ARIC Manuscript Proposal #2912

1.a. Full Title: Subclinical Myocardial Damage Among Cancer Survivors in ARIC

b. Abbreviated Title (Length 26 characters): Cancer and hs-cTnT

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

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3. **Timeline:** All data are currently available. We aim to submit this manuscript to the ARIC publications committee <6 months from the date of approval of this manuscript proposal.

4. **Rationale:**

Cardiovascular disease (CVD) and cancer are important causes of morbidity and mortality in the U.S. and around the world. Early detection and major advances in treatment resulted in large improvements in cancer outcomes. It is estimated that by 2026, 20 million cancer survivors will be alive (1). With the growing number of cancer survivors, considerable attention has been given to determinants of health and disease in this population. Several studies suggest CVD is the leading cause of death among women who survive breast cancer (2). Death from CVD surpasses death from breast cancer approximately 5-10 years after cancer diagnosis, and is particularly important among older women and those with pre-existing cardiac conditions (3). Studies exploring mechanisms and strategies for early detection and prevention of CVD among cancer survivors could have significant public health implications.

There are several reasons for why patients with a history of cancer may be at increased risk for CVD. First, many of the traditional cardiovascular risk factors are also associated with increased risk of cancer (4). There is growing evidence of high burden of such risk factors among cancer survivors. Further supporting the idea of shared triggers for CVD and cancer, is the fact that both conditions are associated with increased markers of chronic inflammation and oxidative stress. Inflammation is thought to play an important role promoting carcinogenesis and tumor progression, and in the development of all forms of CVD (5,6).

Women with a history of breast cancer have a particularly high risk of adverse cardiac events. Cardiotoxicity related to breast cancer treatment with anthracyclines have long been recognized, and can negatively affect patients’ short and long term outcomes (7). Despite the development of newer, more targeted and better tolerated therapies, cardiovascular side effects have continued to challenge the care of these patients (8). One important example if the monoclonal antibody Trastuzumab which revolutionized the care of patients with HER2 positive breast cancer (9). Unfortunately, early during phase III clinical trials it became evident that Trastuzumab was associated with increased risk of heart failure, particularly if used in combination with high doses of anthracyclines. Mediastinal radiation therapy can also lead to myocardial dysfunction and heart failure, atherosclerosis, valvular dysfunction and pericardial disease (10).

New highly sensitive assays for cardiac troponin T (hs-cTnT) are capable of detecting concentrations at levels 10-fold lower than the assays currently used in clinical practice in the U.S. (11). In ambulatory populations without overt cardiac disease, the presence of elevated hs-cTnT is thought to reflect subclinical myocardial damage and is an important marker of increased cardiovascular risk (12). Hs-cTnT has been associated with increased risk of hypertension, left ventricular hypertrophy, coronary heart disease, heart failure and mortality in ARIC and other community-based cohorts (12-14). Whether a history of cancer is associated with the presence of subclinical
myocardial damage assessed using hs-cTnT, unknown. If such association is present independently from cardiovascular risk factors, this could indicate continued myocardial damage as a long-term consequence of cardiotoxic treatments or other unknown factors. It could also be important for early identification of a higher risk subgroup in whom early and aggressive interventions may be appropriate.

In this proposed study using data from ARIC, we aim to investigate the association of having a history of cancer with the presence of subclinical myocardial damage, assessed via high-sensitivity cardiac troponin T (hs-cTnT). Our primary analyses will focus on breast cancer. Secondary analyses will be conducted with all cancers and other cancer subtypes.

5. Main Hypothesis/Study Questions:

Aim: We aim to investigate whether participants with a history cancer, particular breast cancer among women, are more likely to have evidence of subclinical myocardial damage, assessed via hs-cTnT, at visit 5.

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 methodological limitations or challenges if present).

Study design: We will perform cross-sectional analyses investigating the association of history cancer and elevated hs-cTnT at Visit 5. Our primary analysis will be limited to women and will focus on breast cancer. For this analysis, we will limit the study population to female participants who attended Visit 5, and exclude all participants with self-reported cancer as those cases have not been adjudicated. We will also perform analyses restricting the population to participants who attended Visit 5 through 12/31/2012, as cancer cases beyond this date have not been adjudicated creating the potential for substantial misclassification. Analyses will be stratified according to history of clinical CVD (coronary heart disease or heart failure). We will also explore the association of other cancers and subclinical myocardial damage. We will exclude participants missing hs-cTnT or covariates of interest at Visit 5.

