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Association between serum uric acid and prostate cancer risk: The modifying role of *CTGF* genotype

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Abstract

Background: The role of uric acid in prostate cancer risk remains uncertain, with evidence suggesting both carcinogenic and protective effects. Genetic factors may be key modifiers of this association. **Objective:** This study aimed to determine whether the relationship between uric acid and prostate cancer risk differs by the *rs9399005* genotype of connective tissue growth factor (*CTGF*). **Methods:** We examined 6,259 Japanese-American men in Hawaii, cancer-free at baseline (1965–1968, ages 45–68), who were followed for incident prostate cancer until 1999. Hyperuricemia was defined as serum uric acid ≥7.0 mg/dL. *CTGF* genotypes were classified as common allele homozygotes (CC) or minor allele carriers (T). Cox proportional hazards models estimated hazard ratios (HRs), adjusting for age and potential confounders. **Results:** During a median follow-up of 29.7 years, 285 prostate cancer cases were identified. A significant interaction between *CTGF* and hyperuricemia was observed. Among men with the *CTGF–T* genotype, hyperuricemia was not associated with risk (HR = 0.77, 95% confidence interval [CI]: 0.51–1.17). In contrast, among *CTGF–CC* homozygotes, hyperuricemia was linked to a higher risk (HR = 1.91, 95% CI: 1.21–2.99). Men with both the *CTGF–CC* genotype and hyperuricemia had a higher risk (HR = 1.72, 95% CI: 1.17–2.54) compared with all other subjects. **Conclusion:** The association between uric acid and prostate cancer varied by *CTGF* genotype. Hyperuricemia increased risk among *CTGF–CC* homozygotes, whereas a nonsignificant protective effect was seen among *T* allele carriers. **Relevance to patients:** Monitoring and lowering serum uric acid may help reduce prostate cancer risk in men with the *CTGF–CC* genotype.

Keywords: CTGF; Connective tissue growth factor; Uric acid; Hyperuricemia; Gene-environment interaction; Prostate cancer

1. Introduction

Prostate cancer ranks as the second most frequently diagnosed cancer and the fifth leading cause of cancer-related deaths among men worldwide, with an estimated 1.46 million new cases and 396,000 deaths reported in 2022.[1] Despite its high prevalence and substantial impact on health and quality of life, the underlying causes of prostate cancer remain largely unclear. Established risk factors include advancing age, family history, race or genetic predisposition, a Western diet, and alcohol consumption.[2] Identifying new, and particularly modifiable, risk factors and biomarkers is crucial for improving strategies for prevention, early detection, and treatment.

Uric acid, a by-product of purine metabolism, is a known biomarker of inflammation and can be modified by lifestyle changes.[3-5] It has been studied for its potential role in prostate cancer development.[6-15] However, its association with prostate cancer risk remains inconclusive. Some research suggests that elevated uric acid promotes chronic inflammation and oxidative damage, thereby facilitating tumorigenesis, and finds a positive association with prostate cancer risk.[6,7] Gout, a condition associated with hyperuricemia, has been reported to elevate the risk of prostate cancer.[8] Other studies propose that uric acid functions as an antioxidant, reducing oxidative stress and inflammation, both of which contribute to carcinogenesis, and report an inverse relationship between uric acid levels and prostate cancer incidence.[9-11] Yet other investigations found no significant correlation between uric acid levels and prostate cancer risk, implying that uric acid may not play a critical role in the pathogenesis of prostate cancer.[12-15]

One reason these studies have observed conflicting associations between uric acid and prostate cancer is their reliance on conventional epidemiological frameworks, which typically treat exposures and outcomes as having simple, linear, and independent relationships. Such frameworks typically overlook nonlinear dynamics, especially the interactive effects that contribute to the characterization of biological systems. To address this limitation, we propose employing an integrative modeling approach that simultaneously incorporates genetic susceptibility, uric acid levels, and their gene–environment interactions. This approach would capture more of the underlying complexity and potentially reveal subtler associations between uric acid and prostate cancer risk.

