ARIC Manuscript Proposal #3178

PC Reviewed: 6/12/18   Status: _____   Priority: 2
SC Reviewed: _____   Status: _____   Priority: ____

1.a. Full Title: Liver fibrosis scores and prostate cancer risk in the Atherosclerosis Risk in Communities (ARIC) Study

  b. Abbreviated Title (Length 26 characters): Liver fibrosis and Prostate Ca

2.   Writing Group:
     Writing group members: Anqi Wang, Mariana Lazo, Corinne E. Joshu, John R. Barber, David Couper, Anna Prizment, Mara Vitolins, Elizabeth A. Platz for the research team (all are welcome)

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

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3.   Timeline: The proposed manuscript is an analysis of existing data. We anticipate it will take 6-12 months from receipt of the data (analysis will be done at Johns Hopkins) to submission of a manuscript to the ARIC Publications Committee.

4.   Rationale:
     Over the last 25 years, testing for elevated PSA has been widely used for the early detection of prostate cancer in the US.[1] However, some evidence from studies of patients with cirrhosis links poor liver function to a reduction in serum prostate-specific antigen (PSA) concentration among

men.[2-4] We conducted an analyses using the National Health and Nutrition Examination Survey (NHANES) 2001-2010 cycles (manuscript in preparation) and found that in the general US population, men with higher liver fibrosis scores – a non-invasive index to assess individual's liver fibrosis – had lower serum PSA concentration, even after adjustment for potential confounders. The implications of these results are important: men with undiagnosed liver fibrosis (irrespective of the cause - viral hepatitis, heavy alcohol consumption, or nonalcoholic fatty liver disease (NAFLD)) may have lower likelihood of a recommendation for prostate biopsy and thus may miss the chance for an early detection of an occult prostate cancer, if present. Further, the higher burden of liver diseases in certain subgroups e.g. viral hepatitis among Blacks,[5-7] may help explain the racial disparities observed in the incidence of metastatic and lethal prostate cancer. Given that early detection may be beneficial for prostate cancer treatment and survival, a delayed diagnosis of aggressive prostate cancer could contribute to the higher prostate cancer mortality among Black American men.[8] Note, we are not suggesting that men with a substantially reduced life expectancy due to chronic liver disease should be screened for prostate cancer. However, men with early liver fibrosis (well before cirrhosis) may not have a shortened life expectancy and thus, may have prostate cancer as a competing risk of death. These latter men might benefit from early detection.

To date, no firm conclusion has been reached regarding the impact of liver diseases on prostate cancer incidence, mortality, or outcomes following treatment and the results have been inconsistent. Few studies have reported the association between liver diseases and prostate cancer risk. With respect to risk, there was a higher prevalence of prostate cancer among males with hepatitis C antibody positive compared to those antibody negative in a retrospective cohort of US men who underwent transrectal ultrasound guided prostate biopsy.[11] With respect to outcomes, Choi et al. found that NAFLD status was inversely associated with biochemical recurrence (BCR) among Korean men treated for prostate cancer by radical prostatectomy.[12]

Liver impairment resulting from fibrosis may play a complex role in prostate cancer development and progression. The liver plays an important role regulating the levels of androgens, and prostate growth is dependent on androgen levels.[13,14] A decreased prostate volume has been demonstrated as an important predictor of prostate cancer detection.[15] In addition, NAFLD is considered the hepatic manifestation of insulin resistance[16] and studies have observed that males with insulin resistance tend to have an increased risk of prostate cancer.[17-19] Beyond the biological mechanisms, patients with liver disease, seem to have lower level of serum PSA, and thus are likely to have a delayed detection of prostate cancer, which may lead to worse survival. Thus, the biological effects of liver impairment could result in either an inverse or a positive association between liver fibrosis and prostate cancer risk, while the effects of lower PSA on prostate cancer detection could result in an inverse association with prostate cancer risk.

