ARIC Manuscript Proposal #2860

1.a. Full Title: Measures of genitourinary and systemic inflammation in relation to prostate cancer risk and mortality in the ARIC cohort study

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

2. Writing Group:
   Writing group members: Marvin Langston, Siobhan Sutcliffe, Anna Prizment, Elizabeth A. Platz, Corinne E. Joshu, ARIC investigators.

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

First author: Marvin Langston
Address: 600 S. Taylor Ave
         2nd floor, 15E, Box 8100
         St. Louis, MO 63110
         Phone: 314-747-7759
         E-mail: langstonm@wudosis.wustl.edu

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).
Name: Elizabeth Platz
Address: Department of Epidemiology
         Johns Hopkins Bloomberg School of Public Health
         615 N. Wolfe St., Room E6132
         Baltimore, MD 21205
         Phone: 410-614-9674
         Fax: 410-614-2632
         E-mail: eplatz1@jhu.edu

3. Timeline: The proposed manuscript is an analysis of existing data. We anticipate that it will take six months from receipt of the data to perform the data analysis and 12 months to prepare the first draft of the manuscript for circulation to the co-authors.
4. **Rationale:**

Inflammation is increasingly believed to contribute to prostate cancer risk and mortality. Inflammation is common in prostate tissue [1-3], particularly in the peripheral zone where prostate cancer tends to develop [4]; it is observed frequently near areas of proliferative atrophy (termed “proliferative inflammatory atrophy” lesions), which have been proposed as markers of the “field effect” of prostate cancer [5]; and it has been shown to induce epithelial hyperproliferation, atrophy, and occasionally dysplasia and prostatic intraepithelial neoplasia in animal model studies [5-7]. In humans, intraprostatic inflammation was also recently observed to be positively associated with high-grade prostate cancer among men without indication for biopsy in the Prostate Cancer Prevention Trial [8]. Finally, tumor-associated intraprostatic inflammation (accompanied sometimes by focal atrophy) has been found to be positively associated with prostate cancer recurrence or death in most [9-13], but not all [14, 15], studies of prostate cancer patients. Together, these findings suggest that intraprostatic inflammation may play a role in prostate carcinogenesis.

Proposed sources of intraprostatic inflammation are numerous and include urine reflux; trapped spermatozoa; dietary factors, such as heterocyclic amines; estrogens; a break in tolerance to prostate antigens; and genitourinary infections [5]. While much research has focused on sexually transmitted infections and prostate cancer [16], considerably less research has examined other genitourinary infections not typically considered to be sexually transmitted, such as *Escherichia coli* infection [17]. This infection is of interest because it is the causative agent of a large proportion of lower urinary tract and kidney infections; it has been shown to induce prostate epithelial proliferation, dysplasia, and DNA damage in rodent models; and it has been detected in malignant prostate tissue in humans [17]. Despite these promising findings, however, *E. coli* infections, including urinary tract and kidney infections, have only been investigated in a few epidemiologic studies to date [18, 19].

In addition to prostate infections, recent findings from the Department of Defense Serum Repository and Prostate Cancer Prevention Trial suggest that prostate inflammation may also result from non-prostate sources. In our Department of Defense Serum Repository study, we found that men who had recently had infectious mononucleosis or other systemic or localized non-genitourinary infections were more likely to have a large and sustained rise in their levels of prostate-specific antigen (PSA), a marker of prostate inflammation, cell damage, and future prostate cancer risk, than men who had not recently been infected [20]. These sustained rises in PSA were observed even though systemic markers of acute inflammation (e.g., C-reactive protein) declined following infection (Milbrandt et al., in preparation). These PSA rises are similar to those observed in men with periodontal disease [21], osteoarthritis [22], and hepatitis [23], as well as in a recent case report of a man with Chikungunya virus infection [24]. Consistent with our PSA findings, we also found that men seropositive for cytomegalovirus (CMV) infection, a common, chronic viral infection of lymphocytes, were more likely to have evidence of prostate inflammation than seronegative men in the Prostate Cancer Prevention Trial (Umbehr et al., in preparation). Together, these findings raise the possibility that overall inflammatory burden, rather than solely genitourinary-specific inflammatory burden, may contribute to prostate cancer risk and mortality.
To further this line of investigation, we propose to take advantage of data already collected in ARIC pertinent to infections and inflammation to examine markers of genitourinary-specific, as well as non-genitourinary-specific inflammation in relation to prostate cancer risk and mortality.

