Original Article

Association between the serum uric acid levels and prostate cancer: evidence from National Health and Nutrition Examination Survey (NHANES) 1999–2010

Wei Yan[#], Peng Xiang[#], Dan Liu, Yupeng Zheng, Hao Ping

Department of Urology, Beijing Tongren Hospital, Capital Medical University, Beijing, China

Contributions: (I) Conception and design: H Ping; (II) Administrative support: H Ping; (III) Provision of study materials or patients: W Yan, P Xiang; (IV) Collection and assembly of data: W Yan, P Xiang; (V) Data analysis and interpretation: W Yan, P Xiang, D Liu, Y Zheng, H Ping; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Hao Ping, PhD. Department of Urology, Beijing Tongren Hospital, Capital Medical University, No. 1 Dongjiaominxiang Street, Dongcheng District, Beijing 100730, China. Email: pinghaotrh@ccmu.edu.cn.

Background: Uric acid may play a critical role in protection against cancer by the suppression of inflammation. The association between serum uric acid (SUA) levels and prostate cancer risk is debatable yet has received little attention in the American population. Therefore, we used data from the National Health and Nutrition Examination Survey (NHANES) to determine their correlation.

Methods: Using information from NHANES 1999–2010, a total of 62,160 individuals from the general population were included in this cross-sectional study. Additionally, a number of covariates were acquired. Prostate cancer was used to divide the participants into two groups: prostate cancer group (n=315) and non-prostate cancer group (n=7,545). A weighted adjusted logistic regression analysis was conducted to examine the potential correlation between SUA and prostate cancer.

Results: Our study comprised a total of 7,860 participants. After full adjustment for confounders, SUA was not significantly associated with prostate cancer [odds ratio (OR) 0.91, 95% confidence interval (CI): 0.82–1.00, P=0.058]. In participants aged 60 years and above (≥60 years), a higher SUA was significantly associated with a lower risk of prostate cancer (OR 0.88, 95% CI: 0.80–0.96, P=0.003). However, among those younger than 60 years (<60 years), there was no association between SUA and prostate cancer risk (OR 1.29, 95% CI: 0.69–2.42, P=0.42). In addition, in the subgroup analysis stratified by body mass index, hypertension and diabetes, there was no significant correlation between SUA and prostate cancer.

Conclusions: SUA is negatively associated with the risk of prostate cancer in older men, especially for those 60 years of age and beyond.

Keywords: Serum uric acid (SUA); prostate cancer; risk; National Health and Nutrition Examination Survey (NHANES)

Submitted Jan 09, 2024. Accepted for publication Apr 06, 2024. Published online May 22, 2024.
doi: 10.21037/tcr-24-46
View this article at: https://dx.doi.org/10.21037/tcr-24-46

Introduction

Prostate cancer is a diverse, complicated, and highly hormone-dependent illness that ranks second in the world among male cancer diagnoses (14.1%) and is responsible for the fifth-highest number of cancer-related deaths in men globally (6.8%) (1,2). Old age, ethnicity, genetic background, family history, dietary variables, obesity, and smoking are risk factors for prostate cancer development (2-4). Additionally, a favorable correlation was found between a higher risk of prostate cancer and circulating inflammatory

marker C-C motif chemokine ligands 21 and 11, C-reactive protein, greater leukocyte counts and systemic immune-inflammation index (5). However, the quantity of data and number of identified risk factors remain limited.

Serum uric acid (SUA) is a final product formed by purine metabolism and degradation. Numerous publications have reported a connection between elevated SUA levels and inflammation, obesity, metabolic syndrome, diabetes, and metabolic syndrome (6-10). This information sheds new light on SUA and suggests that it may function as a metabolic regulator as well as a pathophysiological factor for a number of disorders, including cancer (6-11). However, there are currently contradictory results about the relationship between SUA levels and prostate cancer (8,12-17). Cohort studies conducted in Heidelberg (14) and Baltimore (13) revealed no correlation between SUA and the incidence of prostate cancer. Additionally, one European-based Mendelian randomization study (16) showed no significant causality between SUA levels and prostate cancer risk. At the same time, other studies showed that there was a positive association between SUA and prostate cancer risk (8,12,15). Besides, two studies indicated that low SUA levels and increased inflammatory markers were determined as risk factors for prostate cancer (17,18).

