ARIC Manuscript Proposal # 1519

PC Reviewed: 05/12/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Serum uric acid, genetic variation and risk of prostate cancer: Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Uric acid and prostate cancer

2. Writing Group:

Writing group members: Corinne Joshu, Elizabeth Platz, Angelo De Marzo, Anna Kottgen**,** Aaron Folsom, Josef Coresh, Elizabeth Selvin; other ARIC investigators are welcome

We have sent this proposal to Eric Boerwinkle and Tamra Meyer but have not yet heard back.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. CJ **[please confirm with your initials electronically or in writing]**

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
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3. Timeline: The proposed manuscript is an analysis of existing data. We anticipate it will take 6-12 months from receipt of the data to submission of a manuscript to the ARIC Publications Committee.

4. Rationale:

Our overall hypothesis is that, as in other cancers, chronic inflammation influences the risk of prostate cancer, the most common cancer and second leading cause of cancer death among men in the United States.[1, 2] More specifically, infection or chemical and physical trauma can injure the prostate epithelium and lead to intraprostatic inflammation. We have identified a number of inflammation-associated factors that are also associated with risk of prostate cancer or its recurrence after surgery, including certain sexually transmitted infections, non-use of aspirin, and variants in genes involved in the immune response.[3-6] In this proposal, we focus on a novel hypothesis that uric acid crystals that deposit in the prostate is one potential source of prostatic injury and inflammation that may lead to prostate cancer. We selected uric acid for study because serum uric acid level has been associated with chronic prostatitis, an inflammatory condition.[7-9] Indeed, clinical studies have tested whether allopurinol, a drug used to treat uric acid-associated gout, reduces prostatitis symptoms.[10, 11]

There may be multiple sources of deposited uric acid crystals in the prostate. One source is urine reflux; that is, when urine inadvertently flows from the urethra, which is surrounded by the prostate, into the prostatic ducts that discharge into the urethra. This source of uric acid cannot be feasibly studied in a population-based cohort study. As in gout, another possible source of uric acid deposition is from the circulation. Very few studies have evaluated the association between serum uric acid and prostate cancer incidence; one reported a positive association,[12] and one was null.[13] The only other relevant study reported no association between serum uric acid and death from male genital cancers, the proportion of which were prostate was unspecified.[14] No study has specifically investigated SNPs in genes involved in uric acid transport and excretion in relation to prostate cancer risk.

Here we propose to evaluate the association between serum uric acid level and incident prostate cancer among men in the ARIC cohort. We will also evaluate candidate SNPs in 3 genes, *ABCG2*, *SLC17A3*, which are possibly related to renal urate transport, and *SLC2A9*, which is related to renal fractional excretion of uric acid,[15] in relation to prostate cancer. Evaluation of the SNPs in relation to prostate cancer may better reflect lifetime exposure to uric acid. SNP rs2231142 in *ABCG2*, SNP rs1165205 in *SLC17A3*, and SNP rs16890979 in *SLC2A9* were found to be associated with uric acid concentration and gout in a recent ARIC study.[16]

5. Main Hypothesis/Study Questions:

The overall objective of this proposal is to examine the association between uric acid and prostate cancer among men in the ARIC cohort.

Hypothesis 1: Higher serum uric acid concentration will be associated with increased risk of prostate cancer independent of known and purported prostate cancer risk factors.

Hypothesis 2: SNPs previously associated with higher serum uric acid concentration (e.g., rs16890979 C, rs2231142 T, and rs1165205 A) will be positively associated with prostate cancer risk.

Hypothesis 3: The genetic risk score associated with an increased risk of both serum uric acid concentration and gout (e.g., a greater total number of at-risk alleles, summed from 3 SNPs; rs16890979, rs2231142, and rs1165205) will be associated with an increased risk of prostate cancer.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study Design: Prospective cohort study with Visit 1 as baseline

Inclusion/Exclusion: Women will be excluded as prostate cancer is the outcome of interest. Men with a cancer diagnosis at baseline, those who did not consent to DNA research and those reporting race other than "black" or "white" will be excluded.

Exposures:

(1) Serum uric acid concentration from Visit 1 and Visit 2.

(2) rs16890979, rs2231142, and rs1165205 genotypes and genetic risk score

Outcome: Prostate cancer

Other variables of interest: Age, race, family history of prostate cancer, height, smoking status, body mass index, physical activity, vitamin and mineral supplement use, statin and aspirin use, diabetes and hypertension status, medications influencing uric acid levels (e.g., thiazides, allopurinol, and uricosuric), C-reactive protein (a non-specific serum marker of inflammation), energy intake, intake of tomato products, calcium, fish, total meat, processed meat (including bacon), and alcohol. These factors, some of which are known or suspected prostate cancer risk factors and some are related to uric acid/gout, will be assessed for confounding and effect modification in the analyses below.

Analysis:

(1) Cox proportional hazard regression will be used to calculate the multivariable-adjusted relative risk of incident prostate cancer in relation to serum uric acid concentration expressed based on distributional cutpoints (e.g., quartiles).

(2) Cox proportional hazard regression will be used to calculate the multivariable-adjusted relative risk of incident prostate cancer in relation to each SNP expressed as variant/variant, variant/wild type vs wild type/wild type.

(3) Cox proportional hazard regression will be used to calculate the multivariable-adjusted relative risk of incident prostate cancer in relation to the genetic risk score expressed based on distributional cutpoints.

