

# Effect of Prostate Cancer on Non-protein Nitrogenous Substances

Sanghapriya Pal<sup>1</sup>, Kiran Dahiya<sup>2</sup>, Rajeev Atri<sup>3</sup>, Hemang Kumar<sup>4</sup>, Aman Chauhan<sup>5</sup>, Shweta Gaur<sup>6</sup>

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## ABSTRACT

**Introduction:** Prostate cancer is one of the most common non-cutaneous malignancies in American males. In 2008, it was the sixth leading cause of death from cancer among males. Population-based cancer registries in India show that this has become a growing health concern in many parts of India. There are many interfaces between cancer and chronic kidney disease (CKD).

**Materials and methods:** Serum levels of urea, creatinine, and uric acid of 50 prostate cancer patients were compared with those of 50 healthy controls, at 95% confidence level taking  $p < 0.05$  as significant. The association of urea, creatinine and uric acid levels with staging, Gleason's scoring and serum prostate-specific antigen (PSA) level was analyzed with the help of appropriate statistical analysis.

**Results:** Among the three prominent non-protein nitrogenous (NPN) substances used for renal assessment, the levels of urea and uric acid in serum were found to be statistically significantly raised ( $p < 0.05$ ) in patients with prostate cancer as compared with healthy controls. The serum levels of creatinine were higher in cases as compared with controls but the difference was not found to be statistically significant ( $p = 0.088$ ). Only uric acid level ( $p = 0.01$ ) changed significantly among the stage A through stage D. We did not find the statistical significant correlation between the level of urea ( $r = -0.05$ ,  $p = 0.75$ ), creatinine ( $r = -0.24$ ,  $p = 0.09$ ) and uric acid ( $r = -0.05$ ,  $p = 0.75$ ) with PSA.

**Conclusion:** From our study, it can be concluded that the evaluation of serum levels of urea, creatinine and uric acid may be of utmost diagnostic and prognostic significance in patients with prostate carcinoma.

**Keywords:** Cancer, Creatinine, Chronic kidney disease, Gleason's scoring, Prostate cancer, Prostate-specific antigen, Urea, Uric acid.

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## INTRODUCTION

Prostate cancer can be included among the most prevalent non-dermatologic malignancies in American men population.<sup>1</sup> In the year of 2008, prostate cancer seemed to be sixth out of all the commonest reasons of cancer-related mortality in men. Population-based cancer registries in India show that this has become a growing health concern in many parts of India.<sup>2</sup> The risk factors include age, family history, hormonal influence, dietary and environmental effects, inflammation and infection specially sexually transmitted infections, such as chlamydia, gonorrhoea, syphilis.<sup>3,4</sup> Nowadays, the prostate-specific antigen (PSA) estimation is the cornerstone of the management, to detect prostate cancer and even to check its reappearance after therapeutic intervention. The biological reference range for PSA in normal individuals is in the range of 0–4 ng/mL and its concentration increases with the presence of malignancy of prostate. Different research articles have suggested that serum PSA concentration of 4–10 ng/mL is associated with 22–27% rise of possibility of cancer, while this possibility can go up to 67% with serum PSA concentration of 10 ng/mL or more. The food and drug administration (FDA) has recognized the estimation of serum PSA concentration as a screening tool for the male population of 50 years or more, with upper limit of normal reference range being 4 ng/mL, along with digital rectal examination (DRE).<sup>5</sup> There are many interfaces between cancer and chronic kidney disease (CKD) resulting in many therapeutic and prognostic applications. Chronic kidney disease has a two-way relationship with cancer. The prevalence of CKD is found to be higher in certain cancer subtypes while elevated risk of cancer is seen in patients with renal transplant and who are on hemodialysis, even in those who are suffering from CKD but not on dialysis.<sup>6</sup> It has been reported that reduced level of

<sup>1,6</sup>Department of Biochemistry, Maulana Azad Medical College, New Delhi, India

<sup>2,3</sup>Department of Biochemistry, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India

<sup>4</sup>Department of Laboratory Medicine, AIIMS, New Delhi, India

<sup>5</sup>Department of Biochemistry, Maharishi Markandeshwar Institute of Medical Sciences & Research, Ambala, Haryana, India

**Corresponding Author:** Sanghapriya Pal, Department of Biochemistry, Maulana Azad Medical College, New Delhi, India, Phone: +91 9475232652, e-mail: sanghapriyapal@gmail.com