Therefore, in order to determine the correlation between SUA levels and prostate cancer risk in the American population, we used data from the 1999–2010 cycles of the National Health and Nutrition Examination Survey (NHANES) for the first time to conduct the investigation.

Highlight box

Key findings

- Serum uric acid (SUA) is negatively associated with the risk of prostate cancer in older men, especially for those 60 years of age and beyond.

What is known and what is new?

- SUA may function as a metabolic regulator as well as a pathophysiological factor for a number of disorders, including cancer. However, there are currently contradictory results about the relationship between SUA levels and prostate cancer risk.
- This manuscript demonstrates SUA may have a protective role in prostate cancer of older adults.

What is the implication, and what should change now?

- SUA is a simple and noninvasive indicator obtained from routine blood tests that should be completely included into prostate cancer care.

We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-46/rc).

Methods

Study population

NHANES is a cross-sectional survey undertaken by the National Center for Health Statistics (NCHS) with the primary goal of acquiring representative demographic, relevant examination, and questionnaire data to measure nutritional and physical health using a sophisticated sample strategy (19). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

We used data from NHANES among men from 1999 to 2010 (six cycles) because there is information related to prostate cancer and SUA. The exclusion criteria were: (I) female participants (n=31,575) and age <18 years (n=13,576); (II) incomplete data of dietary, demographic and health condition (n=5,038); (III) incomplete data of SUA (n=486); (IV) missing data of prostate cancer (n=3,625). Finally, a total of 7,860 individuals were eligible to be included for the analysis (*Figure 1*).

Outcome assessment

NHANES employed a self-administered questionnaire to collect information on the presence or absence of prostate cancer. A survey question titled "Have you ever been told by a doctor or health professional that you have prostate cancer?" was used to determine the respondents' prostate condition. Participants who answered "Yes" were considered to have prostate cancer.

Exposure variable

The information of SUA measurement and quality control have been previously discussed (20,21), and values were displayed in mg/dL. SUA was a continuous variable that we employed in our statistical study.

Covariates of interest

The demographic characteristics evaluated were age (≥60 or <60 years), race (non-Hispanic white or other), poverty income ratio (PIR), educational level (less than high school, high school or above high school). Body mass index (BMI)

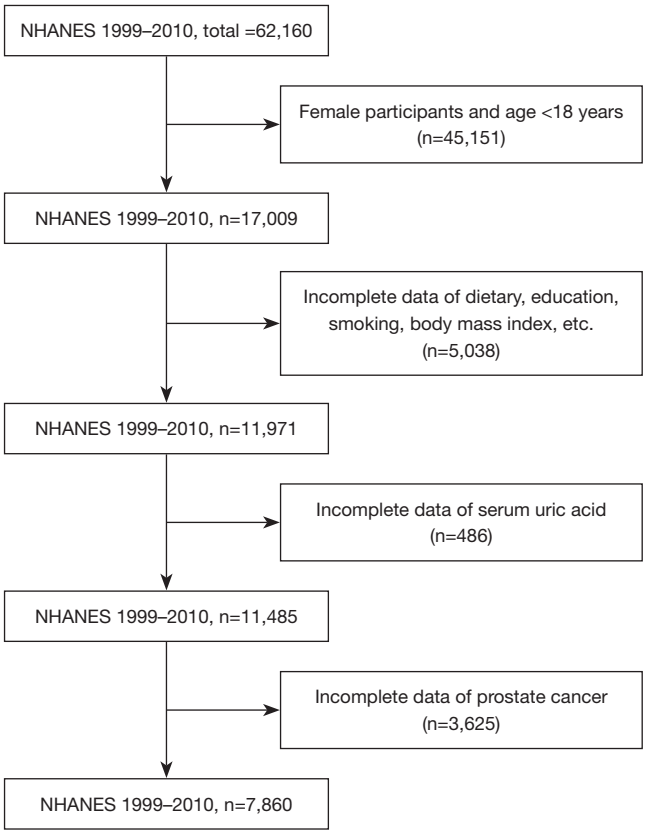

Figure 1 Flowchart of the sample selection from NHANES 1999–2010. NHANES, National Health and Nutrition Examination Survey.

was divided into three categories, including <25, ≥25 and <30, and ≥30 kg/m^2. Health conditions included in the present study were self-report of diabetes (yes, no, or borderline), hypertension (yes or no), alcohol intake (yes or no) and smoking (yes or no). Total energy intake, protein intake, carbohydrate intake and total fat intake were also included.

