ARIC Manuscript Proposal #2477

PC Reviewed: 12/9/14      Status: A      Priority: 2
SC Reviewed: _________      Status: _____      Priority: ____

1.a. Full Title: Impact of Cigarette Smoking and Timing of Smoking Cessation on Prostate Cancer Mortality in the Atherosclerosis Risk in Communities (ARIC) Study

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

2. Writing Group:
   Writing group members: Miranda R. Jones, Elizabeth A. Platz, Corinne E. Joshu and Anna Prizment

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. MJ [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:
   Data analysis – 3 months
   First draft of manuscript – 6 months
4. **Rationale:**
Prostate cancer is the most commonly diagnosed non-skin cancer and the second leading cause of cancer death among men in the United States.\(^1\) A 2009 review of prospective epidemiological studies concluded that current cigarette smoking was associated with a 30% increased risk for fatal prostate cancer compared to never and nonsmokers.\(^2\) When recent smoking was considered (i.e., smoking status assessed within 10 years prior to cancer death) there was a two-fold increase in risk for fatal prostate cancer in men who currently smoked compared to never smokers.\(^2\)\(^-\)\(^7\) Studies have varied in their estimates of risk for prostate cancer death among former smokers and it is likely that the timing of smoking cessation could explain these differences in risk; however few studies\(^4\)\(^,\)\(^7\)\(^,\)\(^8\) have been able to examine timing of smoking cessation with prostate cancer mortality.

In the Physicians Health Study (19,705 male physicians recruited between 1982-1984) men who had smoked \(\geq 15\) pack-years of cigarettes within the preceding 10 years had had over two times greater risk for fatal prostate cancer compared to never smokers however within 10 years after quitting the risk for prostate cancer death was similar to never smokers.\(^9\) Also, in this study, cumulative cigarette pack-years smoked was not associated with risk for prostate cancer death after adjusting for smoking history in the preceding 10 years.\(^4\) In a study of almost 250,000 US veterans (aged 31-84 years as of 1953), an elevated risk for prostate cancer death was observed among current smokers compared to nonsmokers during the initial 8.5 years of follow-up, however this risk decreased with increasing duration of follow-up (Relative risk compared to nonsmokers were 1.71 after 8.5 years of follow-up versus 1.18 after 26 years of follow-up),\(^5\) possibly due to changes in smoking behaviors in the cohort over time. Findings from these studies support that relatively recent, rather than cumulative or past smoking is etiologically relevant for prostate cancer death and that studies of smoking and prostate cancer mortality should consider the impact of changes in smoking behavior during study follow-up.

Compared to White men, Black men have a higher incidence of prostate cancer, are more commonly diagnosed with higher stage and grade tumors, and have a higher risk for death due to prostate cancer.\(^10\)\(^-\)\(^15\) Smoking behaviors also differ by race with Black men having a higher prevalence of smoking (24.2% for Black men versus 22.5% for White men)\(^16\) and having lower rates of smoking cessation\(^17\)\(^-\)\(^19\) compared to White men. However, studies to date have been conducted mainly among White men with only two studies examining the impact of smoking on prostate cancer risk in a cohort including Black men; one examined prostate cancer mortality\(^20\) and the other incident prostate cancer.\(^18\)

The ARIC study represents an ideal opportunity to study the impact of changes in smoking behaviors with prostate cancer mortality. In addition, given the disproportionate burden of prostate cancer and the high prevalence of smoking among Black men and the potential role of smoking in disease development, the ARIC study can make several important contributions to the literature on the role of differences in smoking behaviors to racial differences in prostate cancer mortality.
5. **Main Hypothesis/Study Questions:**
   1. To estimate the impact of smoking status at baseline on prostate cancer mortality.
   2. To estimate the impact of changes in smoking status during follow-up and timing of smoking cessation on prostate cancer mortality.
   3. To examine if the impact of smoking and the timing of smoking cessation on prostate cancer death differs by race and if differences in smoking behaviors explains racial differences in prostate cancer mortality.

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 assess the impact of smoking and timing of smoking cessation on prostate cancer mortality prospectively using baseline and updated smoking variables.

**Inclusion/exclusion**
All ARIC participants with complete data on smoking status at the baseline study visit will be included.

**Exposure: Smoking behavior**
Information of smoking behavior was assessed by participant self-report during the four study visits and via yearly telephone interviews. For this analysis we will utilize data on smoking status at baseline and during the study follow-up.

*Baseline assessment*
Participants will be categorized as never smokers, former smokers, and current smokers at the baseline study visit. Participants who are former smokers at baseline will be further categorized based on how recently they quit: recent quitters (former smokers who quit in the last 10 years) and former smokers who quit more than 10 years ago. For current and former smokers, information of the number of cigarettes per day, age of smoking initiation, age at quitting and pack-years of smoking will also be obtained.

*Follow-up assessment*
Smoking status at each follow-up time (study visit or telephone interview) will be ascertained to be able to model their smoking status as a time-dependent variables (current, former vs never). We will also consider time since quitting. For former smokers at baseline or who quit during follow up, at each failure time subsequent to quitting, the number of years since quitting will be obtained by subtracting the age at quitting from the current age.

**Outcome: Prostate cancer mortality**
Event endpoints will include prostate cancer mortality among for all men and prostate cancer case fatality among men diagnosed with prostate cancer. Separate analyses will be conducted for each endpoint. Deaths from prostate cancer during the follow-up period
will be identified through 2012 according to the International Classification of Diseases, Tenth Revision (ICD-10), code C61.

Statistical analysis
To determine the impact of baseline smoking status on prostate cancer mortality we will estimate hazard ratios (95% confidence intervals [CI]) for death from prostate cancer comparing current and former to never smokers at baseline using Cox proportional hazards models. We will repeat this analysis modeling smoking status as time dependent variables (current, former, vs never).

We will also examine the impact of the timing of smoking cessation on risk of prostate cancer death. To do so, we will enter into the model two variables – current smoker (yes or no) and years since quitting (0 for never and current smokers) at baseline. Given the strong a priori hypothesis that recent smoking (i.e., current or recent quitting) is most influential,² we will model indicator variables for current smoker, former smoker who quit ≤ 10 years ago, and former smoker who quit for >10 years ago, all versus never smoker, as has been previously.⁴ We will repeat these analyses using time-dependent variables.

All analyses will be conducted overall and separately for White and Black men.

To examine the impact of smoking and the timing of smoking cessation on racial differences in prostate cancer death we will estimate hazard ratios (95% CI) for death from prostate cancer comparing Black and White men with White men as the reference group using Cox proportional hazards models separately for each baseline or time-dependent expression of smoking and timing of smoking cessation described above.

We will use models with progressive degrees of adjustment:
Model 1: adjusted for age
Model 2: further adjusted for education and race/ethnicity (for overall only)
Model 3: further adjusted for body mass index, height and physical activity

All statistical analyses and graphical displays will be performed using R 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?
   ___ 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 website at: http://www.cscsalumni.org/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)?
   
   • Proposal# 1638 (first author: Rachel Huxley): Burden of smoking-related morbidity and mortality and benefits associated with smoking cessation in a middle-aged US population: The Atherosclerosis Risk in Communities Study

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* 2011.07 and 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.cscsalumni.org/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.cscsalumni.org/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