Connective tissue growth factor (CTGF), also known as cellular communication network factor 2 (CCN2), is a secreted protein associated with the extracellular matrix (ECM). CTGF interacts with multiple cell surface receptors, ECM components, and cytokines.[16] Transforming growth factorβ (TGFβ), a pleiotropic cytokine with contextdependent tumorsuppressive and tumorpromoting roles, is implicated in prostate cancer initiation and progression.[17,18] CTGF has been shown to modulate TGFβ signaling, thereby influencing prostate cancer pathogenesis.[19] Notably, TGFβ levels are elevated in hyperuricemic individuals and correlate positively with uric acid concentration.[20] Taken together, these observations suggest that CTGF may modulate the relationship between uric acid and prostate cancer development.

The aim of the present study was to determine whether the relationship between serum uric acid and prostate cancer incidence differs by *CTGF* genotype.

2. Methods

2.1. Study cohort

The Kuakini Japan-Hawaii Cancer Study (Kuakini-JHCS) is based on the Kuakini Honolulu Heart Program (Kuakini-HHP) cohort. The Kuakini-HHP Examination 1 was conducted between 1965 and 1968, recruiting 8,006 American men of Japanese ancestry aged 45–68 years, all of whom were residents of the Hawaiian island of Oahu. The Kuakini-JHCS was initiated during the third examination of the Kuakini-HHP cohort, conducted between 1971 and 1974 (n = 6,860; age range 51–75 years), when the cancer surveillance program was established.[21,22]

2.2. Definition of risk factors and potential confounders

All variables in the present study were measured during the Kuakini-HHP Examination 1.[23] The assay for serum uric acid (non-fasting) was performed using an automatic colorimetric method (Technicon AutoAnalyzer Methodology N-13b) with a phosphotungstic acid reagent. Further details can be found in our earlier publication.[24] Hyperuricemia was defined as a serum uric acid level ≥7.0 mg/dL (≥0.416 mmol/L) at baseline, while levels below this threshold were classified as normouricemia. To assess the association of uric acid concentrations with prostate cancer risk, we also categorized participants into quartiles (Q1-Q4) based on their serum uric acid concentrations. Gout, a condition associated with hyperuricemia, was self-reported at baseline.

Body mass index (BMI) was computed as weight in kilograms divided by height in meters squared. Physical activity index (PAI) was quantified as metabolic output during a typical 24-h period by multiplying a weighting factor by the reported number of hours spent in five activity levels (no activity = 1.0, sedentary = 1.1, slight = 1.5, moderate = 2.4, and heavy = 5.0).[25] Smoking was categorized as either a never smoker or a smoker (including past or current cigarette smoking). Pack-years of cigarette smoking were computed for past and current smokers.

Alcohol intake was calculated based on self-reported usual monthly consumption of beer, wine (including Japanese saké [15% alcohol] and fortified wines [17–20% alcohol]), and spirits (including whiskey, gin, brandy, or other liquor) among current drinkers. The factors used to obtain estimates of alcohol content in all beverages consumed were 3.7% for beer, 10% for wine, and 38% for spirits.

Hypertension was defined as systolic blood pressure (BP) ≥140 mm Hg, diastolic BP ≥90 mm Hg, or the self-reported use of antihypertensive medications. Normal BP (normotension) was defined as systolic BP <140 mm Hg, diastolic BP <90 mm Hg, and not taking antihypertensive medication. The percentage of calories from animal protein was calculated using a 24-h dietary recall by dividing the calories from animal protein by the total calories. More detailed information can be found elsewhere.[26]

2.3. Genotyping

Among the 12 tagging single-nucleotide polymorphisms (SNPs) in *CTGF* that we tested in a previous case–control study for association with longevity, carriers of the minor (*T*) allele of rs9399005 had a significantly longer lifespan.[27] Therefore, rs9399005 was chosen as the SNP of interest for the present study.