Statistical analysis

Sample weights, strata, and main sampling units were taken into account while adjusting the analysis of the current study. The Kruskal Wallis Rank Test for continuous variables and the Chi-squared test for categorical variables were used to compare non-prostate cancer and prostate cancer groups. The independent association between SUA and prostate cancer was assessed using multivariate logistic regression analysis. There was no adjustment for any con-founders in Model 1. The analyses were carried out without (Model 1) and with (Model 2) adjustments for confounders. The variables included as adjustments were age, race, educational level, PIR, BMI, diabetes, hypertension, smoking status, alcohol consumption, intake of energy (kcal/day), protein (g/day), carbohydrate (g/day) and fat (g/day). Subgroup analyses were stratified by age, BMI, hypertension, and diabetes. All statistical analyses and visualization were based on R 4.1.2 software. A P<0.05 was considered statistically significant.

Results

Baseline characteristics

Among the 7,860 individuals in our research, 315 (4%) had a diagnosis of prostate cancer. *Table 1* presents the baseline characteristics of the respondents categorized by prostate cancer status.

Individuals in the prostate cancer group were more likely to be older than those in the non-prostate cancer group {73 [interquartile range (IQR), 66–79] *vs.* 53 (IQR, 45–63) years, P<0.001}. Furthermore, the prostate cancer group had a greater percentage of hypertension (51% *vs.* 37%, P<0.001) and a reduced total energy intake [1,979 (IQR, 1,504–2,477) *vs.* 2,315 (IQR, 1,755–3,004) kcal, P<0.001], a lower protein intake [79 (IQR, 58–102) *vs.* 89 (IQR, 65–117) g, P<0.001], a lower carbohydrate intake [238 (IQR, 175–301) *vs.* 267 (IQR, 196–357) g, P<0.001] and a lower fat intake [74 (IQR, 53–102) *vs.* 87 (IQR, 58–120) g, P<0.001]. The median SUA levels were 5.9 mg/dL in the prostate cancer group and 6.0 mg/dL in the non-prostate cancer group.

SUA and prostate cancer

In the unadjusted analysis, SUA was not significant associated with prostate cancer [Model 1, odds ratio (OR) 0.94, 95% confidence interval (CI): 0.85–1.03, P=0.19]. After the fully adjustments for confounders, SUA was not significantly associated with prostate cancer (Model 2, OR 0.91, 95% CI: 0.82–1.00, P=0.058).

Subgroup analyses

We further conducted subgroup analyses stratified by age, BMI, hypertension, and diabetes. Among those younger than 60 years (<60 years), SUA was significantly associated with prostate cancer (Model 1, OR 1.41, 95% CI: 1.02–1.94, P=0.036). However, in Model 2, which had been fully adjusted for all confounders, this correlation was

Table 1 Baseline characteristics of NHANES participants, 1999–2010

Characteristics	Prostate cancer (n=315)	Non-prostate cancer (n=7,545)	P values
Age, years	73 [66–79]	53 [45–63]	<0.001
Age, years			<0.001
<60	14 [9]	3,961 [68]	
≥60	301 [91]	3,584 [32]	
Race			0.12
Non-Hispanic White	204 [82]	4,155 [78]	
Other race	111 [18]	3,390 [22]	
Poverty-income ratio	3.38 [1.97–5.00]	3.60 [1.95–5.00]	0.96
Education			0.54
Less than high school	94 [21]	2,388 [19]	
High school	65 [23]	1,749 [25]	
Above high school	156 [56]	3,408 [56]	
BMI, kg/m^2	27.7 [25.1–30.6]	28.1 [25.3–31.5]	0.16
BMI, kg/m^2			0.58
<25	79 [24]	1,831 [23]	
≥25 and <30	134 [45]	3,200 [43]	
≥30	102 [31]	2,514 [34]	
Smoking			0.74
Yes	192 [61]	4,712 [60]	
No	123 [39]	2,833 [40]	
Alcohol intake			0.009
Yes	238 [76]	6,180 [83]	
No	77 [24]	1,365 [17]	
Hypertension			<0.001
Yes	186 [51]	3,124 [37]	
No	129 [49]	4,421 [63]	
Diabetes			0.76
Yes	48 [11]	1,117 [11]	
No	259 [86]	6,260 [87]	
Borderline	8 [3]	168 [2]	
Total energy, kcal	1,979 [1,504–2,477]	2,315 [1,755–3,004]	<0.001
Protein, g	79 [58–102]	89 [65–117]	<0.001
Carbohydrate, g	238 [175–301]	267 [196–357]	<0.001
Fat, g	74 [53–102]	87 [58–120]	<0.001
Serum uric acid, mg/dL	5.90 [5.20–6.90]	6.00 [5.20–6.90]	0.35

