ARIC Manuscript Proposal #2826

PC Reviewed: 09/13/16 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: NSAIDs for the Prevention and Control of Prostate Cancer

b. Abbreviated Title (Length 26 characters): NSAIDs & Prostate Cancer

2. Writing Group:
Writing group members:

Elizabeth Platz, Corinne Joshu, Anna Prizment. Other ARIC investigators will also be invited to participate.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. LMH_____ **[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:

Activity	Year 1 (June 2016-May 2017)				Year 2 (June 2017-May 2018)			
Quarter	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Data preparation/data cleaning								
Analyze data for Question 1								
Interpret results/prepare manuscript for Question 1								
Analyze data for Question 2								
Interpret results/prepare manuscript for Question 2								

4. Rationale:

Prostate cancer is the second leading cause of cancer death among men in the U.S [1]. The death rate has declined over the past 20 years, likely due to the advent of PSA screening, improved early detection and early treatment, and improvements in treatments for advanced prostate cancer [2]. However, there are still an estimated 26,120 deaths from prostate cancer expected to occur in 2016 [1]. Early detection cannot curb all deaths from prostate cancer, since some prostate cancers progress despite early intervention. As a result, strategies to prevent incidence and progression of prostate cancer are sorely needed.

The proposed project will focus on regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) as potential protective factors for the incidence and progression of prostate cancer. Common types of NSAIDs include aspirin, ibuprofen, and naproxen; though the precise mechanism of action differs for each type, NSAIDs in general act by inhibiting the cyclooxygenase (COX) pathway, thereby inhibiting the production of pro-inflammatory prostaglandins and thromboxanes that promote platelet aggregation [3]. NSAIDs are thus hypothesized to protect against cancer via anti-inflammatory and anti-platelet mechanisms [3]. NSAIDs could potentially be used for primary prevention of prostate cancer or as an adjuvant therapy to improve survival post-diagnosis.

Aspirin in particular has shown promise as an effective anti-cancer agent according to secondary analyses of randomized clinical trials (RCTs) of aspirin and cardiovascular disease. In a meta-analysis of 34 trials, allocation to daily aspirin was observed to reduce total cancer deaths, particularly after five years or more of follow-up (after 5 years, OR 0.63, 95% CI 0.49-0.82) [4]. A meta-analysis of five trials from the United Kingdom also revealed that daily aspirin (≥75 mg) reduced risk of cancer with distant metastasis (HR 0.64, 95% CI 0.48-0.84), including metastasis at diagnosis and at subsequent follow-up [5]. However, these meta-analyses excluded results from two U.S. trials that administered low-dose aspirin every other day, both of which reported null findings for total cancer mortality [6, 7]. After consideration of all available RCTs, the U.S. Preventive Services Task Force (USPSTF) concluded in 2016 that there was enough evidence to recommend aspirin for primary prevention of colorectal cancer, but that the evidence supporting an overall cancer mortality benefit and benefit for other cancer types, such as prostate cancer, was inconclusive [8, 9].

Several observational studies have also examined NSAID use and prostate cancer incidence and mortality. Again, aspirin has been studied most extensively. Algra et al. found that observational studies of aspirin and cancer outcomes can produce estimates similar to those from RCTs, so long as there is "an adequate definition of aspirin exposure, updated assessment of exposure during the follow-up period, and appropriate adjustment for imbalances in baseline

characteristics" [10]. Studies that meet these criteria have found regular use of aspirin to be associated with an approximately 10-20% reduced risk of total incident prostate cancer, and non-aspirin NSAIDs to be associated with a 0-10% reduced risk [11, 12]. However, the effects of NSAIDs on incidence of *lethal* and *fatal* prostate cancer are not yet clear. Two studies observed inverse associations between aspirin use and lethal prostate cancer [13, 14] while a third study found no association [15]. It is also not yet known if pre-diagnostic or post-diagnostic NSAID use influences risk of disease progression among men already diagnosed, as the existing literature is largely inconsistent [16-22]. Additionally, nearly all studies conducted to date have evaluated these associations in white populations, despite the fact that aggressive prostate cancer disproportionately affects blacks [1]. Black men tend to have molecularly distinct prostate cancers [23] with differing relationships to risk factors [24-26], and it is thus unclear if the current studies can be generalized to these men. As a result of these uncertainties, aspirin and non-aspirin NSAIDs are not currently recommended for prevention of prostate cancer, despite accumulating evidence that they may be beneficial. Research is needed to fill these gaps so that any beneficial effects of regular NSAID use can be incorporated into primary and tertiary prevention strategies for prostate cancer.

5. Main Hypothesis/Study Questions:

Research Question 1: Is regular NSAID use associated with risk of total incident prostate cancer, lethal prostate cancer, and/or fatal prostate cancer among men without diagnosed prostate cancer at baseline in the ARIC cohort?
Hypothesis 1a: Regular use of any NSAID, and particularly aspirin, will be associated with a reduced risk of total incident prostate cancer among men without diagnosed prostate cancer at baseline in the ARIC cohort.
Hypothesis 1b: Regular use of any NSAID will also be associated with a reduced risk of lethal and fatal prostate cancer.

