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# Detection of prostate cancer by sialic acid level in patients with non-diagnostic levels of prostate-specific antigen

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ABSTRACT

*Introduction:* Ideally, there will be reproducible markers easily and non-invasively available to test for malignancy, or alternative procedures when there is no accurate marker available. For prostate cancer, one of the most common cancers in men, levels of prostate-specific antigen (PSA) lack specificity and sensitivity for the determination of malignancy when they fall within a range of values termed the 'grey zone'.
*Objective:* To examine the predictive value of sialic acid in prostate neoplasms.
*Study design:* In our study of diagnostic accuracy we recruited 70 men complaining of urinary symptoms who presented in the urology department as outpatients or inpatients. All patients were checked with biopsy and pathology in order to relate benign and malignant lesions of the prostate to levels of sialic acid, a member of a family of acetylated products of neuraminic acid, which has so far proved to be a very sensitive and accurate marker of malignancy.
*Results:* The sialic acid level was found to be elevated in patients with prostate cancer (mean $75.06 \pm 10.4$ mg/dl) and reduced in patients with benign prostate hyperplasia (mean $57.086 \pm 8.7$ mg/dl) ($p < 0.01$); it had a sensitivity of 86% and specificity of 84% in diagnosing malignancy.
*Conclusion:* Sialic acid can be used as an adjunct in predicting prostate malignancy when PSA values fall in the grey zone.

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## 1. Introduction

Prostate cancer represents the most common malignancy in men (32%) and the second most common cause of death due to cancer (14%); consequently, early detection of prostate cancer is crucial [1]. Urinary symptoms, clinical evaluation of the size and shape of the prostate by rectal examination and prostate biopsy are the main parameters to diagnose and stage the disease. Nevertheless, biopsy is a time-consuming and painful procedure, and is inappropriate for screening. The need for less invasive but still indicative methods of diagnosis has led to the investigation of serum markers of the disease.

The best-known marker for prostate cancer is prostate-specific antigen (PSA) [2–4]. Certain PSA values are definitive and accurate, and the test has proved both popular and useful. However, many patients present with only slightly elevated PSA values, and for this group the test does not provide a differential diagnosis between prostate cancer and benign prostate hyperplasia (BPH) [5]. Besides BPH and prostate cancer themselves, other factors can influence PSA levels; they are increased, for example, by any handling of the prostate (prostate biopsy, digital rectal examination), infections, chronic or acute (prostatitis), recent ejaculation and prolonged cycling, which can cause temporary damage to the microenvironment of the gland [4]. In one study that examined a group of patients with normal findings on digital rectal examination, on multivariate analysis the PSA level did not correlate with biopsy findings of cancer. Limitations in PSA specificity led to the unnecessary biopsy of many patients. Of patients who never had a PSA level > 4 ng/ml, 15.2% harboured prostate cancer and 14.9% of those men had a Gleason sum of at least 7, indicating potentially aggressive cancers. Nevertheless, an individualised screening algorithm using digital rectal examination prebiopsy information in addition to PSA level can result in a considerable reduction in unnecessary biopsies [5].

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Sialic acid conjugated with lipids (total sialic acid, TSA) is a tumour marker that was first studied in Memorial Sloan-Kettering Cancer Institute [6]. Sialic acids constitute a family of acetylated products of neuraminic acid and have an active role within the cell membrane by acting as receptors for bioactive molecules or by mediating intracellular actions such as recognition, antigenicity and molecule adhesion in increased tissue invasion and various other procedures that characterise cancer cells and metastatic expansion [7].

Clinical trials have shown that TSA is increased in a wide range of malignant diseases, such as breast cancer, ovarian cancer, lung cancer, gastrointestinal and pancreatic cancer, sarcoma, melanoma, leukaemia, lymphomas (Hodgkin and non-Hodgkin), as well as in urinary cancers [7].

Though it is not at present widely used as such, TSA seems a very promising routine screening marker, either on its own or in combination with well known and established markers [8]. On its own, TSA has not proved useful for the detection of early malignant disease because of its low diagnostic sensitivity, although TSA serum concentration can allow staging of a cancer. TSA serum concentration does also reflect the effectiveness of therapy: a decrease in concentration indicates tumour regression (effective therapy) and an increase the progression of disease (failing therapy). In addition to its role as a useful biochemical indicator for staging, prognosis and monitoring of the effectiveness of treatment, TSA has been used for the early detection of recurrence or metastases [8].

