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Serum urate, genetic variation, and prostate cancer risk: Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background: Evidence is mounting that intraprostatic inflammation influences prostate cancer development. Uric acid crystals depositing in the prostate could result in injury and inflammation increasing prostate cancer risk.

Methods: Included were 6,574 men aged 45–64 years who enrolled in ARIC in 1987–1989. We used Cox proportional hazards regression to estimate the association of serum urate concentration alone, and to improve accuracy, jointly with a genetic risk score (GRS, N=4,983) derived from variants predictive of urate concentration, with prostate cancer (N=813) risk.

Results—Serum urate concentration or joint categories of urate concentration and GRS were not associated with prostate cancer risk (p-trend for quartiles=0.3). Results were generally similar by race and after excluding users of medications that influence uric acid.

Conclusions—Serum urate alone and with a urate-associated GRS were not associated with prostate cancer risk.

Impact—It is unlikely that circulating urate concentration influences prostate cancer development.

Keywords

urate; prostate cancer; genetic

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INTRODUCTION

Evidence is mounting that chronic inflammation influences prostate cancer development (1). Some studies have observed that uric acid is associated with chronic prostatitis, often an inflammatory condition (2). Therefore, urate crystals that deposit in the prostate could be one potential source of prostatic injury and inflammation that may lead to prostate cancer.

Urate crystals from multiple sources may deposit in the prostate. One source is urine reflux (1), which cannot be feasibly studied in a population-based cohort study. Analogous to hyperuricemia, gout, and the joints, another possible source of urate crystal deposition in the prostate is from the circulation; this source can be easily measured by serum urate concentration (3).

Thus, we evaluated the association between serum urate concentration and prostate cancer risk among men in the Atherosclerosis Risk in Communities (ARIC) study. To reflect usual lifetime urate exposure, we evaluated the association of a genetic risk score (GRS) derived from 3 variants associated with serum urate concentration and gout (4), in combination with serum urate, in relation to prostate cancer risk.

METHODS

Men aged 45–64 years in 1987–1989 enrolled in ARIC without any cancer history were included. We used calibrated urate concentration previously measured in serum from Visits 1 and 2, self-reported gout diagnosis and urate-influencing medications use at Visit 1 (4,5). We calculated a GRS from rs16890979 at *SLC2A9*, rs2231142 at *ABCG2*, and rs1165205 at *SLC17A3* by summing the number of alleles associated with higher urate concentration across the three SNPs (unweighted) or by summing the products of the number of alleles and the previously published betas for their association with urate concentration (4) across the three SNPs (weighted). Prostate cancer cases were ascertained through 2012 by cancer registry linkage supplemented with medical records (6).

Cox proportional hazards regression was used to estimate multivariable-adjusted hazard ratios (HR) of total (N=813), lethal (first primary with distant metastasis at diagnosis or led to prostate cancer death as the underlying cause; N=94), and fatal (prostate cancer death as the underlying cause, regardless of whether a first primary; N=59) prostate cancer in relation to urate quartiles (time-varying); hyperuricemia (≥7 mg/dL; time-varying); gout; GRS quartiles; and joint categories of urate (<5.8, ≥5.8 mg/dL) and GRS (tertiles ½, tertile 3) to improve the accuracy of urate classification. In a subanalysis, we excluded (N=330) men using urate-influencing medications, such as thiazides, allopurinol, and uricosurics. We repeated the analyses stratified by race.

For a 2-sided test with alpha=0.05 and power=80%, we could detect HRs ≥1.37 (black ≥1.77, white ≥1.45) comparing Q4 versus Q1 of serum urate or higher urate*higher GRS versus lower urate*lower GRS, or comparing hyperuricemia versus normal. For lethal and fatal disease, we could detect large HRs of ≥2.42 and ≥3.11, respectively.