5. Main Hypothesis/Study Questions:
All aims will be performed first in all eligible male ARIC participants and then separately for White and Black men.

   a) To determine whether self-reported history of genitourinary infections (urinary tract and kidney infections) is associated with risk of any prostate cancer, lethal prostate cancer, and fatal prostate cancer.

   b) To determine whether self-reported cumulative burden of chronic, non-genitourinary infections and inflammatory conditions is associated with risk of any prostate cancer, lethal prostate cancer, and fatal prostate cancer. Chronic infections and inflammatory conditions will include hepatitis, tuberculosis, rheumatoid arthritis, gout, pneumonia, bronchitis, sinusitis/sinus infection, colds/minor upper respiratory tract infections, cold sores, shingles, and periodontal disease.

   c) To determine whether self-reported histories of infections and inflammatory conditions from Aims a) and b) are associated with circulating levels of markers of infection and inflammation. Circulating markers of inflammation will include C-reactive protein (CRP) concentration, fibrinogen concentration, white blood cell count, neutrophil count, neutrophil bands, lymphocytes, monocytes, eosinophils, and basophils.

   d) To determine whether a score comprised of the cumulative genitourinary and non-genitourinary infections and inflammatory burden, as measured by both self-reported histories of infections and inflammatory conditions, and circulating markers of infection and inflammation, is associated with risk of any prostate cancer, lethal prostate cancer, and fatal 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**
   We will use a cohort study design for all aims, except for Aim c). This third aim will use a cross-sectional approach. For Aims a), b) and d), baseline will be visit 4.

   **Inclusion/exclusion**
   All eligible male ARIC participants with complete data on inflammation from visit 4 will be included in the analysis for Aims a) and b). Male participants with complete information on inflammation from visit 4 and circulating markers of infection and inflammation from both visits 1 and 2 will be included in the analysis for Aims c) and d). For all aims, participants will be excluded if they were diagnosed with prostate cancer before the date of exposure assessment.

   **Exposure:**
   **Infections and inflammatory conditions**
   Self-reported information on histories of infections and inflammatory conditions will be obtained...
from the inflammation questionnaire and general information questionnaire administered at visit 4. These infections and inflammatory conditions will include urinary tract and kidney infections (Aim a), hepatitis, tuberculosis, rheumatoid arthritis, gout, pneumonia, bronchitis, sinusitis/sinus infection, colds/minor upper respiratory tract infections, cold sores, shingles, and periodontal disease (Aim b). We will investigate the cumulative burden of these infections and inflammatory conditions as a simple sum of all infections/inflammatory conditions considered. We will divide this sum into categories or quantiles, depending on its distribution to provide a ranking of cumulative infectious/inflammatory burden.

**Circulating markers of infection and inflammation**

Circulating fibrinogen and CRP concentrations were measured at visits 1 and 2 respectively. Circulating leukocytes were measured at visits 1 and 2. These include total white blood cell count, neutrophil count, neutrophil bands, lymphocytes, monocytes, eosinophils, and basophils; and derived measures, such as percentage of total white blood cell count, neutrophil to lymphocyte ratio, and band to neutrophil ratio. Aim c will provide a crude evaluation of the correlation between overall self-reported infectious and inflammatory condition burden with circulating markers of inflammation, although we recognize that circulating markers of infection and inflammation were measured before assessment of self-reported histories of infectious and inflammatory conditions (i.e., visit 4 versus visits 1 and 2) and thus some self-reported infections and inflammatory conditions may have developed after visits 1 or 2.

We will divide all circulating markers into categories or quantiles, depending on their distributions. For Aim c), we will explore each marker separately in relation to self-reported infectious and inflammatory burden. For Aim d), we will create a summary score of self-reported infectious and inflammatory conditions, as well as circulating markers of inflammation. We chose to add circulating markers of inflammation to capture unreported current and past infections, and thus to increase the sensitivity of our measure for infectious and inflammatory condition burden. We will incorporate markers of both acute (e.g., neutrophil count) and chronic (e.g., CRP concentration, lymphocyte or monocyte count) inflammation into our score, and will use findings from Aim c) to guide this process. Finally, we will divide our score into categories or quantiles, depending on its distribution, to rank participants by their cumulative infectious/inflammatory burden.

**Outcome:**

Our outcomes will be a diagnosis of any first primary prostate cancer, lethal prostate cancer, and fatal prostate cancer through 2012. We will use the adjudicated prostate cancer case file.

**Other variables of interest:** Age, race, field center, 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, energy intake, intake of tomato products, calcium, fish, total meat, processed meat (including bacon), and alcohol. These factors will be investigated as potential confounders, as well as effect modifiers in the case of race.

