ARIC Manuscript Proposal # 3013

1.a. **Full Title**: Association of high-sensitivity cardiac troponin T and natriuretic peptide with cancer risk and mortality in the community-based cohort

b. **Abbreviated Title (Length 26 characters)**: hs-cTnT/BNP and cancer risk

2. **Writing Group**:
   Writing group members: Yejin Mok, Roberta Florido, Ron C. Hoogeveen, Josef Coresh, Christie M. Ballantyne, Corinne Joshu, Elizabeth Selvin, Elizabeth 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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**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**: Analyses and manuscript preparation will be performed over the next 6 months.

4. **Rationale**:
   Cardiovascular disease (CVD) and cancer are important causes of morbidity and mortality worldwide and share several important modifiable risk factors and pathophysiology.\textsuperscript{1-5} Since survival from CVD has improved over decades, patients with prevalent CVD are increasing.\textsuperscript{3} Survivors of CVD are at increased risk for CVD related outcomes as well as non-CVD related comorbidities,\textsuperscript{6} and some studies suggested a link between CVD and cancer risk. In previous studies, patients with CVD had a 19\%-60\% higher cancer risk compared to subjects who were
free of CVD,\textsuperscript{7,8} and patients who developed heart failure after myocardial infarction had approximately 2-fold higher risk of cancer incidence compared to those who did not develop heart failure.\textsuperscript{8,9} However, since patients with cardiac disease may experience a more medical surveillance than general population,\textsuperscript{10} these findings could be influenced by detection bias.

Cardiac troponin T (cTnT) and N-terminal pro-B-type natriuretic (NT-proBNP) have been suggested as a marker of cardiac damage and as key components in diagnosis of myocardial infarction and heart failure, respectively.\textsuperscript{11,12} In addition, higher levels of these cardiac markers are related to cardiovascular events among those free of clinical CVD.\textsuperscript{13-16} On the other hand, cTnT and NT-proBNP could have predictive power beyond cardiovascular event. In previous ARIC study, high levels of high sensitive cTnT (hs-cTnT) and NT-proBNP were associated with mortality, not only from CVD but also non-CVD causes.\textsuperscript{17} One study involving patients with coronary artery disease observed that NT-proBNP was independently associated with cancer risk.\textsuperscript{18} If these cardiac markers are related to cancer risk independently of clinical cardiovascular events during follow up in the general population, that would further support the potential pathophysiological link between cardiac abnormality and cancer risk. Also, such an investigation will inform whether information on hs-cTnT and NT-proBNP may be useful to identify persons at high risk of cancer and potentially benefitting from cancer screening. This perspective seems important since it is likely that hs-cTnT and NT-proBNP would be measured more broadly for CVD risk evaluation in the future. Therefore, we will evaluate whether these cardiac markers are associated with cancer risk in the Atherosclerosis Risk in Communities (ARIC) study.

5. Main Hypothesis/Study Questions:
We hypothesize the elevated levels of hs-cTnT and NT-proBNP in middle-age will be associated with cancer risk independently of clinical cardiovascular events during follow-up.

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).

Design: Prospective cohort study
- We will quantify the association of hs-cTnT and NT-proBNP at visit 2 or 4 with the cancer risk and mortality after adjusting for confounders.
- Visit 4 will have slightly less cancer cases but shows higher levels of hs-TnT and NT-proBNP than visit 2 and thus will be our primary visit.

Inclusions:
- All ARIC participants with data on hs-cTnT, NT-proBNP and other necessary covariates at visit 2 and 4 will be included in the analyses.

Exclusions:
- Individuals diagnosed with cancer prior to baseline (visit 2 or 4 as appropriate)
- Race other than black and white
- Participants who had a history of cardiovascular disease (coronary heart disease, stroke and heart failure) prior to baseline (visits 2 or 4)
**Exposures:**
- hs-cTnT: hs-cTnT was measured by a novel highly sensitive assay with a lower limit of detection of 3 ng/L.
- NT-pro-BNP: NT-pro-BNP was measured by an electrochemiluminescent immunoassay with lower limit of detection 5 pg/mL.

**Covariates of interest:** demographic characteristics (age, race, gender, education, income), alcohol intake, smoking status, body mass index, waist circumference, family history of cancer, history of cardiovascular disease (coronary heart disease, stroke or heart failure), hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, reported history of hypertension, or use of antihypertensive medication), use of anti-hypertensive medications, diabetes (fasting blood glucose ≥126 mg/dl, non-fasting glucose ≥200 mg/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) through 2012
- Cancer mortality as the underlying cause through 2012
- 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: the case file is for post-menopausal women only
  - Bladder: 189 first primary
  - Endometrial: 109 first primary
  - Colon/rectum*
  - Kidney/other urinary: 142 first primary
  - Lung*
  - Pancreas*
  - Prostate*
  - Stomach: 61 first primary

**Statistical Analysis:**
1. hs-cTnT will be categorized into five categories (undetectable, 3-5, 6-8, 9-13, and 14+ ng/L) and NT-proBNP will be categorized into five categories corresponding to the same percentiles of each category of hs-cTnT. We will summarize basic characteristics according to the 5 categories of hs-cTnT and NT-proBNP.
2. We will first quantify the association of hs-cTnT and NT-proBNP with the risk of cancer using Kaplan-Meier method stratified by age and gender.

3. We will calculate risk differences between categories of cardiac markers to help understand the clinical importance of any association observed.

4. The primary analysis will use Cox proportional hazards regression models after adjusting for potential confounder factors. hs-cTnT and NT-proBNP will be treated as categorical (aforementioned five groups) and continuous variables with splines with knots at thresholds defining the five groups) in the models.

5. We will implement a few approaches to see the impact of incident CVD events during follow-up
   i. Adjust those CVD events as time-varying covariates
   ii. Censor those CVD events

6. We will conduct a few sensitivity analyses:
   - We will repeat analysis in several subgroups by demographic (age, race and gender), presence/absence of comorbidities (diabetes, hypertension, kidney dysfunction), and lifestyle (smoking, alcohol intake).
   - We will do competing risk analyses using Fine and Gray’s method to determine effect estimates in the presence of a competing risk.²⁰
   - Adjusted for uptake of medical care (annual exam), access to medical care (health insurance), and life course SES

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)?
We could not find any proposals exploring hsTnT and NT-proBNP as exposures for cancer incidence and mortality.

#1811: Association of high sensitive Troponin T (hs-cTnT), N-Terminal pro-brain natriuretic peptide (NT-proBNP) and high sensitivity C-reactive protein (hs-CRP) with cause-specific mortality: ARIC 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* _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.

References


