ARIC Manuscript Proposal #2693

PC Reviewed: 1/12/16 Status: A Priority: 2
SC Reviewed: _________ Status: _____ Priority: _____

1.a. Full Title: Association of SNPs in genes involved the inflammatory pathway with prostate cancer incidence and mortality in the Atherosclerosis Risk in Communities (ARIC) Study

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

2. Writing Group:
   Writing group members: Danyelle Winchester, Elizabeth A. Platz, Corinne Joshu, Jianfeng Xu, and other interested ARIC investigators

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

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3. Timeline:
Data analysis – 6 months
First draft of manuscript – 8 months
4. Rationale:

Inflammation plays a role in the development of several cancers, and evidence is emerging that it may also influence the development of prostate cancer (1–3). In the placebo arm of the Prostate Cancer Prevention Trial (PCPT), we previously found that the prevalence of inflammation in the benign areas of prostate biopsies was associated with an increased risk of prostate cancer, especially higher-grade disease (4). We also reported that some variants in genes involved the immune response were associated with risk of prostate cancer, grade of disease and PSA concentration in the placebo arm (5). In addition, genome-wide association studies (GWAS) (6,7) have also identified a small number of inflammation-related single nucleotide polymorphisms (SNPs) as being associated with prostate cancer risk.

While most GWAS studies have focused on the association between SNPs and prostate cancer incidence, there is one GWAS study that have examined the association between SNPs and death from prostate cancer in men diagnosed with the disease at baseline. In a GWAS conducted for prostate cancer specific mortality in a combined cohort that included participants from Physicians' Health Study and Health Professionals Follow-up Study, no SNPs reached the genome-wide significance, although three independent SNPs had p ≤ 1 x 10^{-7} (8). However, previous studies have reported positive associations between individual SNPs and prostate cancer case-fatality (9–13). Also, some prostate cancer risk variants have been validated and confirmed by replication studies as associated with death from prostate cancer in men with the disease (14,15). Yet, there remains a lack of information about GWAS performed for prostate cancer mortality in men without the diagnosis at baseline. Lethal prostate cancer is now considered to be the most clinically relevant prostate cancer phenotype in studies addressing prostate cancer etiology.

There is some evidence to suggest an association between inflammation and prostate cancer mortality in men with the disease as measured by tissue inflammation and circulating levels of inflammatory markers (16–18). Also, studies support that variants in genes encoding components of the immune response, such as interleukin-6 (IL6) (19) and macrophage inhibitory cytokine-1 (MIC1) (20), are associated with an increased risk of prostate cancer case-fatality. However, limited information is known about the variants in inflammatory pathway genes and prostate cancer mortality in men without a diagnosis at baseline.

Thus, we propose to analyze data from a GWAS performed in ARIC to determine whether variants in genes involved in the immune response are associated with prostate cancer mortality as well as prostate cancer incidence and case fatality. The previous studies referenced above have been limited to white populations. The ARIC study provides an opportunity to further examine whether variants in genes involved in the immune response are associated with prostate cancer incidence (sample size is expected to be too small for outcomes), also in African-Americans. In addition, we previously reported in a different cohort that environmental factors may modify the association
between SNPs and prostate cancer risk (21). Therefore, we will conduct stratified analyses to determine whether modifiable factors that are known to be pro-inflammatory and are associated with fatal prostate cancer – smoking and obesity – modify the association between the SNPs and prostate cancer incidence, mortality and case-fatality.

5. **Main Hypothesis/Study Questions:**
1. To determine whether SNPs in genes involved in the inflammation/immune response pathway are associated with prostate cancer incidence in a cohort of white and black men without the diagnosis of prostate cancer at baseline.
2. To determine whether SNPs in genes involved in the inflammation/immune response pathway are associated with prostate cancer mortality in a cohort of white and black men without the diagnosis of prostate cancer at baseline.
3. To determine whether SNPs in genes involved in the inflammation/immune response pathway are associated with death from prostate cancer in men from the cohort of white and black men with the diagnosis 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**
We will use the BioCarta pathway database to identify genes involved in the immune response/inflammation pathway, and then identify the SNPs in those genes that are present on the Affymetrix Genomewide SNP Array 6.0, which was used in ARIC). Using those SNPs, we will conduct two prospective cohort analyses to determine if SNPs in genes involved the inflammation pathway are associated with risk of prostate cancer (incidence) and mortality in men without the diagnosis at baseline (cohort 1) and risk of death from prostate cancer in men with the diagnosis (cohort 2).

**Inclusion/exclusion**
All ARIC participants with adequate genotyping data available will be included in this study. We will exclude all participants who did not provide informed consent to DNA usage for future studies and/or to studies of other chronic diseases like cancer.