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RESULTS

Overall, 6,574 men (mean age=54 years) were included. Of them, 23.2% (N=1,523) were black men, who were more likely to have diabetes, and less likely to use aspirin and statins and to have health insurance compared to white men. Urate quartiles and hyperuricemia were not significantly associated with total (P-trend=0.3; HR=0.94, 95% CI 0.79–1.12; Table 1), lethal (P-trend=0.8; HR=0.86, 95% CI 0.50–1.48) or fatal (P-trend=0.9; HR=0.77, 95% CI 0.43–1.39) prostate cancer. These patterns were generally present in black and white men, with one exception: in black men, non-significant HRs of fatal disease >1.00 in the top 3 quartiles of serum urate (Q2–4 versus Q1: HR=2.66, 95% CI 0.90–7.86), although hyperuricemia was not associated (HR=1.07, 95% CI 0.47–2.44). Results were similar after excluding urate-influencing medication users (total: P-trend=0.4, hyperuricemia HR=0.97, 95% CI 0.80–1.17; lethal: P-trend=0.6, HR=0.98, 95% CI 0.57–1.68; fatal: P-trend=0.9, HR=0.84, 95% CI 0.46–1.53). Patterns by race were similar to those when not excluding medication users. A self-reported gout diagnosis was not significantly associated with prostate cancer overall or by race (HRs 0.61–1.10).

Among 4,953 men (75.8%) who provided consent for genetic research and had values in urate-association variants, neither unweighted nor weighted GRS were associated with total, lethal, or fatal prostate cancer overall or by race (per allele increase, HRs 0.85–1.09, all P-trend>0.1). Joint categories of urate or hyperuricemia and GRS were not associated with risk overall (Table 2) or by race (e.g., hyperuricemia*higher unweighted GRS vs normal*lower GRS: black, HR=1.02, 95% CI 0.64–1.62, white, HR=1.11, 95% CI 0.76–1.63). Joint categories were not significantly associated with lethal or fatal disease overall or by race.

DISCUSSION

In this first study to investigate serum urate in combination with variants in genes predictive of urate concentration in relation to prostate cancer, no association between urate measures and prostate cancer risk was observed overall or in black or white men, though the power to detect a slight difference may be limited after stratification. Our findings are consistent with previous studies investigating serum urate and prostate cancer (7,8). Taken together with previous evidence, serum urate is unlikely to influence prostate cancer development.

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Table 1.

Serum uric acid concentration and prostate cancer risk, 6,574 men in the ARIC study, 1987–2012

	Overall			White men			Black men		
	Person-years	**HR***	**(95%CI)**	**Person-years**	**HR**	**(95%CI)**	**Person-years**	**HR**	**(95%CI)**
Quartiles**									
1st (< 5mg/dL)	29,629	1	(Ref)	23,783	1	(Ref)	5,847	1	(Ref)
2nd (5.0–5.7 mg/dL)	30,604	0.92	(0.75–1.11)	25,133	1.00	(0.80–1.26)	5,471	0.73	(0.50–1.06)
3rd (5.8–6.7 mg/dL)	31,348	0.89	(0.73–1.08)	25,328	0.90	(0.71–1.14)	6,020	0.85	(0.59–1.21)
4th (≥ 6.8 mg/dL)	27,393	0.89	(0.73–1.10)	19,616	0.89	(0.68–1.15)	7,776	0.86	(0.61–1.22)
P-trend			0.3			0.2			0.7
Quartiles collapsed									
1st (< 5mg/dL)	29,629	1	(Ref)	23.783	1	(Ref)	5,847	1	(Ref)
2nd–4th (≥ 5.0 mg/dL)	89,345	0.90	(0.76–1.06)	70,076	0.94	(0.77–1.14)	19,269	0.82	(0.61–1.09)
Uric acid cutpoint									
Normal (< 7 mg/dL)	95,621	1	(Ref)	77,345	1	(Ref)	18,275	1	(Ref)
Hyperuricemia (≥ 7 mg/dL)	23,354	0.94	(0.79–1.12)	16,513	0.89	(0.70–1.12)	6,840	1.01	(0.77–1.34)

*Model adjusted for age (continuous), joint race by center (White from Minnesota; White from Washington Co. or Forsyth Co.; Black from Jackson; Black from Washington Co. or Forsyth Co.), education (<high school, high school with some college, college graduate), height (continuous), updated body mass index (BMI, kg/m^2, continuous), updated cigarette smoking status (current/former smoker who quit <10 years ago; former smoker who quit ≥10 years ago, never smoker), updated diabetes status (no diabetes, pre-diabetes, undiagnosed diabetes, diagnosed diabetes), updated aspirin use, and updated statin use.