Exposures: Cancer diagnoses in ARIC were ascertained through linkage with state cancer registries in Minnesota, North Carolina, Maryland and Mississippi. Additional information was obtained directly from participants of family members during annual follow-up calls, and review of hospital discharge codes from all hospitalizations.

Outcomes: The primary outcome will be subclinical myocardial damage, defined as elevated hs-cTnT at Visit 5. Elevated hs-cTnT will be defined using age- and sex-specific cutoffs in older adults (15). We will perform additional sensitivity analyses using hs-cTnT >14ng/L as the outcome. This latter cut point is the manufacturer reported the 99th percentile for a reference healthy population and the cutoff used in many prior studies.

Covariates: Covariates of interest will be assessed at Visit 5 and include: age, sex, race-center, smoking status, total cigarette-years, alcohol use, BMI, LDL and HDL-
cholesterol, triglycerides, use of lipid lowering medications, systolic blood pressure, use of anti-hypertensive medications, LVH, diabetes, and estimated GFR.

Main Analyses:
1. Table 1: we will examine the distribution of demographics, cardiovascular risk factors and hs-cTnT, limited to those women who attended visit 5, according to history of breast cancer.
2. Table 1S: we will examine the distribution of demographics, cardiovascular risk factors and hs-cTnT among all participants according to history of any cancer and cancer subtypes limited to those who attended visit 5.
3. We will conduct progressively adjusted logistic regression to examine the association of history of breast cancer and elevated hs-cTnT among women who attended visit 5.
4. We will conduct analyses stratified by CVD status, and assess for possible interaction between CVD and history of breast cancer on the outcome of elevated hs-cTnT.
5. We will perform analyses stratified by year of breast cancer diagnosis given temporal trends in breast cancer treatment.
6. We will repeat the analysis above stratified by age and race, and also test for formal interaction by these variables.
7. We will perform additional analyses to examine the association of other cancers and elevated hs-cTnT in all participants who attended visit 5.
8. Adjustment models:
   a. Model 1: age, gender, race-center
   b. Model 2: Model 1+smoking status, total cigarette-years and alcohol use
   c. Model 3: Model 2+ BMI, LDL and HDL-cholesterol, triglycerides, use of lipid lowering medications, systolic blood pressure, use of anti-hypertensive medications, LVH, diabetes, estimated GFR

Sensitivity Analyses:
1. To examine survival bias, we will compare the distribution of cardiovascular risk factors at Visits 1-4 and intervening cardiovascular events among participants who died following a cancer diagnosis prior to visit 5 to those participants with a cancer diagnosis who did attend visit 5 and those participants who remained free of cancer by visit 5.
2. We will compare the main results to results after excluding individuals with a cancer diagnosis within one year of Visit 5, given the possibility of ongoing radio or chemotherapy around the time of collection of blood samples for hs-cTnT measurement.
3. We will also conduct exploratory analyses examining hs-cTnT at visits 2 and 4 among early cases of cancer (occurring prior to those visits); this analysis will necessarily be exploratory given the small numbers of cases. We will also compare prior (pre-cancer) hs-cTnT levels among those persons with a history of cancer by visit 5.
4. We will perform additional sensitivity analyses using hs-cTnT >14ng/L as the outcome.

Limitations:
1. Residual confounding.
2. Lack of information on cancer treatment.
3. Lack of information on cancer staging.
4. Possibility of multiple cancer recurrences that are not accounted for.
5. Cancer ascertainment only through 12/31/2012.
6. Lack of detailed information on history of cancer prior to Visit 1.
7. Potential for survivor bias.

7.a. Will the data be used for non-CVD analysis in this manuscript?  
____ Yes  ___X__ 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?  
____ Yes  ___X__ No
(This file ICTDER03 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)?

Published manuscripts:


**Manuscript proposals:**

ARIC Manuscript Proposal # 1520: Statins, cholesterol, and prostate cancer in the Atherosclerosis Risk in Communities (ARIC) study

ARIC Manuscript Proposal #2826: NSAIDs for the Prevention and Control of Prostate Cancer

ARIC Manuscript Proposal #2812: Statins and bladder cancer

ARIC Manuscript Proposal #2795: Atrial Fibrillation and the Risk of Cancer: the ARIC Study

ARIC Manuscript Proposal #2711: Physical Activity and Lifetime Risk of Incident Cardiovascular Disease, and Cancer: the 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* 2013.20 ___)
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/

12. 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.