ARIC Manuscript Proposal #2910

PC Reviewed: 12/13/16	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Chronic kidney disease measures and cancer risk in the community

b. Abbreviated Title (Length 26 characters): CKD and cancer risk

2. Writing Group:

Writing group members: Yejin Mok, Shoshana Ballew, Yingying Sang, Josef Coresh, Corinne Joshu, Elizabeth A. Platz, Kunihiro Matsushita; others welcome

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

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3. Timeline: Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale:

Chronic kidney disease (CKD), usually defined as reduced estimated glomerular filtration rate (eGFR) or elevated albuminuria, is a major and growing global public health problem.[1] The prevalence of CKD continues to rise[2] and contributes to adverse outcomes such as cardiovascular disease[3 4], infections,[5] metabolic and endocrine disorders,[6 7] frailty,[8] and cognitive impairment.[9]

Recently, cancer has been attracting attention as another potential complication of CKD.[10-19] However, previous studies have demonstrated conflicting results. Since those studies used different definitions of CKD (reduced kidney function[10-15] vs. albuminuria[16 17] and only one study accounting for both[19]) and cancer (mortality[11 13 16 18 19] vs. incidence including non-fatal

cases[10 12 15 17] and overall cancer[14 18] vs. site-specific cancer[10-13 15-17 19]), it is hard to derive common conclusions.

Therefore, we aim to quantify the associations of both eGFR and albuminuria with cancer incidence and mortality in the Atherosclerosis Risk in Communities (ARIC) Study. The ARIC Study will uniquely allow us to assess the state-of-the-art measures of eGFR (based on the CKD-EPI equation using serum creatinine and cystatin C[20 21]) and albuminuria (urine albumin-to-creatinine ratio [ACR]).

5. Main Hypothesis/Study Questions:

1. eGFR and ACR will be associated with overall cancer and some site-specific cancers, independently of each other and other cancer risk factors.
2. The association will be more robust for ACR compared to eGFR.
3. The association will be stronger for cancer mortality than for cancer incidence, since CKD can influence treatment decision and response.

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).

Inclusions:

- All ARIC participants with serum creatinine, urinary albumin, creatinine and other necessary covariates at visit 4 will be included in the analyses.

Exclusions:

- Individuals diagnosed with cancer prior to baseline (visit 4)
- Ethnicity other than black and white

Exposures:

- CKD-EPI Cystatin C + creatinine equation for eGFR as primary equation since this is the best available equation.
  $135 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-0.601} \times \min(S_{cys}/0.8, 1)^{-0.375} \times \max(S_{cys}/0.8, 1)^{-0.711} \times 0.995^{Age} \times 0.969$ [if female] x 1.08 [if black]
  (κ is 0.7 for female and 0.9 for male; α is -0.248 for female and -0.207 for male)
- CKD-EPI creatinine-based eGFR as secondary equation since creatinine-based eGFR is widely used in clinical practice
  $141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] x 1.159 [if black] (κ is 0.7 for female and 0.9 for male; α is -0.329 for female and -0.411 for male)
- ACR as a measure of albuminuria as recommended in the Kidney Disease Improving Global Outcomes (KDIGO) CKD guidelines[22]
- Covariates of interest: socio-demographic characteristics (age, race, gender, education), alcohol intake, smoking status, body mass index, family history of cancer, history of cardiovascular disease (coronary heart disease, stroke or heart failure), hypertension (systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90mmHg, reported history of hypertension, or use of antihypertensive medication),

use of anti-hypertensive medications, diabetes (fasting blood glucose ≥126mg/dl, non-fasting glucose ≥200mg/dl, reported history of diabetes, or use of diabetes medication), use of anti-diabetes medications, lipid parameters (Total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride), C-reactive protein (CRP), and statin use.

Outcomes:

- Cancer incidence (first primary invasive)
- Cancer mortality
- System-specific cancer
    - Digestive system: stomach, colon and rectum, liver, pancreas
    - Respiratory system: lung, laryngeal
    - Genitourinary: breast, endometrial (women), prostate (men), bladder, kidney
    - Hematopoietic: multiple myeloma, leukemia
- Site-specific with at least 50 cases (based on preliminary evaluation the following sites should have >50 incident cases [* with >50 mortality cases])
    - Breast
    - Bladder
    - Endometrial
    - Colon/rectum*
    - Kidney/other urinary
    - Lung*
    - Multiple myeloma
    - Pancreas*
    - Prostate*
    - Stomach

Statistical Analysis:

1. According to the KDIGO guideline[22] and previous literature[23], eGFR will be categorized as <30, 30-44, 45-59, 60-89, and ≥90 ml/min/1.73m^2, and ACR will be categorized <10, 10-29, 30-299, and ≥300 mg/g.
2. We will summarize baseline characteristics by categories of eGFR and ACR as well as the status of incident cancer.
3. Subsequently, we will quantify the association of eGFR and ACR with cancer risk (incidence and mortality, separately) using Cox proportional hazards models. Those models will adjust for covariates listed above as well as each of CKD measures (ACR will be accounted for in the analysis for eGFR and vice versa). We will also assess risk of developing cancer according to cross-categories of eGFR and ACR using Cox proportional hazard model.
4. We will conduct a few sensitivity analyses.
    a. To compare the contributions of eGFR and ACR to cancer risk in subgroups, we will perform subgroup analysis according to age, gender, race, smoking status, and clinical conditions (diabetes, hypertension, and history of cardiovascular disease).

b. In sub-analysis, we will repeat the analysis for total cancer the excludes prostate cancer since kidney function may affect PSA concentration which is an important tool for detection of prostate cancer.[24 25]
c. We will do competing risk analyses using Fine and Gray's method to determine effect estimates in the presence of a competing risk.[26]

5. We will repeat the analysis using creatinine-based eGFR.

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 _ x _ 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)?
#1348: Chronic kidney disease and risk of hospitalization: The Atherosclerosis Risk in Communities Study; Bash LD. This proposal includes all hospitalizations, but our proposal would focus on overall and site-specific cancer incidence. A key author of MP 1348, Josef Coresh, is included in the current proposal.

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* _2002.02 and_ 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.

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