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cystatin C and elevated levels of urea and creatinine are associated with higher risk of renal dysfunction in prostate cancer.<sup>3</sup> Moreover, uric acid, produced from xanthine by xanthine oxidoreductase, has been hypothesized to provide a defense against human cancers by scavenging singlet oxygen and inhibiting lipid peroxidation. The protective antioxidant effect of uric acid has been identified in many conditions. Nevertheless, in many studies, elevated serum level has been found statistically associated with premature cancer death in both the sexes, indicating its more complex role in cancer biology.<sup>7</sup>

Besides uric acid, other renal parameters are also expected to be affected by prostate carcinoma, therefore, the present study was planned to evaluate the serum levels of urea, creatinine and uric acid in patients with prostate carcinoma and correlate them with the disease severity and the serum level of PSA.

## MATERIALS AND METHODS

The present study was conducted in the Department of Biochemistry, Pt. BD Sharma PGIMS, Rohtak, in association with the Department of Radiation Oncology, Pt. BD Sharma PGIMS, Rohtak. For this, 50 newly diagnosed histopathologically proven prostate carcinoma patients (cases) were enrolled along with 50 age and sex matched apparently normal individuals. Diagnosis of carcinoma prostate was established by detailed history, clinical examination, and histopathological examination. After explaining the study to each individual, permission for their inclusion in the study was obtained from each of them. The patients suffering from any other malignancy or any other prostatic illness, gout, and any renal abnormality were excluded.

On diagnosis, a measure of histologic aggressiveness is assigned using Gleason grading system.<sup>8</sup> Staging was done according to American Urological Association (AUA) staging system (Modified Jewett Staging System).<sup>9</sup> Cases are grouped into one with Gleason's score  $\leq 7$  and other with  $>7$ . The serum concentration of urea, creatinine, and uric acid were compared between these two groups and also among the different stages.

Serum samples of all the subjects were analyzed for urea, creatinine, and uric acid on autoanalyzer (Randox Suzuka) using standard kit methods,<sup>10-12</sup> and for PSA by XEMA EIA tPSA kit.<sup>13</sup> The data were compiled and subjected to appropriate statistical analysis. The difference between cases and controls was tested at 95% confidence level taking  $p < 0.05$  as significant.

## RESULTS

The mean age of cases was  $67.86 \pm 9.91$  years (45–86 years) and that of controls was  $65.48 \pm 6.28$  years (50–78 years). The difference of age between two groups seems was statistically nonsignificant ( $p > 0.05$ ). Out of 50, 49 (98%) of cases and 48 (96%) of controls were married ( $p = 0.5577$ ). Among 50 cases, 19 presented with dysuria and 6 with retention of urine as the main symptom. Lower back pain, burning micturition, hematuria, increased frequency of urine, urinary incontinence, decreased output of urine, decreased force of urine, and diffuse bony pain was the main presenting symptom in 5, 5, 4, 4, 2, 2, 1, and 1 patients, respectively. Only one was asymptomatic. Twenty-nine (58%) cases had Gleason score  $\leq 7$  and 21 (42%) had  $>7$ . About 10 (20%), 2 (4%), 13 (26%) and 25 (50%) patients presented at stage A, B, C, and D, respectively. The mean level of serum PSA among the patients was  $229.30 \pm 526.49$  ng/mL with the range of (1.5–2533.49 ng/mL).

The serum concentration of urea, creatinine, and uric acid in cases and controls are compared in Table 1. Comparative analysis

of these analytes in between two groups of patients has been displayed in Table 2 and on the other hand, comparative analysis among different stages of disease has been displayed in Table 3. Figures 1 to 3 shows the correlation of urea, creatinine, and uric acid with PSA.

## DISCUSSION

The mean age of cases was  $67.61 \pm 9.85$  years (45–86 years) and that of controls was  $46.43 \pm 14.21$  years (19–72 years) ( $p > 0.05$ ). Cancer can be regarded as the disease of old age because it has been seen that the incidence of most cancers increases with the increasing age. Age may be considered as the surrogate measure of the complex biological process aging, which is believed to be one of the most important contributing factors to the pathogenesis of cancer.<sup>14</sup> In the present study, age of the healthy individuals was matched with the cases to exclude any bias in the study.

