or older [12]. Prognostic biomarkers that can identify or predict clinically significant CaP in patients are important in management of the disease. Novel biomarkers could be useful to determine the benefit of such screening in these patients. Ideally these prognostic/predictive biomarkers would be less invasive to obtain, are useful to screen CaP patients particularly for older ones, and guide their management to provide maximum benefit whilst minimizing the risks from the side-effects of treatments.

In this review biomarkers are grouped into three categories: the conventional biomarkers found prior to the proteomic era, the innovative proteomic biomarkers and the diagnostic proteomic patterns. Conventional biomarkers are molecules found in tissues or human body fluids; they can be proteins, DNA or RNA. The second type particularly refers to biomarkers found using proteomic techniques. The proteomic pattern type is a new approach which involves looking at mass spectrometric patterns rather than individual molecules. These patterns are produced using mass spectrometry (MS) particularly the surface-enhanced laser desorption and ionization time-of-flight (SELDI-TOF) or matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF).

## 2. Conventional biomarkers

For CaP diagnosis, PSA is the only conventional biomarker accepted by the U.S. Food and Drug Administration (FDA). Whilst not an ideal biomarker, its use as the main screening biomarker for CaP in many countries has resulted in the apparent increase of the disease's incidence rates and a decrease in mortality rates.