ARIC Manuscript Proposal #2912

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

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 ____ 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:

Alexandra K. Lee, John W. McEvoy, Ron C. Hoogeveen, Christie M. Ballantyne, Elizabeth Selvin. Severe Hypoglycemia and Elevated High-Sensitivity Cardiac Troponin T in Older Adults With Diabetes- The ARIC Study. J Am Coll Cardiol. 2016;68(12):1370-1371

Joshu CE, Prizment AE, Dluzniewski PJ, Menke A, Folsom AR, Coresh J, Yeh HC, Brancati FL, Platz EA, Selvin E. Glycated hemoglobin and cancer incidence and mortality in the Atherosclerosis in Communities (ARIC) Study, 1990-2006. Int J Cancer. 2012 Oct 1;131(7):1667-77.

Rasmussen-Torvik LJ, Shay CM, Abramson JG, Friedrich CA, Nettleton JA, Prizment AE, Folsom AR. Ideal cardiovascular health is inversely associated with incident cancer: the Atherosclerosis Risk In Communities study. Circulation. 2013 Mar 26;127(12):1270-5.

Prizment AE, Folsom AR, Dreyfus J, Anderson KE, Visvanathan K, Joshu CE, Platz EA, Pankow JS. 2013. Plasma C-reactive protein, genetic risk score, and risk of common cancers in the Atherosclerosis Risk in Communities study. Cancer Causes Control. 24(12):2077-87.

Kucharska-Newton AM, Rosamond WD, Mink PJ, Alberg AJ, Shahar E, Folsom AR. 2008. HDL-cholesterol and incidence of breast cancer in the ARIC cohort study.. Ann Epidemiol. 18(9):671-7.

Kucharska-Newton AM, Rosamond WD, Schroeder JC, McNeill A M, Coresh J, Folsom AR. 2008. HDL-cholesterol and the incidence of lung cancer in the Atherosclerosis Risk in Communities (ARIC) study.. Lung Cancer. 61(3):292-300.

Ahmed RL, Schmitz KH, Anderson KE, Rosamond WD, Folsom AR. 2006. The metabolic syndrome and risk of incident colorectal cancer.. Cancer. 107(1):28-36.

Tande AJ, Platz EA, Folsom AR. 2006. The metabolic syndrome is associated with reduced risk of prostate cancer.. Am J Epidemiol. 164(11):1094-102.

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.

1. Miller KD, Siegel RL, Lin CC et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016;66:271-89.
2. Patnaik JL, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. Breast Cancer Res 2011;13:R64.
3. Bradshaw PT, Stevens J, Khankari N, Teitelbaum SL, Neugut AI, Gammon MD. Cardiovascular Disease Mortality Among Breast Cancer Survivors. Epidemiology 2016;27:6-13.
4. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared Risk Factors in Cardiovascular Disease and Cancer. Circulation 2016;133:1104-14.
5. Libby P. Inflammation and cardiovascular disease mechanisms. Am J Clin Nutr 2006;83:456S-460S.
6. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860-7.
7. Lefrak EA, Pitha J, Rosenheim S, Gottlieb JA. A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer 1973;32:302-14.
8. Moslehi JJ. Cardiovascular Toxic Effects of Targeted Cancer Therapies. N Engl J Med 2016;375:1457-1467.
9. Cote GM, Sawyer DB, Chabner BA. ERBB2 inhibition and heart failure. N Engl J Med 2012;367:2150-3.
10. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments. Nat Rev Cardiol 2015;12:547-58.
11. de Lemos JA. Increasingly sensitive assays for cardiac troponins: a review. JAMA 2013;309:2262-9.
12. Saunders JT, Nambi V, de Lemos JA et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Circulation 2011;123:1367-76.
13. de Lemos JA, Drazner MH, Omland T et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA 2010;304:2503-12.
14. McEvoy JW, Chen Y, Nambi V et al. High-Sensitivity Cardiac Troponin T and Risk of Hypertension. Circulation 2015;132:825-33.
15. Gore MO, Seliger SL, Defilippi CR et al. Age- and sex-dependent upper reference limits for the high-sensitivity cardiac troponin T assay. J Am Coll Cardiol 2014;63:1441-8.