Research Question 2: Is regular pre-diagnostic or post-diagnostic NSAID use associated with progression and case-fatality among men diagnosed with prostate cancer within the ARIC cohort?
Hypothesis 2: Pre-diagnostic and post-diagnostic use of any NSAID will be associated with reduced progression and case-fatality among men diagnosed with prostate cancer within the ARIC cohort.

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 population: For the first research question, the study population will include all men within the ARIC cohort without diagnosed prostate cancer or any other invasive cancer at baseline (n=6,709). For the second research question, the study population will include all men diagnosed with first primary prostate cancer at any point during follow-up (n=836).

Exposure assessment: For ARIC Visits 1-5, participants were asked to bring all medications taken during the past two weeks; medication names and concentrations were recorded. NSAID use will be ascertained from these interviews. Detailed information on regular aspirin use was also collected at ARIC Visit 4. During the medications interview for this visit, participants were asked if they took aspirin on a regular basis, and if they responded yes, they were asked to provide the strength of the aspirin used (<300, 300-499, ≥500mg), days per week of aspirin use, number of pills taken per week, their reason for taking aspirin, and the date that they began taking aspirin regularly. In 1998, a question asking whether participants were currently taking aspirin regularly (at least once a week for several months) was also added to the annual follow-up interviews. This additional exposure information will be utilized in sub-analyses for aspirin use.

Outcome of interest: Outcomes for the first research question will include total incident prostate cancer, lethal prostate cancer (defined as prostate cancer that is advanced at diagnosis (stage T4, N1, or M1) or that metastasizes or causes death at any point during follow-up), and fatal prostate cancer. Outcomes for the second research question will include prostate cancer progression (defined as the development of metastases during follow-up in those without metastases at diagnosis or case-fatality) and case-fatality.

Statistical analysis: To address the first research question, Cox proportional hazards regression will be used to calculate cause-specific hazard ratios of total incident prostate cancer, lethal prostate cancer, and fatal prostate cancer comparing users to non-users of NSAIDs. The time metric will be time since age 45; men who join the ARIC cohort at an older age will be treated as late entries. Men will contribute person-time at risk until the outcome of interest, death due to other causes, or last known follow-up. Three exposures of interest will be examined: use of aspirin, use of a non-aspirin NSAID, and use of any NSAID. Other non-aspirin NSAIDs will be examined individually if there are a sufficient number of users. Men will be classified as users or non-users of NSAIDs in a time-varying manner based on medication use reported at each study visit. For analyses of aspirin, the additional information collected at Visit 4 will also allow for examination of aspirin strength, frequency of use, and duration of use in relation to each outcome. For these sub-analyses, the time metric will be time since age 55 (the approximate age of individuals at ARIC Visit 4). All models will be adjusted for potential confounders, including age, body mass index (BMI), level of physical activity, smoking status, other medication use, diabetes, and cardiovascular disease history. Analyses will be conducted overall and by race (white, black) as well as BMI category (≥30, <30 kg/m^2). All analyses will be conducted using SAS version 9.4.

To address the second research question, Cox proportional hazards regression models will be used to calculate cause-specific hazard ratios of progression and prostate cancer-specific mortality for users versus non-users of NSAIDs. The primary exposures of interest will be use of aspirin, use of a non-aspirin NSAID, and use of any NSAID; separate models will be used to examine these exposures pre-diagnostically and post-diagnostically. Pre-diagnostic NSAID use will be treated as a time-fixed dichotomous variable, while post-diagnostic NSAID use will be treated as time-varying. Covariates considered for inclusion in multivariable models will be age at diagnosis, year of diagnosis, BMI, smoking status, physical activity, other medication use, and stage and grade at diagnosis. Analyses of pre-diagnostic NSAID use will also adjust for time

between assessment of use and diagnosis, while analyses of post-diagnostic NSAID use will adjust for pre-diagnostic use, since pre-diagnostic use can confound the relationship between post-diagnostic use and cancer outcomes [27]. Effect modification by race and BMI category will be assessed using stratified models.

Challenges and proposed solutions: Due to the observational nature of this study, there is potential for bias due to differential screening rates among men who take NSAIDs regularly and men who do not. Regular NSAID users may be in greater contact with physicians, and may consequently undergo PSA screening more often. This could lead regular NSAID users to appear more likely to be diagnosed with early-stage prostate cancer and less likely to be diagnosed with advanced disease, which could bias effect estimates away from the null. To account for possible screening bias, a sensitivity analysis will be conducted in which models are adjusted for the self-reported frequency of receiving routine physical examinations, as reported at Visit 1 in the ARIC Health and Medical History Form.

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)?

None

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.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If amanuscript 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, 2008which 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 policyfromhttp://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, underPublications, 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.

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