Genotyping was performed using DNA extracted from the buffy coat of blood samples collected at Kuakini-HHP Examination 4 (1991–1993), and the samples were kept at –70°C. For participants who did not attend the Kuakini-HHP Examination 4, we used serum samples available from Examination 3. For the latter, DNA was amplified using a combination of QIAmp cell-free DNA isolation followed by REPLI-g Single-Cell WGA and WTA amplification (QIAGEN Sciences, Germantown, MD, USA). Genotyping was performed using TaqMan on an Applied Biosystems QuantStudio 12K Flex system (ThermoFisher Scientific, Waltham, MA, USA).

2.4. Ascertainment of prostate cancer

All incident cancer cases diagnosed between 1965 and 1999 were captured by the Kuakini-JHCS surveillance program. For cancer incidence among subjects who died before or did not participate in the Kuakini-JHCS examination (1971–1974), ascertainment was conducted retrospectively according to the criteria of the Kuakini-JHCS surveillance program when the cancer surveillance program began.[22] Prostate cancer incidence was determined by a physician consensus group using hospital records, tumor registry data, and confirmation through histological evidence. The Kuakini-JHCS surveillance program concluded on December 31, 1999.

2.5. Statistical analysis

Baseline characteristics were compared between subjects with and without hyperuricemia, and with different *CTGF* genotypes: common allele (*C*) homozygotes (genotype *CC*: termed *CTGF–CC*) and minor allele (*T*) carriers (genotypes *CT* or *TT*: termed *CTGF–T*), the latter having been found to be associated with longevity in our previous study.[27] Continuous variables were analyzed using Student's *t*-test, while categorical variables were compared using the χ^2 test.

Cox proportional hazard models were used to assess the association of hyperuricemia and *CTGF* genotype with prostate cancer. The main effects, hazard ratio (HR), and 95% confidence intervals (95% CI) of hyperuricemia and *CTGF* genotype on prostate cancer incidence were estimated using a multivariate Cox proportional hazard model that included hyperuricemia and/or *CTGF* genotype while adjusting for confounders. This model was referred to as the main effect model. The interaction effect of hyperuricemia and *CTGF* genotype was tested using a "full model," which extended the main effect model by including an interaction term between hyperuricemia and *CTGF* genotype. The goodness of fit between the full model and the main effect model was compared using likelihood ratio tests. Stratified analyses were conducted to assess the association between hyperuricemia and prostate cancer within each *CTGF* genotype. The Cox proportional hazard assumption was tested for the stratified Cox models. All tests were two-sided, and a $p<0.05$ was considered statistically significant. All statistical analyses were performed using the Statistical Analysis System version 9.4 (Cary, NC, USA).

3. Results

3.1. Baseline characteristics

From the 8,006 middle-aged men who participated in Kuakini-HHP Examination 1, we excluded 82 men with any type of cancer at baseline, 35 men without uric acid measurements, 1,399 men without *CTGF* rs399005 genotype data, and 231 men who self-reported having a history of gout at baseline. As a result, our analytical sample included 6,259 subjects. Over a median follow-up period of 29.7 years, 285 prostate cancer cases were identified from baseline to December 1999. Table 1 presents the baseline characteristics of subjects by hyperuricemia status and *CTGF* rs399005 genotype. Subjects with hyperuricemia were younger, less physically active, had a higher BMI, had a higher prevalence of hypertension, smoked more cigarettes, drank more alcohol, and had a higher dietary percentage of calories from animal protein intake. However, no baseline variables were associated with the *CTGF* genotype.

Table 1. Baseline characteristics by hyperuricemia status and *CTGF* rs9399005 genotype