5. **Main Hypothesis/Study Questions**:
The overall objective of this proposal is to examine the association between liver fibrosis scores and prostate cancer incidence and mortality in men <u>without</u> a diagnosis of chronic liver disease at baseline in ARIC. We will exclude men with a diagnosis of chronic liver disease because it may not be appropriate to screen them for prostate cancer because of reduced life expectancy. We propose this work to contribute to understanding whether liver fibrosis in men without a diagnosed chronic liver condition affects the validity of PSA-based prostate cancer screening. As mentioned in the rationale, we are assuming that we will observe an inverse association between

liver fibrosis and prostate incidence. To begin to distinguish between an inverse association due to liver fibrosis leading to 1) lower PSA in turn leading to fewer biopsies and thus reduced detection of extant tumors (detection bias), versus 2) a lower probability of prostate cancer development (biology), we will examine prostate cancer incidence and mortality separately.

Question 1: Is a higher liver fibrosis score associated with risk of prostate cancer incidence?

Question 2: Is a higher liver fibrosis score associated with risk of lethal prostate cancer incidence? By lethal prostate cancer, we mean first primary cases that are metastatic at diagnosis or first primary cases that progress to prostate cancer death

Question 3: Is a higher liver fibrosis score associated with risk of prostate cancer mortality?

Overarching hypotheses:

If reduced PSA level delays the detection of prostate cancer, then the incidence of prostate cancer among males with liver fibrosis is expected to be lower than those without fibrosis. However, lethal prostate cancer and prostate cancer mortality is expected to be higher, since early detection of prostate cancer coupled with appropriate treatment should reduce prostate cancer death. An alternative hypothesis is that if liver fibrosis results in a lower probability of prostate cancer development, then the incidence is expected to be lower AND both lethal prostate cancer and prostate cancer mortality are also expected to be lower in those with liver fibrosis than those without liver fibrosis.

It is also possible that an inverse association between liver fibrosis and prostate cancer risk could be due to a combination of detection bias and biology. In our NHANES study, we found that males with an abnormal liver fibrosis score had a 0.33 (95% CI: 0.11-0.96) lower odds of a PSA >4 ng/mL, a clinical indication for prostate biopsy. If in ARIC we observe an RR substantially less than 0.33 (or alternatively, less than 0.11, the lower 95% bound of the NHANES estimate), this might be evidence that both biology and bias may underlie an inverse association between liver fibrosis and prostate cancer risk, especially if the association with prostate cancer mortality is also inverse or null.

With respect to race, we expect the same patterns for prostate cancer incidence in Black and White men. However, for mortality, if liver fibrosis decreases the detection of prostate cancer only and given that Black men have more aggressive prostate cancer (higher Gleason sum, higher prostate cancer mortality rates), the RR for liver fibrosis score and prostate cancer mortality may be higher than that for White men.

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 study with Visit 2 as baseline for the analysis.

Inclusion/Exclusion: Men without a cancer diagnosis at baseline (Visit 2), and we will exclude from the analysis:

- Men with missing data on liver enzymes or platelet count,
- Men with missing data on other covariates of interest,
- Men who reported a race other than Black or White,
- Black men from the Minneapolis and Washington County field centers,
- Men with a known diagnosis of chronic liver diseases as assessed at ARIC Visit 3 (it may not be appropriate to screen these men for prostate cancer because of reduced life expectancy)

Exposures:

Biochemical markers related to liver function – aspartate aminotransferase (AST), alanine aminotransferase (ALT), – platelet count and albumin will be obtained based on Visit 4. To assess liver fibrosis of participants, we will estimate three non-invasive fibrosis scores for each man: AST/platelet ratio index (APRI), fibrosis 4 index (FIB-4) and NAFLD fibrosis score (NFS).