The values are presented as weighted median [interquartile range] or unweighted counts [weighted %]. NHANES, National Health and Nutrition Examination Survey; BMI, body mass index.

Table 2 ORs and 95% CIs for the associations between serum uric acid and prostate cancer

Population	Model 1		Model 2	
	OR (95% CI)	P values	OR (95% CI)	P values
General population	0.94 (0.85–1.03)	0.19	0.91 (0.82–1.00)	0.058
Age				
<60 years	1.41 (1.02–1.94)	0.04	1.29 (0.69–2.42)	0.42
≥60 years	0.88 (0.81–0.96)	0.003	0.88 (0.80–0.96)	0.003
BMI, kg/m^2				
<25	1.09 (0.85–1.39)	0.48	0.95 (0.74–1.22)	0.66
≥25 and <30	0.97 (0.83–1.13)	0.69	0.90 (0.77–1.07)	0.23
≥30	0.82 (0.67–1.01)	0.059	0.87 (0.72–1.04)	0.13
Hypertension				
Yes	0.89 (0.77–1.03)	0.11	0.92 (0.80–1.05)	0.23
No	0.91 (0.76–1.09)	0.31	0.89 (0.74–1.07)	0.21
Diabetes				
Yes	0.94 (0.77–1.15)	0.52	0.88 (0.70–1.10)	0.26
No	0.94 (0.84–1.05)	0.29	0.91 (0.81–1.02)	0.11

Model 1: no covariates were adjusted. Model 2: age, race, educational level, poverty-income ratio, BMI, diabetes, hypertension, smoking status, alcohol intake, intake of energy, protein, carbohydrate and fat were adjusted. In the subgroup analyses, the Model 2 was not adjusted for the stratification variable itself. OR, odds ratio; CI, confidence interval; BMI, body mass index.

not significant (OR 1.29, 95% CI: 0.69–2.42, P=0.42). In participants aged 60 years and above (≥60 years), SUA was associated with a lower risk of prostate cancer (Model 1, OR 0.88, 95% CI: 0.81–0.96, P=0.003). Interestingly, after complete adjustment for confounders, this negative correlation remained unchanged (Model 2, OR 0.88, 95% CI: 0.80–0.96, P=0.003).

In the subgroup analysis stratified by BMI, hypertension, and diabetes, no significant correlation was found between SUA and prostate cancer. Detailed data can be found in *Table 2*.

Discussion

The current study examined the relationship between SUA and prostate cancer using a large cross-sectional design that is nationally representative. In this present study, we found that SUA was inversely correlated with prostate cancer in men aged 60 years or older, but not significant in the younger group (<60 years) or in all participants, indicating that SUA may have a protective role in prostate cancer of older adults.

Previous observational studies on the association of SUA and prostate cancer showed conflicting findings. An association between higher SUA levels and decreased risk of prostate cancer was found in studies conducted in Turkey (17) and India (18), which is consistent with our findings. However, several research from Heidelberg (14), Baltimore (13) and European-based Mendelian randomization (16) concluded that there was no relationship between SUA and the incidence of prostate cancer. Additionally, studies utilizing populations from Sweden (22), Japan (8,23), and Korea (12) revealed a positive association between SUA and prostate cancer. The following explanations might account for this contradicting outcome. Many observational studies have rigorously controlled for confounding variables, however, there may still be some unmeasured or unknown variables that affect the results (12-14,23). Moreover, a small number of prostate cancer cases or a short follow-up period in some observational studies may cause a loss of this association (17,18). Furthermore, the distinct features of the genome and prostate cancer among populations in Europe, North America, and East Asia may contribute to this difference.