**Serum uric acid was available at visits 1 and 2 and were updated in the model. Quartiles based on visit 1 serum uric acid concentration distribution

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Table 2:

Joint serum uric acid concentration and genetic risk score (GRS) categories and prostate cancer risk, 4,983 men in the ARIC study, 1987–2012

	Overall			White men			Black men		
Joint categories**	**Person-years**	**HR***	**(95%CI)**	**Person-years**	**HR**	**(95%CI)**	**Person-years**	**HR**	**(95%CI)**
Unweighted GRS:									
Lower uric acid/Lower GRS	35,540	1	(ref)	30,213	1	(ref)	5,327	1	(ref)
Lower uric acid/Higher GRS	11,492	1.03	(0.81–1.32)	9,176	1.13	(0.85–1.51)	2,316	0.79	(0.48–1.29)
Higher uric acid/Lower GRS	31,345	0.94	(0.78–1.13)	24,947	0.93	(0.74–1.17)	6,397	0.89	(0.63–1.27)
Higher uric acid/Higher GRS	14,264	1.04	(0.83–1.31)	11,070	1.09	(0.83–1.43)	3,194	0.88	(0.58–1.35)
Normal/Lower GRS	55,222	1	(ref)	46,499	1	(ref)	8,723	1	(ref)
Normal/Higher GRS	19,524	1.03	(0.85–1.25)	15,731	1.16	(0.93–1.45)	3,794	0.73	(0.49–1.08)
Hyperuricemia/Lower GRS	11,663	0.92	(0.72–1.18)	8,662	1.03	(0.76–1.39)	3,001	0.71	(0.46–1.08)
Hyperuricemia/Higher GRS	6,231	1.12	(0.84–1.50)	4,515	1.11	(0.76–1.63)	1,716	1.02	(0.64–1.62)
Weighted GRS:									
Lower uric acid/Lower GRS	36,331	1	(ref)	30,574	1	(ref)	5,757	1	(ref)
Lower uric acid/Higher GRS	10,701	0.96	(0.74–1.24)	8,816	1.07	(0.79–1.44)	1,886	0.67	(0.38–1.17)
Higher uric acid/Lower GRS	31,706	0.93	(0.77–1.12)	24,566	0.93	(0.74–1.16)	7,140	0.87	(0.62–1.22)
Higher uric acid/Higher GRS	13,902	1.01	(0.80–1.28)	11,451	1.04	(0.79–1.37)	2,451	0.88	(0.56–1.39)
Normal/Lower GRS	56,138	1	(ref)	46,671	1	(ref)	9,466	1	(ref)
Normal/Higher GRS	18,609	0.98	(0.80–1.20)	15,558	1.09	(0.87–1.36)	3,051	0.69	(0.45–1.07)
Hyperuricemia/Lower GRS	11,899	0.92	(0.72–1.17)	8,468	1.01	(0.74–1.37)	3,430	0.76	(0.51–1.12)
Hyperuricemia/Higher GRS	5,995	1.10	(0.81–1.49)	4,709	1.09	(0.75–1.59)	1,286	1.02	(0.60–1.72)

*Model adjusted for age (continuous), joint race by center (White from Minnesota; White from Washington Co. or Forsyth Co.; Black from Jackson; Black from Washington Co. or Forsyth Co.), education (<high school, high school with some college, college graduate), height (continuous), updated body mass index (BMI, kg/m^2, continuous), updated cigarette smoking status (current/former smoker who quit <10 years ago; former smoker who quit ≥10 years ago, never smoker), updated diabetes status (no diabetes, pre-diabetes, undiagnosed diabetes, diagnosed diabetes), updated aspirin use, and updated statin use.

**Lower uric acid: below the median concentration of 5.8 mg/dL; higher uric acid: at or above the median concentration; normal: < 7 mg/dL; hyperuricemia: ≥ 7 mg/dL; lower GRS: bottom and middle tertiles; higher GRS: top tertile.

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