Variables	Hyperuricemia status			*CTGF* rs9399005 genotype		
	Yes	No	*p*	*CTGF–CC*	*CTGF–T*	*p*
n	1410	4849		2245	4014	
Continuous variables, mean±SD						
Age (year)	53.5±5.3	54.0±5.4	0.0014*	54.0±5.4	53.9±5.4	0.53
BMI (kg/m^2)	25.0±3.1	23.5±2.9	<0.0001	23.9±3.1	23.8±3.0	0.19
Smoking (pack-years)	23.9±24.3	22.3±23.5	0.031	22.9±23.6	22.5±23.8	0.52
Alcohol intake (oz/month)	20.7±29.7	10.9±19.9	<0.0001	13.4±24.3	12.9±22.1	0.38
Physical activity index	32.4±4.5	33.0±4.5	<0.0001	32.8±4.6	32.9±4.5	0.84
Percentage of calories from animal protein	12.7±4.4	12.4±4.2	0.018	12.4±4.3	12.4±4.2	0.84
Uric acid (mg/dL)	8.0±0.9	5.4±1.0	<0.0001	5.9±1.4	6.0±1.5	0.14
Categorical variables, n (%)						
Smoking status						
Never smoker	431 (30.6)	1530 (31.6)	0.49†	694 (30.9)	1267 (31.6)	0.59
Ever smoker	978 (69.4)	3319 (68.4)		1551 (69.1)	2746 (68.4)	
Missing	1	0		0	1	
Alcohol drinking status						
Non-drinker	391 (27.8)	1886 (38.9)	<0.0001	805 (35.9)	1472 (36.7)	0.51
Drinker	1014 (72.2)	2958 (61.1)		1437 (64.1)	2535 (63.3)	
Missing	5	5		3	7	
Hypertension status						
Normotensive	700 (49.6)	3118 (64.3)	<0.0001	1343 (59.8)	2475 (61.7)	0.15
Hypertensive	710 (50.4)	1731 (35.7)		902 (40.2)	1539 (38.3)	
Missing	0	0		0	0	

Notes: *p-value from t-test for continuous variables; †p-value from χ^2 test for categorical variables.
Abbreviations: BMI: Body mass index; CTGF: Connective tissue growth factor.

3.2. Descriptive data for prostate cancer

Table 2 shows the age-adjusted incidence rates of prostate cancer by hyperuricemia status for the whole cohort and by *CTGF* genotypes. Among men having a *CTGF–T* genotype, hyperuricemia was associated with a lower incidence of prostate cancer compared to normouricemia (12.7 vs. 18.0 cases/10,000 person-years). In contrast, among men with the *CTGF–CC* genotype, hyperuricemia showed an increased prostate cancer incidence compared to normouricemia (25.5 vs. 17.5 cases/10,000 person-years). These data suggest that the association between hyperuricemia and prostate cancer incidence may vary depending on *CTGF* genotype.

Table 2. Age-adjusted incidence rates of prostate cancer (per 10,000 person-years) by hyperuricemia status in the overall cohort and stratified by *CTGF* genotype

Overall/Sub-cohort	Hyperuricemia	Normouricemia	*p*
Overall cohort			
n (cases)	1410 (60)	4849 (225)	
Incidence rate	17.2	17.8	0.99
CTGF–T			
n (cases)	922 (29)	3092 (146)	
Incidence rate	12.7	18.0	0.11
CTGF–CC			
n (cases)	488 (31)	1757 (79)	
Incidence rate	25.5	17.5	0.036

Abbreviation: CTGF: Connective tissue growth factor.

3.3. Main and interaction effects of hyperuricemia and *CTGF* genotype on prostate cancer

Table 3 presents the main and interaction effects of hyperuricemia and *CTGF* genotype on prostate cancer, estimated by: (i) Cox models adjusted for age only and (ii) multivariate Cox models further adjusted for BMI, smoking (pack-years), alcohol intake (oz/month), hypertension, PAI, and percentage of calories from animal protein. At the population level,

neither hyperuricemia (HR = 1.11, 95% CI: 0.82–1.51, p=0.49) nor *CTGF–CC* genotype (HR = 1.11, 95% CI: 0.87–1.42, p=0.39) was significantly associated with prostate cancer in the main effect models. However, the "full model" showed that interaction effects between hyperuricemia and *CTGF* genotype were statistically significant in both the age-adjusted model (p=0.0082) and the fully adjusted model (p=0.010), indicating that the association between hyperuricemia and prostate cancer varies across the *CTGF–CC* and *CTGF–T* genotypes. A significant likelihood-ratio test confirmed that including this interaction substantially improved model fit, making the "full model" the preferred basis for interpretation.