Li *et al.* (24) showed that only gout and nephrolithiasis had convincing evidence of a clear association among the 136 health outcomes linked to SUA levels that were examined in meta-analyses of observational studies, meta-analyses of randomized controlled trials, and Mendelian randomization studies.

Uric acid plays a crucial role in preventing the production of free oxygen radicals and lipid peroxidation, and it has significant antioxidant and anti-cancer properties (14,25,26). Indeed, upregulated oxidative stress profiles and compromised antioxidant defense systems may play a role in men with prostate cancer (27). Moreover, higher levels of SUA were associated with a lower risk of mortality from overall cancer (28). Although the precise mechanism is not yet clear, uric acid may regulate tumor occurrence and development by modulating fructose metabolism, Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) pathway, inflammation, mammalian target of rapamycin (mTOR)/serine threonine protein kinase (AKT) pathway and xanthine oxidoreductase receptor (6,28). Allopurinol is commonly used to treat hyperuricemia. Using data from Taiwan, Lai *et al.* (29) showed that prostate cancer patients had a 1.42-fold higher likelihood of exposure to allopurinol compared to non-prostate cancer patients. There might be a relationship between allopurinol usage, low SUA levels, and prostate cancer.

Our study has several restrictions. Due to the cross-sectional nature of this investigation, a potential causal relationship between prostate cancer and SUA could not be established. The characteristics of prostate cancer were unclear, and the diagnosis was primarily based on self-report. The dataset used in this study [1999–2010] is relatively old and lacks information on the severity/clinical significance of prostate cancer. Furthermore, the likelihood of diagnosis of non-clinically significant prostate cancer was higher in that era due to screening trends. In this study, the population from the United States was the only ethnic group analyzed. The association between SUA and prostate cancer exhibits a wide range of complexities, necessitating the conduction of an extensive analysis encompassing larger sample sizes and diverse populations to derive more comprehensive conclusions.

Conclusions

In summary, our research demonstrated a strong correlation between elevated SUA levels and a lower risk of prostate cancer in men aged 60 years and up. SUA is a simple and noninvasive indicator obtained from routine blood tests that should be completely included into prostate cancer care. Larger-scale cohort studies with longer follow-up times are required to validate this association in the future.

Acknowledgments

Funding: This work was supported by the National Natural Science Foundation of China (Grant Nos. 82072833 and 82272864 to H.P.).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-46/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-46/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-46/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.