Among cases, 64% were smokers while in controls, 22% were smokers. By applying Chi-square test to the data, smoking was found to be associated with prostate cancer in a statistically highly significant manner ( $p < 0.01$ ). The association of smoking with different cancers has been well established. It is because that smoking causes an increase in serum levels of testosterone and a decrease in the bioavailable estradiol in men, and also in cigarette, various carcinogens are found. Although its role in prostate cancer is conflicting in various studies, the present study indicates a significant association of prostate cancer with smoking.<sup>15</sup> On the other hand, alcohol intake might be included in the etiology of cancer in the population. In 2018, the American Society of Clinical Oncology affirmed that more than 5% of new oncological patients could be accredited to alcohol intake.<sup>16</sup> Although this association is conflicting in various literature, in our study, among both the cases

**Table 1:** Comparison of serum levels of urea, creatinine and uric acid in patients with prostate cancer (cases) and healthy controls

Parameter	Group	Mean $\pm$ SD	Range	p-value
Urea (mg/dL)	Cases	$35.82 \pm 13.63$	18–78	0.00082
	Control	$27.06 \pm 11.34$	15–90	
Creatinine (mg/dL)	Cases	$1.17 \pm 0.66$	0.5–4.6	0.08847
	Control	$0.99 \pm 0.29$	0.6–2.1	
Uric acid (mg/dL)	Cases	$5.18 \pm 1.74$	2.5–9.8	0.034386
	control	$4.52 \pm 1.23$	2.2–7.1	

**Table 2:** Association of Gleason's score with urea, creatinine and uric acid

Parameter	Gleason's score $\leq 7$	Gleason's score $>7$	p-value
Urea (mg/dL)	$33.86 \pm 12.12$	$37.77 \pm 15.56$	0.34
Creatinine (mg/dL)	$1.30 \pm 0.81$	$0.98 \pm 0.27$	0.05
Uric acid (mg/dL)	$4.96 \pm 1.40$	$5.46 \pm 2.09$	0.35

**Table 3:** Comparison of serum urea, creatinine, uric acid levels among different stages

Parameters	Stage A	Stage B	Stage C	Stage D	p-value
Urea (mg/dL)	$28.04 \pm 6.50$	$34 \pm 5.66$	$39.65 \pm 19.16$	$36.58 \pm 12.54$	0.24
Creatinine (mg/dL)	$1.11 \pm 0.42$	$0.9 \pm 0$	$1.2 \pm 0.26$	$1.19 \pm 0.88$	0.93
Uric acid (mg/dL)	$4.24 \pm 1.27$	$5.35 \pm 0.35$	$6.4 \pm 2.24$	$4.89 \pm 1.30$	0.01