3.4. Association of hyperuricemia and uric acid levels with prostate cancer incidence stratified by *CTGF* genotypes

To illustrate the differing relationships between hyperuricemia, serum uric acid concentration, and prostate cancer risk according to *CTGF* genotype, we conducted genotype-stratified analyses. Table 4 presents HRs and 95% CIs for prostate cancer incidence, comparing: (i) individuals with hyperuricemia versus those with normouricemia, and (ii) participants in the higher serum uric acid quartiles (Q2-Q4) versus those in the lowest quartile (Q1), within each *CTGF* genotype. All estimates were obtained using Cox proportional hazards models adjusted for potential confounders.

Table 3. Main and interaction effects of hyperuricemia and *CTGF* genotype on prostate cancer incidence estimated using Cox models

Model	Main-effect model				Full model		Likelihood ratio test*
	Effect of hyperuricemia		Effect of *CTGF–CC* versus *CTGF–T*		Interaction		
	HR (95% CI)	*p*	HR (95% CI)	*p*	Coefficient	*p*	*p*
1	1.00 (0.75–1.33)	0.99	–	–	–	–	–
2	–	–	1.14 (0.90–1.44)	0.29	–	–	–
3	1.00 (0.75–1.33)	0.98	1.14 (0.90–1.44)	0.29	0.78	0.0082	0.0083
4	1.11 (0.82–1.50)	0.50	–	–	–	–	–
5	–	–	1.11 (0.87–1.42)	0.40	–	–	–
6	1.11 (0.82–1.51)	0.49	1.11 (0.87–1.42)	0.39	0.76	0.010	0.011

Notes: Model 1: Hyperuricemia, adjusted for age; Model 2: *CTGF* genotype, adjusted for age; Model 3: Hyperuricemia and *CTGF* genotype, adjusted for age; Model 4: Hyperuricemia, adjusted for age and confounders (BMI, smoking, alcohol intake, hypertension, physical activity, percentage of calories from animal protein); Model 5: *CTGF* genotype, adjusted for age and confounders; Model 6: Hyperuricemia and *CTGF* genotype, adjusted for age and confounders. *p-value of the test for goodness of fit between the full model and the main-effect model. The terms "main effect" and "interaction effect" refer to statistical associations and are not intended to imply causality.
Abbreviation: CTGF: Connective tissue growth factor.

Table 4. Association of hyperuricemia and quartiles of uric acid with prostate cancer incidence in the whole cohort and each *CTGF* genotype

Uric acid	Whole cohort		*CC* (*n*=2,245)		*CT* (*n*=2,977)		*TT* (*n*=1,037)		*T* (*n*=4,014)	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Hyperuricemia status										
Normouricemia (ref)	1		1		1		1		1	
Hyperuricemia (≥0.416 mmol/L)	1.11 (0.82–1.50)	0.50	1.91 (1.21–2.99)	0.005	0.69 (0.42–1.12)	0.13	1.06 (0.47–2.42)	0.88	0.77 (0.51–1.17)	0.22
Quartiles of uric acid (mg/dL)										
Q1 (0.7–5.0) (ref)	1		1		1		1		1	
Q2 (5.1–5.8)	1.05 (0.75–1.46)	0.79	0.99 (0.56–1.76)	0.97	1.17 (0.74–1.84)	0.51	0.83 (0.31–2.19)	0.70	1.08 (0.72–1.63)	0.72
Q3 (5.9–6.8)	1.08 (0.77–1.50)	0.66	1.05 (0.59–1.85)	0.87	1.10 (0.69–1.75)	0.69	1.12 (0.47–2.70)	0.80	1.08 (0.72–1.63)	0.71
Q4 (6.9–14.8)	1.11 (0.77–1.59)	0.57	2.01 (1.16–3.50)	0.014	0.66 (0.38–1.16)	0.15	0.97 (0.36–2.58)	0.95	0.73 (0.45–1.18)	0.20
p-value for homogeneity	0.94		0.025		0.21		0.94		0.34	

Notes: HRs and 95% CIs were estimated from multivariate Cox models, adjusted for age, BMI, smoking (pack-years), alcohol intake (oz/month), hypertension, physical activity index, and percentage of calories from animal protein.