**Cohort 1:** men only, no reported cancer diagnosis of any site at baseline

**Cohort 2:** men only, no cancer reported cancer diagnosis of any site at baseline, had a prostate cancer diagnosis during follow-up, and has a date of prostate cancer diagnosis (needed because date of diagnosis becomes the start of follow-up).

**Exposure:**
Already genotyped (Affymetrix Genomewide SNP Array 6.0) and imputed SNPs in genes involved in inflammation and more generally, the immune response.

**Outcome:**
**Prostate cancer incidence**

We will use the ARIC prostate cancer case file 1987-2012. Prostate cancer incidence data was obtained from cancer registries, hospital records, and death certificates. A subanalysis will be conducted excluding men whose prostate cancer diagnosis was only ascertained by death certificate.

**Prostate cancer mortality and case-fatality**

Event endpoints will include prostate cancer mortality among all men and prostate cancer case fatality among men diagnosed with prostate cancer. Only deaths from prostate cancer as the underlying cause will be considered. Separate analyses will be conducted for each endpoint. Deaths from prostate cancer (ICD-10 code C61) during the follow-up period have been identified from death certificates and the National Death Index through 2012.

**Statistical analysis**

To determine whether SNPs in genes involved in the inflammation/immune response pathway are associated with prostate cancer incidence, we will use Cox proportional hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (CI) assuming an additive model or a co-dominant model adjusting race and using age as the time scale. At this time, modifiable risk factor for prostate cancer incidence are uncertain. To determine if the association between inflammation SNPs and prostate cancer differs by race, we will repeat the analysis stratified by race and will test for statistical interaction between the SNPs and race using the likelihood ratio test.

To determine whether SNPs in genes involved in the inflammation/immune response pathway are associated with prostate cancer mortality, we will perform Cox proportional hazards models to estimate HRs and 95% CI of prostate cancer mortality assuming an additive model or a co-dominant model adjusting for race and using age as the time scale. While it is unlikely that risk factors for fatal prostate cancer confound the genes-prostate cancer association, we will nevertheless additionally for smoking, body mass index, and height. We will determine whether the number of Black men is large enough for stratified analysis, and if so, will perform the analysis stratified as per above. If no, in a subanalysis, we will restrict to White men.

To determine whether SNPs in genes involved in the inflammation/immune response pathway are associated with prostate cancer case fatality, we will perform Cox proportional hazards regression to estimate HRs and 95% CI of prostate cancer specific death among men with a diagnosis of the disease assuming an additive model or a co-dominant model adjusting for age and race and beginning follow-up at the date of diagnosis (time scale is time since diagnosis). Where data are available, we will additionally adjust for stage and grade at diagnosis to be able to assess the association between these SNPs and outcome beyond the influence of these SNPs on the development of more aggressive disease and/or stratify by stage (localized or advanced) or grade (Gleason <7, 7+) of disease. We will additionally adjust for risk factors for the
prostate cancer death – smoking, body mass index, and height. If the sample size for Black men is large enough for stratified analysis, will perform the analysis stratified as per above. If no, in a subanalysis, we will restrict to White men.

After performing the above analyses, we will develop genetic risk scores (GRS) using the top-hits approach, in which we will select those SNPs that were associated with incidence, mortality, or case fatality in this cohort. To generate a GRS, we will sum across the associated SNPs the number of risk alleles for each SNP. We will consider whether weighting each risk allele by its association in other studies is appropriate for this cohort. We will not use the RRs from this study as the weights to avoid over fitting the data. To determine whether the derived GRSs are associated with prostate cancer outcomes above, we will use Cox proportional hazards models to estimate HRs and 95% CIs. We will model the GRS in several ways, including as a count and in quantiles based on distribution in cohort 1.

For each of the above outcomes, we will also conduct analyses stratified by the modifiable factors smoking and obesity, and also for the non-modifiable factors age and height. The presence of a statistical interaction for each SNP or GRS and modifiable and non-modifiable factors will be evaluated using the likelihood ratio test.

Finally, we will consider whether a pathway-based approach to the analysis is feasible (22).

All statistical analyses will be performed using STATA statistical software.

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? ___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
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.cscu.unc.edu/ARIC/search.php

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)?

- Proposal# 1724 (first author: Fred Schumacher): Pleiotropic Effects of Cancer Risk Variants on Prostate Cancer Risk
- Proposal #2203 (first author: Cheryl Bushnell): Chronic inflammation and race-ethnic disparities in ischemic stroke: the ARIC study

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

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number* 2011.07)
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.

REFERENCES