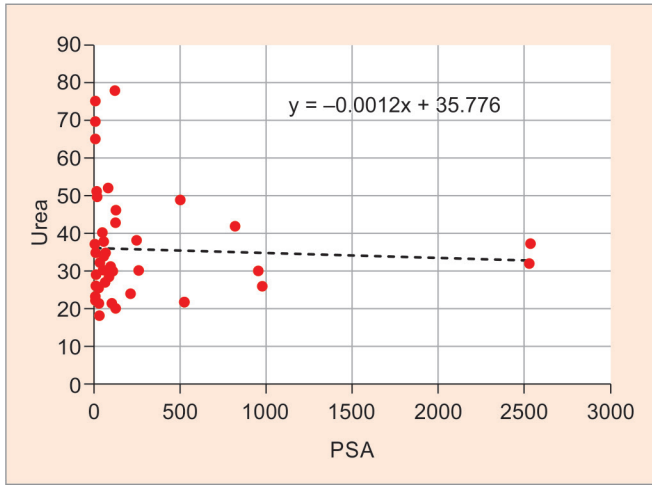


Fig. 1: Showing correlation between urea and PSA

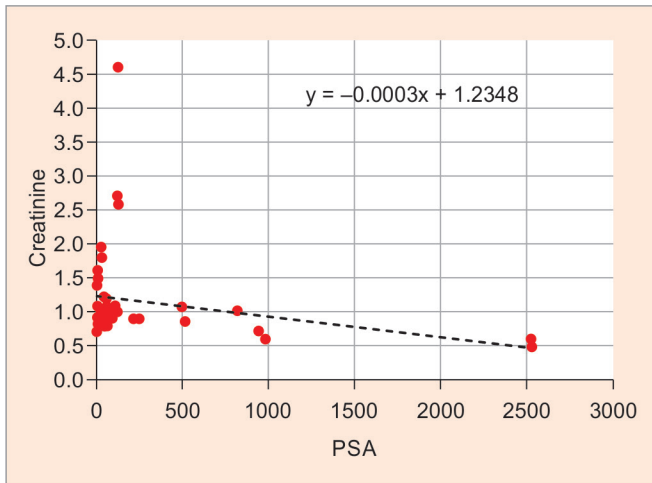


Fig. 2: Showing correlation between creatinine and PSA

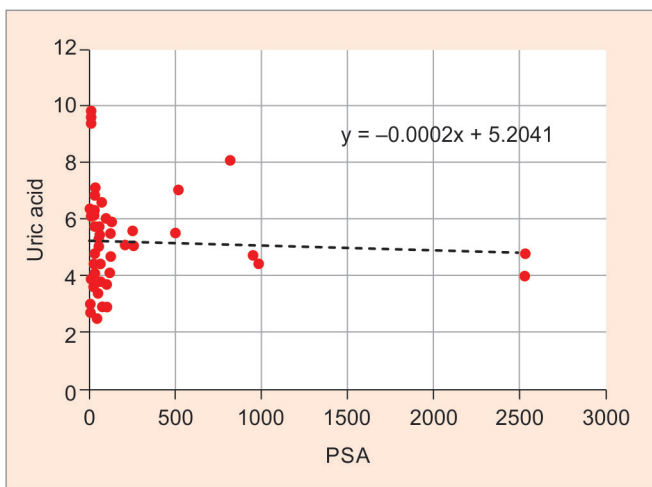


Fig. 3: Showing correlation between uric acid and PSA

and controls, only 12% of subjects were alcoholic. The association of alcohol intake with cases was not statistically significant at all ( $p > 0.05$ ).

Among the three prominent non-protein nitrogenous (NPN) substances used for renal assessment, the concentration of urea and uric acid in serum were found to be statistically significantly raised ( $p < 0.05$ ) in patients suffering from prostate cancer as compared with healthy people. The serum concentration of creatinine was increased in cases as compared with controls but the difference was not found to be statistically significant ( $p = 0.088$ ). Moreover, we did not find the statistically significant correlation between the level of urea ( $r = -0.05$ ,  $p = 0.75$ ), creatinine ( $r = -0.24$ ,  $p = 0.09$ ) and uric acid ( $r = -0.05$ ,  $p = 0.75$ ) with PSA. While comparing between two groups of patients-with Gleason's score  $\leq 7$  and with Gleason's score  $> 7$ , the level of urea and uric acid were increased and that of creatinine was decreased in the latter group but none of the difference was statistically significant ( $p = 0.34$ ,  $0.35$ , and  $0.05$ , respectively). There were no significant difference in the level of urea ( $p = 0.24$ ) and creatinine ( $p = 0.93$ ) among the patients of different stages of disease, although uric acid level ( $p = 0.01$ ) changed significantly among the stage A through stage D. Renal function assessment is important in the patients of cancer regarding etiology, prognosis, and effect of therapies. There is overlapping of etiologies of cancer and kidney disease. The examples include age, obesity, physical inactivity, smoking, hypertension, type II diabetes mellitus, cardiovascular disease, male gender. Elder people suffers from renal insufficiency, while heading toward seventies, kidney function is reduced to 40%. Various physiological changes like reduced renal mass, decreased kidney perfusion, and reduced nephron activity can be ascribed to this. Moreover, with increasing age, there are a lot of comorbidities, so, it is very obvious that cancer patients, who are usually elderly, probably have some degree of renal impairment. Type 2 diabetes is a common cause of different kidney diseases in USA and itself an etiological attribute for various cancers. This association is actually more complex because most diabetics seems to be associated with increased weight, even in the range of obesity, further increasing risk for cancer in diabetics.<sup>6,17</sup> Inflammation is the underlying event of many diseases, such as cardiovascular disease and cancers. Common conditions inducing inflammation are obesity, hyperglycemia, hypertension, hypertriglyceridemia explaining why cardiovascular diseases and cancer share common risk factors.<sup>18</sup> From the literature, we can see that CKD may be a risk factor for cancer. Increased risk for cancer can be seen in patients after transplantation and those on regular dialysis. In United Kingdom in 2010 malignancy was the most frequent reason of mortality in patients receiving kidney transplant (23%).<sup>17</sup> Similarly, increased risk has been reported in the individuals suffering from CKD but not on dialysis. Till now, the underlying mechanism of association is not well understood. Among multiple factors, immunosuppression may be one contributor to the cancer risk, which can be induced by the pre- or post-transplant treatment with immunosuppressant or can be due to uremia-associated repression of immunity. The CKD induces the inflammatory microenvironment which is also implicated in cancer development. Albuminuria, an accompaniment of various inflammatory states of renal system, has also been very frequently seen in various cancers particularly of genitourinary tract or lung. Conversely, cancer may lead to the kidney disease. Chronic kidney disease can be seen more frequently in some types of cancer. Acute kidney injury is frequently seen in hepatic and renal malignant diseases and also in multiple myeloma. It can be due to loss of blood volume resulting from systemic infection, excessive vomiting or diarrhea, microbial toxins or deposition of M-protein