APRI and FIB-4 indices were developed to predict fibrosis and cirrhosis among patients with hepatitis C[20,21] and have been validated in other chronic liver diseases in later studies to accurately identify patients with significant fibrosis.[22-25] Given its simplicity and validity, APRI is recommended by the World Health Organization to identify fibrosis stage in resource-constrained areas.[26] The NFS was developed to identify advanced fibrosis in patients with NAFLD and showed 0.84 of the area under the ROC curve.[27] Scores will be calculated by following equations:

$$\text{APRI} = ((\text{AST [U/L]} / \text{upper limit of normal}) / \text{platelet count } [10^9/\text{L}]) \times 100 \tag{1}$$

$$\text{FIB-4} = (\text{Age [yrs]} \times \text{AST [U/L]}) / (\text{platelet count } [10^9/\text{L}] \times \text{ALT [U/L]}^{1/2}) \tag{2}$$

$$\text{NFS} = -1.675 + (0.037 \times \text{age [yrs]}) + (0.094 \times \text{BMI [kg/m}^2]) + (1.13 \times \text{impaired fasting glucose}$$
$$\text{or diabetes}) + (0.99 \times \text{AST/ALT}) - (0.013 \times \text{platelet count } [10^9/\text{L}]) - (0.66 \times \text{albumin (g/dL)})$$
$$\tag{3}$$

To calculate the fibrosis scores, we will use Visit 2 liver enzyme levels but will carry forward Visit 1 platelet count for everyone, due to the high proportion of missing Visit 2 platelet count (mostly in Jackson site). We will use 33 U/L as upper-limit of normal of AST in alignment with our previous study using NHANES data. [28] Visit 2 body mass index (BMI) will be calculated as weight (kg) divided by height (m^2) squared. Participants will be classified as having impaired fasting glucose or diabetes, if they had fasting glucose >100 mg/dL (if not fasting: >140 mg/dL) [29], they self-reported a physician's diagnosis of diabetes, or they used a diabetes medication. We will define abnormal fibrosis score as: APRI>1, FIB-4>2.67 or NFS>0.676. [30,31] Fibrosis scores will also be examined using quantiles. We used these scores in our previous NHANES study to assess the liver fibrosis in relation to PSA in the general male population (*manuscript in preparation*). The majority of men had scores in the normal range, and the scores were spread across the normal range.

Outcome: Among men without a cancer diagnosis at Visit 2 (baseline), first primary incident prostate cancer, lethal prostate cancer (defined as metastasis to any organ or prostate cancer–specific death) and prostate cancer deaths occurring after Visit 2 through 2012 among participants

eligible for this analysis. We will use the ARIC prostate cancer case file, which was developed using data from the MN, NC, MD, and MS state cancer registries, medical records, and hospital discharge codes.

Other variables of interest: Age at Visit 2, race and field center, diabetes, BMI, waist circumference, cigarette smoking status, alcohol consumption, family history of prostate cancer (Visit 3), and statin and aspirin use (known or purported risk factors for total or lethal prostate cancer).

Socioeconomic status (SES) and its correlates, such as access to and uptake of health care, may confound the association between liver fibrosis and prostate cancer. Generally, patients with poor liver function are more likely to have lower SES and poor access to care, which may limit opportunities for cancer screening.[32] These factors include childhood, early adulthood, and later adulthood SES each calculated using data from an ancillary study at Visit 4 as done previously in ARIC[33]; US Census tract data on neighborhood income for the year 1990[34]; typical frequency of routine medical examinations at Visits 1, 2, and 3 (at least once a year, at least once every five years, less than once every five years, do not have routine physical examinations, unknown); health insurance status (Yes, No) at Visit 1; type of health insurance (private, Medicare, Medicaid, Other) at Visit 2; usual type of medical care (private MD, HMO, Walk-in Clinic, Regular Clinic, Hospital Emergency Room, Other) at Visit 2.

Chronic liver disease status will be acquired based on the result of the question "Has a doctor ever told you that you have cirrhosis or another chronic liver disease" at Visit 3, and for those who did have a record on Visit 3, we will complement with hospital discharge summary for liver reasons (ICD-9: 571 or ICD-10: K74) for men with a history of hospitalization.

Analysis:
Person-years at risk will be calculated from the date of Visit 2 until the date of prostate cancer diagnosis (or death), death from another cause, loss to follow-up, or the administrative censoring date, whichever occurs first.