Sialic acid was first used in 1986 for the screening and identification of patients with prostate cancer. In that study it had 94.2% sensitivity [9], and a later study similarly reported increased sialic acid levels in cancer patients [10]. Most further studies demonstrated a tendency of sialic acid levels to increase in prostate cancer and decrease in BPH, but with weak statistical significance [11,12]. Recently Melegy et al. and Goswami et al. [13,14] suggested that measurement of serum TSA levels combined with the free/total PSA ratio could serve as a useful adjunct to diagnosis.

PSA levels lack specificity and sensitivity for the determination of malignancy when they fall within a range of values termed the 'grey zone' (4.0–10.0 ng/ml). Romppanen et al. [15] were the first to show that the sialic acid level is accurate in predicting prostate malignancy for this group of patients when it is expressed in the form of a ratio to PSA.

The aim of our study was to investigate the predictive value of sialic acid in the differential diagnosis of BPH and prostate cancer, in patients with non-diagnostic levels of PSA (i.e. levels in the grey zone). We estimated sialic acid's diagnostic accuracy and compared it with the accuracy of PSA.

## 2. Methods

### 2.1. Study sample

The study was conducted at Laikon University Hospital, a major tertiary institution. Its catchment area covers the city of Athens, and the study participants would thus represent an average sample of all socioeconomic groups. The recruitment of patients began in August 2009 and ended in July 2010. Patients were recruited either by recommendation by other physicians, or by self-reporting of the patients, on the basis of urinary incontinence, dribbling, frequent urination, pain during urination or any other evidence of prostate enlargement or stenosis of the urethra. All patients were males between 60 and 80 years of age who had never received treatment for prostate symptoms.

Distribution of severity of disease was uniform among patients with the target condition, which means that all patients suffered from either prostate cancer or BPH. Gleason scores (which is a scale that distinguishes among severity of disease) were not correlated to the parameters measured, because this was not the purpose of the study. Given the study's prospective design, none of the patients demonstrated missing results regarding the primary outcome (prediction of prostate cancer).

Criteria for a patient to be included were primarily the detection of a PSA value within the 'grey zone' (4.0–10.0 ng/ml). Only patients that fulfilled these criteria were included. Among those, and according to the biopsy result, we formed 2 groups (one with patients suffering from prostate cancer and one with patients suffering from BPH) with an equal number of patients for each group.

Exclusion criteria were the presence of another neoplastic condition in the past, the concurrent presence of another chronic illness (not cured), as well as a non-recent diagnosis of prostate cancer.

All patients included in the study agreed to take part and signed a consent form as part of their diagnostic evaluation. Ethics approval was obtained by the Athens University Hospital Ethics Committee.

### 2.2. Data collection

Clinical examination and blood collection were performed in the urology department of the University Hospital of Athens, for both inpatients and outpatients. All information concerning personal history and demographic data, as well as the follow-up data regarding progression of the disease, was collected from patient charts within the University Hospital. The same diagnostic criteria and methods were used for all patients.

### 2.3. Study design

This study was prospective, and all measurements and parameters were designed in advance. A questionnaire accompanied the procedure, to facilitate the collection of the following information for each patient: age, body weight, body mass index (BMI), serum markers (PSA and sialic acid) and prostate gland ultrasound. Patients also underwent digital rectal examination and prostate biopsy.

Patients were divided into two groups (A and B). Group A consisted of patients with prostate cancer ($n = 35$), on the basis of a clinical suspicion and serum markers, further confirmed by biopsy and pathology. Group B consisted of patients with benign prostate hyperplasia ($n = 35$), similarly confirmed by biopsy and pathology. Only patients presenting with PSA in the grey zone were studied, because by definition the study would aim to discover the potential strength of another marker only in patients with non diagnostic levels of PSA. For both groups we determined the serum levels of sialic acid and PSA. The groups were matched for age and for BMI (Table 1).

### 2.4. Test methods

Blood was collected after the patient had fasted, early in the morning. Both PSA and sialic acid levels may be influenced by the invasive procedures of rectal examination and prostate biopsy, a potential confounding factor that was avoided by obtaining serum before any other intervention.

Samples were left for a few minutes at room temperature before centrifugation at 2000 rpm for 15 min. Serum was isolated and

**Table 1**
Matching of study groups at baseline for age and BMI (mean + SD).

| | Prostate cancer (group A) | BPH (group B) | Statistical significance |
|---|---|---|---|
| Age (years) | 73.05 ± 6.8 | 69.5 ± 8.2 | 0.0527 |
| BMI (kg/m$^2$) | 27.2 ± 4.8 | 28.3 ± 2.3 | 0.2257 |