Among men with the *CTGF–CC* genotype, hyperuricemia was significantly associated with an increased risk of prostate cancer compared to normouricemic individuals (HR = 1.91, 95% CI: 1.21–2.99, p=0.005). Within this genotype group, only those in the highest serum uric acid quartile (Q4) had a significantly elevated risk relative to Q1 (HR = 2.01, 95% CI: 1.16–3.50, p=0.014). In contrast, participants with the *CTGF–T* genotype showed nonsignificant inverse associations for hyperuricemia (HR = 0.77, 95% CI: 0.51–1.17, p=0.22) and for Q4 versus Q1 (HR = 0.73, 95% CI: 0.45–1.18, p=0.20).

3.5. Relative risk (RR) of prostate cancer for exposure groups defined by the *CTGF* genotype and hyperuricemia

Figure 1 illustrates the adjusted RR of prostate cancer among four exposure groups defined by *CTGF* genotype (*CTGF–CC* and *CTGF–T*) and hyperuricemia status. RRs were estimated using a multivariate Cox model adjusted for potential confounders, with men carrying the *CTGF–T* genotype and normouricemia (normal) serving as the reference group. Notably, individuals with both the *CTGF–CC* genotype and hyperuricemia exhibited the highest prostate cancer risk among all other exposure groups. Specifically, these individuals had a significantly increased risk (HR = 1.72, 95% CI: 1.17–2.54) compared to all other subjects.

4. Discussion

In this study, we first examined whether hyperuricemia (defined as uric acid ≥7.0 mg/dL) and the *CTGF* genotype were independently associated with prostate cancer incidence. Next, we assessed whether the *CTGF* genotype modified the association between hyperuricemia and prostate cancer by testing an interaction between the *CTGF* genotype and hyperuricemia. We found no overall association between hyperuricemia and prostate cancer incidence, consistent with previous studies using simple causeandeffect models.[12-15] The *CTGF* genotype alone likewise showed no independent effect on risk. However, a significant interaction between *CTGF* genotype and hyperuricemia (p=0.010), estimated from the multivariate "full model," indicated that the impact of elevated uric acid on prostate cancer varies by *CTGF2* genotype. Genotype-specific analyses revealed that among men homozygous for the common allele (*C*), hyperuricemia was associated with a 1.91fold increased prostate cancer risk compared to men with normouricemia. In contrast, among carriers of the minor allele (*T*), hyperuricemia exhibited a nonsignificant inverse association. These findings underscore the importance of stratifying analyses by *CTGF* genotype in future studies of uric acid and prostate cancer to avoid obscuring associations within specific subpopulations.

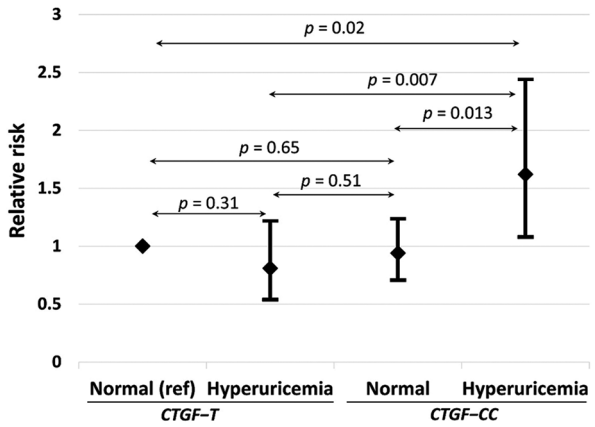

Figure 1. Relative risk of prostate cancer for the exposure groups defined by *CTGF* genotype and hyperuricemia status. The relative risks were estimated from Cox models adjusted for age, BMI, smoking (pack-years), alcohol intake (oz/month), physical activity index, and percentage of calories from animal protein; *CTGF*–T and normouricemia (Normal) were treated as the reference group.
Abbreviations: BMI: Body mass index; CTGF: Connective tissue growth factor.