in multiple myeloma. Blocking of urinary tract due to tumors can lead to acute kidney injury too. Infiltration by cancer cells into glomeruli can precipitate nephrotic syndrome.<sup>6,17</sup>

The blood level of urea is positively associated with the bulk of tumor as is reported in a variety of cancers. Raised NPN substances have been observed in cancer cachexia which results in loss of skeletal muscle due to increased protein degradation and reduced synthesis. These may be attributed to physical inactivity of the patients and decreased availability of the amino acids which rather gets utilized for the synthesis of acute phase proteins.<sup>19</sup> A study on small cell lung cancer reported that raised serum urea could be associated with elevated probability of premature mortality in patients receiving chemotherapy. Elevated urea may result from catabolism state characterized by increased protein turn over in advanced cancer.<sup>19</sup>

A strong prospective relationship of higher serum creatinine within normal ranges has been found with increased risk of prostate cancer.<sup>20</sup> Another study has shown that increased serum urea and creatinine and decreased cystatin C may be associated with increased risk of renal dysfunction in prostate cancer.<sup>3</sup> Similarly, it has been reported that elevated serum urea and creatinine may give an early clue to carcinoma prostate.<sup>21</sup>

Uric acid has antioxidant properties. Increased oxidative stress due to inflammatory processes in the body can damage the cellular structures including deoxyribonucleic acid (DNA) contributing to carcinogenic process.<sup>4,7</sup> It was hypothesized that uric acid can involve in primary defense mechanism as it can scavenge the reactive oxygen species, inhibit lipid peroxidation.<sup>7</sup> There are various pharmacologic agents which are exclusively used in the management of hyperuricemia such as allopurinol, an inhibitor of xanthine oxidoreductase.<sup>4,7</sup> In a study, positive correlation between prostate cancer and allopurinol use has been reported.<sup>22</sup> Contrary to this, another study revealed that increased serum uric acid can be linked to prostate cancer and prostatitis as compared with normal controls.<sup>23</sup>

Tumor lysis syndrome (TLS) occurs due to increased cellular destruction in response to treatment leading to different metabolites like potassium coming out of cells and ultimately affecting the kidneys.<sup>7,17</sup> As part of TLS, hyperkalemia can cause arrhythmia, hyperphosphatemia leads to secondary hypocalcemia resulting in tetany, dysrhythmias, and precipitation of calcium phosphate crystal in different organs including kidney causing acute kidney injury. Uric acid can also affect kidney by tubular crystal deposition, constricting vasculature, altered autoregulation, decreased perfusion, crystal-induced inflammatory reactions. Tumor lysis syndrome causes systemic inflammatory response syndrome, affecting different organs, which is mediated by an array of cytokines.<sup>24</sup> A case report of spontaneous TLS in a patient of prostate cancer has been reported. Tumor lysis syndrome in malignancy is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia due to rapid destruction of malignant cells and massive release of cellular substances. In literature, six cases of TLS have been described, out of which, two developed following treatment with cytotoxic chemotherapeutic agents, two after treatment with androgen blockers, one following radiation and another one following both radiation and androgen blockade.<sup>25</sup>

Therefore, it can be concluded that evaluation of serum levels of urea, creatinine, and uric acid may be of utmost diagnostic and prognostic significance in patients with prostate carcinoma.

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