In secondary analyses:
(1) All analyses will be stratified by race.
(2) Men reporting the intake of medications influencing uric acid levels such as thiazides, allopurinol, and uricosuric medications will be excluded.
(3) Same as 3 above, with high serum uric acid level added to the score as a possible way to decrease misclassification of lifelong exposure to uric acid.

Project Specific Limitations:
We do not have target-organ measurements of uric acid or inflammation as a consequence of uric acid crystals in the prostate. We do not know the etiologically relevant time for measurement of uric acid levels in relation to prostate cancer development.

7.a. Will the data be used for non-CVD analysis in this manuscript? X Yes ____ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? X Yes ____ No
(This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? X Yes ____ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
X Yes ____ No

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
X Yes ____No

9.The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.
ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

X Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

1. #1343 - Stage II of a Genome-Wide Association Study for Genetic Variants Associated with Uric Acid Levels and Gout; published
2. #759 - Serum uric acid and risk of stroke: the ARIC study; published
3. #1077r - Uric Acid and Hypertension; published
4. #1311 - Serum uric acid, lung function and chronic obstructive pulmonary disease in adults, published
5. #525 Elevated uric acid as a risk factor for coronary heart disease: ARIC study; published
6. #313 Association between serum uric acid and asymptomatic carotid atherosclerosis: the ARIC study; published
7. #1078 Metabolic Syndrome and Prostate Cancer Incidence, published
8. # 1444 Adiponectin (ADIPOQ) and adiponectin receptor (ADIPOR1, and
9. ADIPOR2) SNPs and the incidence of cancer: ARIC study
10. # 1280 Interactions between diabetes, diabetes genes, and the androgen receptor gene on risk of prostate cancer.
11. #1229 - Uric Acid & Metabolic Syndrome

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? X Yes ____ No

11.b. If yes, is the proposal

X A. primarily the result of an ancillary study (list number* 1995.04)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

References

1. De Marzo AM, Platz EA, Sutcliffe S, et al. Inflammation in prostate carcinogenesis. *Nat Rev Cancer.* Apr 2007;7(4):256-269.

2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin.* Mar-Apr 2008;58(2):71-96.

3. Wang MH, Helzlsouer KJ, Smith MW, et al. Association of IL10 and other immune response- and obesity-related genes with prostate cancer in CLUE II. *Prostate.* Jun 1 2009;69(8):874-885.

4. Sutcliffe S, Giovannucci E, Gaydos CA, et al. Plasma antibodies against Chlamydia trachomatis, human papillomavirus, and human herpesvirus type 8 in relation to prostate cancer: a prospective study. *Cancer Epidemiol Biomarkers Prev.* Aug 2007;16(8):1573-1580.

5. Sutcliffe S, Giovannucci E, Alderete JF, et al. Plasma antibodies against Trichomonas vaginalis and subsequent risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev.* May 2006;15(5):939-945.

6. Platz EA, Rohrmann S, Pearson JD, et al. Nonsteroidal anti-inflammatory drugs and risk of prostate cancer in the Baltimore Longitudinal Study of Aging. *Cancer Epidemiol Biomarkers Prev.* Feb 2005;14(2):390-396.

7. Hou BS, Xia XY, Pan LJ, et al. [Determination of uric acid in the expressed prostatic secretion of chronic prostatitis patients and its clinical significance]. *Zhonghua Nan Ke Xue.* Mar 2008;14(3):245-247.

8. Motrich RD, Olmedo JJ, Molina R, Tissera A, Minuzzi G, Rivero VE. Uric acid crystals in the semen of a patient with symptoms of chronic prostatitis. *Fertil Steril.* Mar 2006;85(3):751 e751-751 e754.

9. McNaughton CO, Wilt T. Allopurinol for chronic prostatitis. *Cochrane Database Syst Rev.* 2002(4):CD001041.

10. Ziaee AM, Akhavizadegan H, Karbakhsh M. Effect of allopurinol in chronic nonbacterial prostatitis: a double blind randomized clinical trial. *Int Braz J Urol.* Mar-Apr 2006;32(2):181-186.

11. Persson BE, Ronquist G, Ekblom M. Ameliorative effect of allopurinol on nonbacterial prostatitis: a parallel double-blind controlled study. *J Urol.* Mar 1996;155(3):961-964.

12. Kolonel LN, Yoshizawa C, Nomura AM, Stemmermann GN. Relationship of serum uric acid to cancer occurrence in a prospective male cohort. *Cancer Epidemiol Biomarkers Prev.* Apr-May 1994;3(3):225-228.

13. Hiatt RA, Fireman BH. Serum uric acid unrelated to cancer incidence in humans. *Cancer Res.* May 15 1988;48(10):2916-2918.

14. Strasak AM, Rapp K, Hilbe W, et al. Serum uric acid and risk of cancer mortality in a large prospective male cohort. *Cancer Causes Control.* Nov 2007;18(9):1021-1029.

15. Vitart V, Rudan I, Hayward C, et al. SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout. *Nat Genet.* Apr 2008;40(4):437-442.

16. Dehghan A, Kottgen A, Yang Q, et al. Association of three genetic loci with uric acid concentration and risk of gout: a genome-wide association study. *Lancet.* Dec 6 2008;372(9654):1953-1961.