Notably, neither hyperuricemia nor the *CTGF–CC* genotype alone was associated with prostate cancer risk (Table 3). However, individuals with both hyperuricemia and the *CTGF–CC* genotype exhibited an increased risk (Figure 1). This finding aligns with one of the gene-environment interaction scenarios described by Ottman,[28] where the simultaneous presence of a genetic variant and an environmental factor is required to raise disease susceptibility.

An earlier publication from our group indicated that uric acid was associated with the risk of prostate cancer during the first 10 years of follow-up, but not thereafter.[24] In contrast, the present study's tests of the Cox proportional hazards assumption for hyperuricemia, conducted within each *CTGF* genotype, indicated that the HR for prostate cancer associated with hyperuricemia remained constant throughout the follow-up period.

Our findings have significant clinical relevance. We recommend that clinicians consider genetic testing for *CTGF* in men with hyperuricemia and provide personalized recommendations to mitigate prostate cancer risk. For instance, in men homozygous for the *CTGF* rs9399005 common allele (*C*), lifestyle modifications (such as reducing red meat and sugar consumption, quitting smoking, limiting alcohol intake, and increasing physical activity) should be strongly encouraged, alongside pharmacological interventions such as urate-lowering therapy.

Uric acid is known to exert both antioxidative and pro-inflammatory effects in cancer development. Based on our

observations, we propose a new hypothesis: the impact of uric acid on prostate cancer may be modulated by *CTGF* genotype. In men homozygous for the *CTGF* common allele (*C*), uric acid may act as a pro-inflammatory agent, potentially increasing the risk of prostate cancer. In contrast, among carriers of the *CTGF* minor allele (*T*), uric acid may exert antioxidative effects, serving as a protective factor, or have no significant impact on prostate cancer risk. Antioxidants that can react with molecular oxygen and are reducing agents can act as prooxidants in the event that they become overloaded.

Figure 2 illustrates our interpretation of the effects of the *CTGF* gene on the tumorigenesis of prostate cancer. Soluble uric acid (a metabolic damage-associated molecular pattern, DAMP) activates the NLRP3 inflammasome,[29] causing interleukin-1 beta (IL-1β) release and reactive oxygen species (ROS) generation, which in turn converts latent TGF-β to its active form. Active TGF-β signals through SMAD2/3 to induce *CTGF* (*CCN2*) transcription.[30,31] CTGF is a matricellular factor that strongly induces fibroblast activation (cancer-associated fibroblast, CAF) and ECM deposition and has been implicated in promoting tumor angiogenesis.[32] These stromal changes create a reactive tumor microenvironment (with CAFs, dense ECM, and new vessels) that fosters prostate cancer cell motility and metastatic spread.