Cox proportional hazards regression will be used to estimate the adjusted RRs for the association between liver fibrosis scores and (1) overall prostate cancer incidence; (2) lethal prostate cancer incidence; and (3) prostate cancer mortality. We will express the liver fibrosis scores in several ways: continuous, quantiles, or binary (abnormal vs. normal, using previously used cut points[30,31]). To reduce confounding by SES and access to and uptake of medical care, a propensity score will be generated and entered into the Cox model. First, we will model the association between liver fibrosis score scores (normal vs. abnormal) and the array of lifecourse SES (or SES at each of the 3 points in life) and correlated variables using logistic regression to predict the propensity score for each participant. Then, we will add the propensity score, either as a continuous variable or as an array of indicator variables for quantiles, to the Cox model that includes terms for liver fibrosis score, age at Visit 2, race and field center, diabetes/impaired fasting glucose status, BMI, waist circumference, cigarette smoking status, alcohol consumption, family history of prostate cancer (Visit 3), and statin and aspirin use. These analyses will be conducted among the overall population and stratified by race. Given that cost of living may vary across the field centers, we will perform a sensitivity analysis in which we develop the propensity score including field center. In addition, we will also perform several other sensitivity analyses:

1) cross-categorizing the men with respect to all three of the scores (APRI, FIB-4, NFS) and examining the association between the cross-categorized score and prostate cancer incidence and mortality, in order to improve the accuracy of liver fibrosis classification;

2) not adjusting for diabetes/impaired fasting glucose status and compare the results to the main analysis to see if dysglycemia is in the causal pathway between liver fibrosis and prostate cancer incidence;

3) incorporating Visit 4 fibrosis scores (calculated using Visit 4 liver enzymes levels and carrying forward Visit 3 platelet for everyone) and performing the analysis with time-updated fibrosis scores;

4) including all males regardless of chronic liver disease status in the analysis;

5) including all males regardless of chronic liver disease status in the analysis and performing analysis with time-updated fibrosis scores;

6) using Visit 2 platelet count to calculate fibrosis scores and carrying forward Visit 1 platelet for those males without Visit 2 platelet count;

7) using Visit 2 platelet count to calculate fibrosis scores and conducting a complete case analysis.

As discussed in the Main Hypothesis/Study Questions, if an inverse association between higher liver fibrosis score and total prostate cancer incidence is observed, we will differentiate between the explanation of 1) detection bias due to lower PSA and 2) reducing prostate carcinogenesis.

If we observe a positive association between liver fibrosis and prostate cancer mortality we will evaluate the magnitude of contribution of liver fibrosis to prostate cancer mortality in Black versus White men. We would calculate the partial population attributable risk (PAR) of an abnormal liver fibrosis score for prostate cancer mortality separately in White and Black men.

Minimum detectable association:
As summarized in the table below, we calculated the minimum detectable associations for total prostate cancer incidence (789 cases out of 6,498 males). Assuming a linear association between liver fibrosis score and prostate cancer incidence, with 80% power for a 2-sided test with alpha=0.05, we can detect as statistically significant an RR of prostate cancer of 0.82 per unit increase in fibrosis score. If we divide the fibrosis score into two categories – abnormal and normal fibrosis score – and examine the association between the binary variable of liver fibrosis and prostate cancer incidence, given the prevalence estimated from our previous NHANES study (proportions of abnormal fibrosis score defined by APRI, FIB-4 and NFS: 2.1%, 3.6% and 5.6%), we can detect as statistically significant an RR of 0.50 for APRI, 0.59 for FIB-4, and 0.65 for NFS. Moreover, the study population is younger in our NHANES study (mean age=55.1 years) than the ARIC study, and the proportions of abnormal fibrosis score would be higher in the ARIC study. Therefore, the estimated minimum detectable association should be conservative.

