ARIC Manuscript Proposal #2812

1.a. Full Title: Statins, cholesterol, and bladder cancer in the Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): Statins and bladder cancer

2. Writing Group:
   Writing group members: Meera Chappidi, Corinne Joshu, Elizabeth Platz, Alison Mondul, other ARIC investigators are welcome

   I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __MRC____ [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: This proposed project is an analysis of existing data that we anticipate will take 6 months from the time of the availability of the bladder cancer case file; development of this case file is currently underway.

4. Rationale:

   Previous epidemiological studies have reported inconsistent results on the association between statin (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor) use and the risk of
bladder cancer with some studies demonstrating an increased risk with statin use and other studies demonstrating no association between statin use and bladder cancer risk. [1] However, basic science studies conducted in bladder cancer mouse models and cell lines have shown that statins result in decreased tumor cell growth. [2-4] The pathophysiologic mechanism for decreased carcinogenesis with statins is hypothesized to be multifactorial. [4] Potential pathways include LDL receptors regulating tumor cell growth through receptors on tumor cells, LDL cholesterol inhibiting the antitumor activity of macrophages and T cell proliferation, and statins affecting the expression of Ras and Rho proteins which are known to be associated with bladder cancer pathogenesis. [5-8] Further support for the harmful effects of cholesterol on bladder cancer risk comes from studies that show increased risk of bladder cancer in individuals with higher dietary cholesterol and untreated hyperlipidemia. [9,10]

Based on the current literature, it is unclear whether statin use is associated with increased risk, decreased risk, or no change in bladder cancer incidence. Elucidating this association is important because smoking, which is a major risk factor for bladder cancer is also associated with hyperlipidemia. Therefore, a large proportion of smokers who are already at an increased risk of bladder cancer also have a clinical indication to be prescribed statins.

The ARIC study represents an ideal cohort to be able to study the association of statin use and bladder cancer risk more in depth than previous studies since it contains detailed data on statin use and lipoprotein subfractions collected at multiple time points. This will allow us to incorporate time-dependent modeling strategies and examine the importance of changes in cholesterol and statin use over time. Previous studies in ARIC have not focused on bladder cancer, but a similar analysis to the one detailed in this proposal is currently being carried out for prostate cancer.

5. Main Hypothesis/Study Questions:

Our overall hypothesis is that lower cholesterol, whether naturally or through the use of statins, will be associated with a lower risk of bladder cancer.

Question #1: Is there an association between statin use and bladder cancer incidence and/or mortality? We hypothesize statin use will be associated with a lower risk of bladder cancer.

Question #2: What is the association between the duration of statin use and bladder cancer risk? We hypothesize longer durations of statin use will be associated with a lower risk of bladder cancer.

Question #3: Is lower total cholesterol associated with a lower risk of bladder cancer? We hypothesize lower cholesterol is associated with a decreased risk of bladder cancer.

Question #4: What are the associations of HDL, LDL, apolipoproteins A1 and B, and triglycerides with bladder cancer? We hypothesize higher LDL, higher apolipoprotein B, higher triglycerides, lower HDL, and lower apolipoprotein A1 levels will be associated with an increase risk of bladder cancer.
Question #5: What are the associations of consistently lower cholesterol, decreasing cholesterol, increasing cholesterol, and consistently high cholesterol with bladder cancer risk? We hypothesize consistently low cholesterol and decreasing cholesterol will be associated decreased bladder cancer risk compared to increasing cholesterol and consistently high cholesterol.

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

Analysis: Cox proportional hazards models

Exclusions: Participants who had cancer at baseline, who were missing cancer information at baseline, and/or who did not fast at least 8 hours. These exclusions are the same as those used in prostate cancer analyses that were investigating the association of metabolic syndrome and prostate cancer risk in ARIC. [11]

Exposures: Statin use, total cholesterol, HDL, LDL, triglycerides, apolipoprotein A1, and apolipoprotein B. Statin use will be modeled as baseline use as well as time-dependent updated use. For cholesterol, triglycerides, and apolipoprotein variables we will examine baseline values, time-dependent updated values (i.e. simple and cumulative updated), and categories of change in these values over time. We will categorize these values using both quartiles and clinical cut-points. The clinical cut-points we will use to categorize levels into “high” and “low” will be 50 mg/dL for HDL cholesterol and 150 mg/dL for triglycerides. The use of both clinical cut-points and quartiles is consistent with previous analyses in the ARIC cohort done in lung and colon cancer. [12,13] We also plan on examining the association of very high and very low values of cholesterol, triglycerides, and apolipoprotein levels by looking at the top and bottom 5-10% of these variables.

Outcomes: Incident bladder cancer. This will be further stratified into a group with non-invasive and invasive bladder cancer as has been done in the Health Professionals Follow-Up Study to evaluate bladder cancer risk. [14] Depending on the completeness of stage and grade at diagnosis information available we may further stratify into low-grade non-invasive, high-grade non-invasive, muscle invasive, and metastatic disease as this would increase the clinical relevance of the results of these analyses. We will also evaluate bladder cancer mortality (~36 bladder cancer deaths) to determine whether patterns of associations are the same as for incidence.

Covariates: Age, race, waist-hip ratio, body mass index, diabetes (self-reported and/or based on glucose measurements, possibly incorporating timing of diagnosis – there may be a different relationship between recently diagnosed diabetes and bladder cancer than between longer-term diabetes and bladder cancer), cardiovascular disease co-morbidities, smoking, alcohol consumption, physical activity, education level, dietary factors (particularly calcium intake), aspirin and other NSAIDS, medications to treat diabetes (particularly metformin).

Stratification Variables: We will stratify by race (depending on number of cases), cholesterol-lowering medication use (for the cholesterol analyses), cholesterol level (for the cholesterol-
lowering medication use analyses), and BMI. We may restrict to non-diabetics and/or men without major cardiovascular co-morbidities.

**Limitations:** In regards to assessing baseline statin use, the data available may be limited because in 1987-1989, the years of the baseline questionnaire, statin drugs were still not frequently prescribed. Moreover, in this questionnaire there is no information on the dosage of the statin. We are also limited in our ability to get stage and grade at diagnosis information for all individuals diagnosed with bladder cancer. However, we have already begun work on the bladder cancer case file, and characterizing information has been available for the majority of cases. Overall, the richness of the ARIC data on cholesterol, triglycerides, and apolipoproteins levels that is available at multiple time points is unparalleled by other contemporary cohort and warrants an investigation into the association of these variables with the risk of bladder cancer.

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”? ____ 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](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)?

• ARIC manuscript #1520: Mondul A, Platz EA, Selvin E, Coresh J, Folsom AR. Statins, cholesterol, and prostate cancer in the Atherosclerosis Risk in Communities (ARIC) study. Analysis ongoing.


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; 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.cscc.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.cscc.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