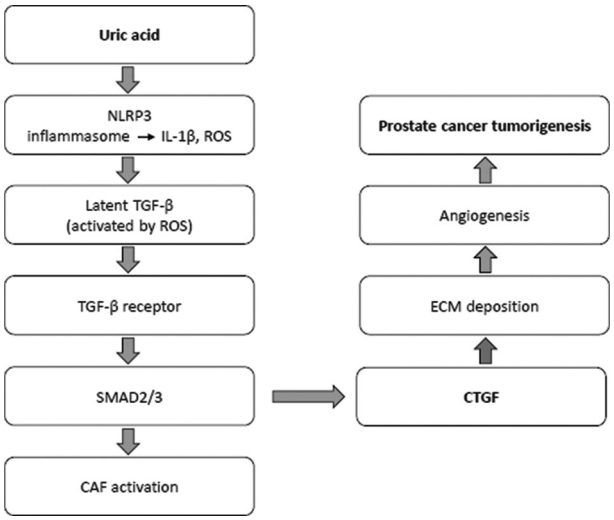

Figure 2. Proposed pathway diagram linking uric acid to *CTGF* expression and prostate cancer risk through TGF-β/SMAD signaling in the tumor microenvironment. Soluble uric acid (a metabolic DAMP) activates the NLRP3 inflammasome, causing IL-1β release and ROS generation, which in turn converts latent TGF-β to its active form. Active TGF-β signals through SMAD2/3 to induce *CTGF* (*CCN2*) transcription. CTGF is a matricellular factor that strongly induces fibroblast (CAF) activation and ECM deposition and has been implicated in promoting tumor angiogenesis. These stromal changes create a reactive tumor microenvironment (with CAFs, dense ECM, and new vessels) that fosters prostate cancer cell motility and metastatic spread. Experimental studies and reviews describe UA as an inflammasome-activating DAMP, TGF-β/SMAD-driven induction of CTGF, and CTGF's roles in fibrosis and angiogenesis. The pro-metastatic effects of CTGF in prostate cancer are supported by reports of enhanced prostate cancer cell migration and bone metastasis. Preclinical efficacy of TGF-βR inhibitors in prostate cancer models is documented. All pathways and interventions shown are grounded in these references.
Abbreviations: CAF: Cancer-associated fibroblast; CTGF: Connective tissue growth factor; DAMP: Damage-associated molecular pattern; ECM: Extracellular matrix; IL-1β: Interleukin-1 beta; ROS: Reactive oxygen species; TGF-β: Transforming growth factor beta.

CTGF plays an integral part in maintaining stem cell niches for hematopoietic stem cells,[33] osteoblasts,[34] and mesenchymal stem cells.[35] We propose that the longevity variant of *CTGF*, rs9399005 (*T*), maintains a healthy stem-cell niche without the toxic environment that would otherwise promote carcinogenesis and malignancy. The longevity variant (*T*) of rs9399005 is predicted to increase the binding of the transcription factor SRF that stimulates both cell proliferation and differentiation.[36] This enhanced binding may contribute to healthier tissue renewal and resistance to oncogenic stress. There should be further research, including studies using cell lines and animal models, to validate this hypothesis and establish a theoretical foundation for developing targeted prevention and treatment strategies.

Several limitations of this study should be acknowledged. The current study was restricted to American men of Japanese ancestry, necessitating replication in other racial groups to validate our findings. In addition, as with other cohort and longitudinal studies involving consecutive examinations, participants who completed the Kuakini-HHP Examinations 3 and 4 (where blood samples were collected for genotyping) were generally healthier than those who did not participate, as noted in a previous publication.[37] Another limitation was the availability of only a single uric acid measurement in this cohort, preventing us from assessing the longitudinal impact of uric acid on prostate cancer incidence.

A key strength of our study is that all participants underwent the same risk factor assessments and were monitored using a standardized surveillance protocol for outcomes. In addition, the large cohort size and long follow-up period further strengthen our findings. The American men of Japanese descent studied were particularly unique, as the genetic homogeneity of Japanese populations is higher than that of most other racial groups.[38] In general, Asian populations exhibit a greater degree of linkage disequilibrium between SNPs, which enhances the identification of genotype-disease associations.[39] Moreover, to the best of our knowledge, our hypothesis has not been tested previously. Furthermore,

our surveillance system was highly comprehensive, supported by the fact that our study was conducted in an island population, which allowed for meticulous follow-up.

5. Conclusion

In this population-based cohort study, we found that the effect of serum uric acid on prostate cancer incidence, whether protective or harmful, varies according to an individual's *CTGF* rs9399005 genotype. Men who were homozygous for the *CTGF* common allele (*C*) and had hyperuricemia exhibited the highest risk of prostate cancer compared to other exposure groups. These findings suggest that lowering uric acid levels in this subgroup may help reduce prostate cancer risk. Further research is needed to confirm these results.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Randi Chen
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Ethics approval and consent to participate

This prospective study was conducted in the Department of Research, Kuakini Medical Center, and was approved by the Institutional Review Board of Kuakini Medical Center (#18-02). Written informed consent was obtained from participants or, when they were unable, from their families or caregivers, for clinical examinations, procedures, and access to medical records for disease surveillance.

Consent for publication

All participants provided written consent for publication of their de-identified data at each Kuakini-HHP examination.

Availability of data

Data used in this work are available from the corresponding author or Dr. Kamal H. Masaki (km1@hawaii.rr.com) upon reasonable request.

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