2. Pérez-Gómez JM, Montero-Hidalgo AJ, Fuentes-Fayos AC, et al. Exploring the role of the inflammasomes on prostate cancer: Interplay with obesity. Rev Endocr Metab Disord 2023;24:1165-87.
3. Sathianathen NJ, Konety BR, Crook J, et al. Landmarks in prostate cancer. Nat Rev Urol 2018;15:627-42.
4. Bergengren O, Pekala KR, Matsoukas K, et al. 2022 Update on Prostate Cancer Epidemiology and Risk Factors-A Systematic Review. Eur Urol 2023;84:191-206.
5. Luo Z, Wang W, Xiang L, et al. Association between the Systemic Immune-Inflammation Index and Prostate Cancer. Nutr Cancer 2023;75:1918-25.
6. Allegrini S, Garcia-Gil M, Pesi R, et al. The Good, the Bad and the New about Uric Acid in Cancer. Cancers (Basel) 2022;14:4959.
7. Fini MA, Elias A, Johnson RJ, et al. Contribution of uric acid to cancer risk, recurrence, and mortality. Clin Transl Med 2012;1:16.
8. Deng Y, Huang J, Wong MCS. Association between serum uric acid and prostate cancer risk in East Asian populations: a Mendelian randomization study. Eur J Nutr 2023;62:1323-9.
9. Mi N, Huang J, Huang C, et al. High serum uric acid may associate with the increased risk of colorectal cancer in females: A prospective cohort study. Int J Cancer 2022;150:263-72.
10. Yang J, Wang Y, Zhao Q, et al. Association of serum uric acid with increased risk of cancer among hypertensive Chinese. Int J Cancer 2017;141:112-20.
11. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med 2008;359:1811-21.
12. Kim YR, Choi CK, Lee YH, et al. Association between Albumin, Total Bilirubin, and Uric Acid Serum Levels and the Risk of Cancer: A Prospective Study in a Korean Population. Yonsei Med J 2021;62:792-8.
13. Wang A, Barber JR, Tin A, et al. Serum Urate, Genetic Variation, and Prostate Cancer Risk: Atherosclerosis Risk in Communities (ARIC) Study. Cancer Epidemiol Biomarkers Prev 2019;28:1259-61.
14. Kühn T, Sookthai D, Graf ME, et al. Albumin, bilirubin, uric acid and cancer risk: results from a prospective population-based study. Br J Cancer 2017;117:1572-9.
15. Kuo CF, Luo SF, See LC, et al. Increased risk of cancer among gout patients: a nationwide population study. Joint Bone Spine 2012;79:375-8.
16. Jiang M, Ren L, Chen S, et al. Serum Uric Acid Levels and Risk of Eight Site-Specific Cancers: A Mendelian Randomization Study. Front Genet 2021;12:608311.
17. Benli E, Cirakoglu A, Ayyıldız SN, et al. Comparison of serum uric acid levels between prostate cancer patients and a control group. Cent European J Urol 2018;71:242-7.
18. Singh S, Jaiswal S, Faujdar G, et al. Comparison of serum uric acid levels between localised prostate cancer patients and a control group. Urologia 2024. [Epub ahead of print]. doi: 10.1177/03915603241228892.
19. Mirel LB, Mohadjer LK, Dohrmann SM, et al. National Health and Nutrition Examination Survey: estimation procedures, 2007-2010. Vital Health Stat 2 2013;(159):1-17.
20. Nguyen S, Choi HK, Lustig RH, et al. Sugar-sweetened beverages, serum uric acid, and blood pressure in adolescents. J Pediatr 2009;154:807-13.
21. Wang J, Zhou J, Shao Z, et al. Association between serum uric acid and homocysteine levels among adults in the United States: a cross-sectional study. BMC Cardiovasc Disord 2023;23:599.
22. Östman JR, Pinto RC, Ebbels TMD, et al. Identification of prediagnostic metabolites associated with prostate cancer risk by untargeted mass spectrometry-based metabolomics: A case-control study nested in the Northern Sweden Health and Disease Study. Int J Cancer 2022;151:2115-27.
23. Kolonel LN, Yoshizawa C, Nomura AM, et al. Relationship of serum uric acid to cancer occurrence in a prospective male cohort. Cancer Epidemiol Biomarkers Prev 1994;3:225-8.
24. Li X, Meng X, Timofeeva M, et al. Serum uric acid levels and multiple health outcomes: umbrella review of evidence from observational studies, randomised controlled trials, and Mendelian randomisation studies. BMJ 2017;357:j2376.
25. Nakayama A, Kurajoh M, Toyoda Y, et al. Dysuricemia. Biomedicines 2023;11:3169.
26. Dziaman T, Banaszkiewicz Z, Roszkowski K, et al. 8-Oxo-7,8-dihydroguanine and uric acid as efficient predictors of survival in colon cancer patients. Int J Cancer 2014;134:376-83.
27. Oh B, Figtree G, Costa D, et al. Oxidative stress in prostate cancer patients: A systematic review of case control studies. Prostate Int 2016;4:71-87.
28. Taghizadeh N, Vonk JM, Boezen HM. Serum uric acid levels and cancer mortality risk among males in a large general population-based cohort study. Cancer Causes Control 2014;25:1075-80.
29. Lai SW, Kuo YH, Liao KF. Allopurinol and the risk of prostate cancer. Postgrad Med J 2020;96:102.

Cite this article as: Yan W, Xiang P, Liu D, Zheng Y, Ping H. Association between the serum uric acid levels and prostate cancer: evidence from National Health and Nutrition Examination Survey (NHANES) 1999–2010. Transl Cancer Res 2024;13(5):2308-2314. doi: 10.21037/tcr-24-46