**Statistical analysis:**

*Aims a-c:*
We will use Cox proportional hazards regression to estimate minimally- and multivariable-adjusted associations between each exposure and prostate cancer outcome. Participants will contribute time at risk from visit 4 until prostate cancer diagnosis, death, loss to follow-up or administrative censoring in 2012. All models will include terms for age. Confounding will be investigated by adding each covariate individually and in combination to the regression model, and examining its influence on the exposure of interest. Variables found to shift the point estimate for any of the exposures of interest by an appreciable degree (e.g., >10%) will be retained in all models. Analyses will also be performed separately by race, and differences in the magnitude of association by race will be evaluated by including an interaction term(s) between the exposure of interest and race, and determining its significance by the likelihood ratio test. Stratified analyses by aspirin use will also be performed.

**Anticipated methodologic limitations or challenges:**
The focus of our proposal is on the influence of the cumulative burden of genitourinary infections and inflammatory conditions on prostate cancer risk and mortality, rather than on the influence of any one infection, in particular. Therefore, while we recognize that use of self-reported infection history will introduce some degree of exposure misclassification, we believe that participants’ cumulative infectious/inflammatory burden rankings will likely be more accurate, particularly at the extremes of the distribution (i.e., a top to bottom rank comparison will likely compare participants with high to low burden). In addition, we will examine the possible influence of exposure misclassification on our findings by performing sensitivity analyses limited to infections with high to moderate sensitivity in previous validation studies (shingles [25, 26], arthritis [27-29], gout [30], tuberculosis [25], and bronchitis [27, 28, 31], see table below).

<table>
<thead>
<tr>
<th>Infection</th>
<th>Studies</th>
<th>Gold Standard</th>
<th>Sensitivity Range</th>
<th>Specificity Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shingles</td>
<td>[25, 26]</td>
<td>Physician diagnosis or medical records</td>
<td>84-100%</td>
<td>98%</td>
</tr>
<tr>
<td>Arthritis</td>
<td>[27-29]</td>
<td>Physician diagnosis or medical records</td>
<td>56-85%</td>
<td>76-93%</td>
</tr>
<tr>
<td>Gout1</td>
<td>[30]</td>
<td>Discharge diagnosis or medication usage</td>
<td>84-95%</td>
<td>-</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>[25]</td>
<td>Combined medical records and medication usage</td>
<td>89%</td>
<td>-</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>[27, 28, 31]</td>
<td>Physician diagnosis or medical records</td>
<td>32-92%</td>
<td>93-97%</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>[32]</td>
<td>Medical records</td>
<td>8-25%</td>
<td>99-100%</td>
</tr>
<tr>
<td>Urinary tract and kidney infections</td>
<td>[33, 34]</td>
<td>Physician diagnosis or medical records</td>
<td>48-61%</td>
<td>88-89%</td>
</tr>
<tr>
<td>Sinusitis/sinus infection</td>
<td>[33, 34]</td>
<td>Physician diagnosis or medical records</td>
<td>36-57%</td>
<td>89%</td>
</tr>
</tbody>
</table>

**Validity of self-reported genitourinary infections and inflammatory conditions**
Periodontal diseases [35-39] Dental Exam 24-65% 60-94%
Pneumonia\textsuperscript{2} [40] Medical records 47% 77%

\textsuperscript{1}Validated in the ARIC study cohort
\textsuperscript{2}Includes bronchitis as well
\textsuperscript{3}No studies were found on the validity of self-reported colds/minor upper respiratory conditions, or cold sores

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 ICTDER 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? \_\_\_ Yes \_\_X\_ 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”? \_\_\_ 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)?
#2826 - NSAIDs for the Prevention and Control of Prostate Cancer

#1825 - White Blood Cell Differential Counts, Cancer Incidence and Cancer-Specific Mortality in the Atherosclerosis Risk in Communities (ARIC) Study

#2187 - Circulating beta-2 microglobulin (B2M) and cancer risk and mortality: Atherosclerosis Risk in Communities (ARIC) Study

#1519 - Serum uric acid, genetic variation and risk of prostate cancer: Atherosclerosis Risk in Communities (ARIC) Study

#1429 - Inflammatory and allergy markers as predictors of colorectal cancer risk (CRC): Atherosclerosis Risk in Communities (ARIC) study

#2762 - Periodontal disease and cancer risk in the Atherosclerosis Risk in Communities (ARIC)
11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes   __X__ No

11.b. If yes, is the proposal
      __X__  A. primarily the result of an ancillary study (list number* 2011.07, 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.cscu.unc.edu/aric/forms/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscu.unc.edu/aric/index.php, under Publications, Policies & Forms.  
http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.
References

40. Eze-Nliam C, Cain K, Bond K et al. Discrepancies between the medical record and the reports of patients with acute coronary syndrome regarding important aspects of the medical history. BMC health services research 2012; 12: 1.