Table. Minimum detectable association (relative risk [RR]) for abnormal fibrosis scores and prostate cancer incidence and mortality

Fibrosis indicator	Minimum detectable RR with 80% power (alpha=0.05, 2-sided test)	
	Prostate cancer incidence	Prostate cancer mortality (inverse/direct association)

	Linear (per unit increase in score)	Binary (abnormal vs. normal)	Linear (per unit increase in score)	Binary (abnormal vs. normal)
APRI		0.50		0.20/ 5.00
FIB-4	0.82	0.59	0.55/1.82	0.28/ 3.57
NFS		0.65		0.34/ 2.94

Then, we calculated the statistical power for prostate cancer mortality (84 cases out of 6,498 males). We are uncertain about the direction for prostate cancer mortality, since liver fibrosis could be protective when men with liver disease biologically have a lower probability of developing prostate cancer, or be a risk factor when men with liver disease have a lower detection rate of early-stage prostate cancer. Making the same assumptions as for incidence, we can detect as statistically significant an RR of 0.55 or 1.82 per unit increase fibrosis score. For abnormal liver fibrosis, we can detect an RR of 5.00 for APRI, 3.57 for FIB-4 and 2.94 for NFS or higher or 0.20 for APRI, 0.28 for FIB-4 and 0.34 for NFS. As mentioned above, the estimated minimum detectable association should be conservative due to higher proportions of abnormal fibrosis scores in the ARIC study.

To conclude, we will have sufficient power to detect moderate to large association or more extreme between liver fibrosis score and prostate cancer incidence and mortality. Minimum detectable associations will be smaller or larger than these when stratifying by race. Keeping in mind our goal, we will focus on patterns (irrespective of statistical significance), as described in **Main Hypothesis/Study Questions**.

Limitations
There are several limitations for this study. First, PSA test and prostate biopsy information is not available in ARIC. Men who are frequently screened for PSA are more likely to have prostate cancer detected at an early stage, and thus would be less likely to die from prostate cancer. Moreover, if PSA concentration were available, we would be able to more directly evaluate our hypothesis that lower PSA concentration result in delayed detection of asymptomatic prostate cancer among men with liver fibrosis. Second, the sample size for prostate cancer mortality is small (63 cases out of 4,840 males), resulting in limited statistical power to detect modest to moderate associations. Third, we will use non-invasive indicators to define liver fibrosis, which may result in misclassification compared with imaging and the gold standard liver biopsy. To improve accuracy of liver fibrosis classification, we will perform a sensitivity analysis in which we will cross-categorize the men with respect to all three of the scores. In doing so, we expect that men who "truly" have liver fibrosis would be more likely score high on two or three of these scores, while those who "truly" do not have liver fibrosis would be more likely to score low on all three of these scores. Fourth, while we will exclude men with a known diagnosis of liver disease, men with and without unrecognized severe liver fibrosis will likely be different on many demographic, health, and lifestyle characteristics. We will attempt to take these into account by multivariate adjustment including adjustment for SES-access to care variables using propensity scores. Finally, we will not be able to conclusively distinguish between bias versus biology as explanations for the pattern we observe. Nevertheless, this study will provide some information to

begin to understand more about prostate cancer risk in men in the US, where the prevalence of liver conditions that precede liver fibrosis is on the rise.

Strengths
Despite the limitations, there are several important strengths of ARIC for addressing the present research question. First, ARIC is a large prospective study with careful physiologic measures and follow-up. Liver enzymes were measured without indication/suspicion of liver fibrosis; their concentrations are needed to non-invasively assess the likelihood and severity of liver fibrosis. In addition, the participants were from four distinct geographic sites in the United States and included a large proportion of African Americans.

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 ICTDER04 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)?

MS Proposals on liver disease/fibrosis: #2065, #2934, #1824 – Mariana Lazo is an ARIC investigator who focuses on liver disease/fibrosis. She is a co-author on the NHANES paper that is the basis for this ARIC manuscript proposal and she is a co-author on this one. Co-authors include ARIC Cancer Working Group members, including those who developed the prostate cancer case file.

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

     A. primarily the result of an ancillary study (list number* 2011.07 (ARIC cancer), 1995.04 (cancer))

     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.

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