ARIC Manuscript Proposal # 3257

PC Reviewed: 10/9/2018  Status: _____  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

1.a. Full Title: Heart Failure Prediction in Cancer Survivors

b. Abbreviated Title (Length 26 characters): Biomarkers, cancer, CHF

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

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3. Timeline:

Analysis is anticipated to begin as soon as approval is obtained. The manuscript is to be prepared as soon as analyses are available. The analysis and manuscript preparation is anticipated to take place within one year of approval of the proposal.

4. Rationale:

Improvements in cancer treatments have led to increased life expectancy in cancer patients, however, a subgroup of patients develop significant cardiovascular side effects which may include cardiomyopathy, myocardial ischemia, myocarditis, thromboembolism, hypertension, myocarditis and arrhythmias (1,2). Breast cancer patients are particularly susceptible, with cardiomyopathy developing in ~ 8% of those treated with anthracyclines and 27% in those receiving both anthracycline and trastuzumab (3). Notably, some of the highest risk patients never develop cardiomyopathy, while some who receive low doses of anthracyclines develop subsequent heart failure. Furthermore, with the improvement in cancer care, cardiovascular diseases (CVD) have become a leading source of morbidity and mortality in cancer survivors (4). Therefore, there is a significant need for the development of a risk prediction model to help identify cancer patients at high risk of CVD and particularly heart failure.

Cardiac troponin T and I (cTnT and cTnI) are well-established biomarkers of myocardial injury (5), and have been associated with incident CVD -especially heart failure hospitalization. In 2000, Cardinale et al. demonstrated the prognostic importance of cTnI in patients treated with high dose chemotherapy. In 204 patients treated with high dose chemotherapy for advanced or resistant cancers, detectable cTnI correlated with greater reductions in left ventricular systolic function, and this persisted at the 7-month follow-up (6). A subsequent study looking at 703 cancer patients undergoing high-dose chemotherapy found that those who had undetectable cTnI levels shortly after initiating chemotherapy and 1 month post chemotherapy, had no significant reduction in left ventricular function and a very low incidence of cardiac events (1%) including death, acute pulmonary edema, heart failure, left ventricular ejection fraction (LVEF) reduction >25% or life-threatening arrhythmias. Patients who had positive cTnI levels shortly after initiating high dose chemotherapy as well as one month later, had significantly reduced LVEF and high incidence of cardiac events (84%) at follow up (7). More recently, in a multicenter cohort of 78 patients with breast cancer treated with doxorubicin and trastuzumab, cTnI and myeloperoxidase were associated with reduction in LVEF of at least 10% (8). Overall, these studies provide evidence that biomarkers may predict adverse cardiovascular effects in high-risk cancer patients. However, the use of biomarkers in identifying CVD risk in a broad cancer population is less well characterized.
Speckle-tracking echocardiography including global-longitudinal strain assessment, has been shown to be a clinically relevant non-invasive method of identifying sub-clinical LV dysfunction in chemotherapy treated patients (9). In 81 women treated with anthracyclines followed by taxanes and trastuzumab, peak systolic longitudinal myocardial strain and cTnI predicted subsequent cardiotoxicity (10). This study among others, have led to the current Expert Consensus document, and recommends global longitudinal strain (GLS) assessment at baseline and follow up during chemotherapy. Those with a change in GLS >15% from baseline are likely to be of greatest risk for developing cardiotoxicity (9). This emerging technology has great potential to be combined with biomarkers to create a risk calculator, and effectively identify patients with the greatest and least risk for cardiomyopathy following chemotherapy.

The Atherosclerosis Risk in Communities (ARIC) study has not only measured biomarkers and GLS but has now characterized cancer phenotypes. Using previously developed biomarker models of predicting CVD and heart failure (11,12) we propose to study the ability of the biomarkers in predicting incident CVD, incident HF, and incident GLS in the ARIC cancer survivors.

5. Main Hypothesis/Study Questions:

**Hypothesis:** Serum biomarkers including troponin T (measured with a high sensitivity assay), NT-pro BNP and galectin-3 are associated with and will predict incident cardiovascular events (all cause mortality, heart failure hospitalization, myocardial infarction, stroke) in cancer (excluding non-melanoma skin cancers) survivors.

**Study questions:**

What are the visit 4 levels of biomarkers cTnT, NT-pro BNP and galectin-3 in cancer survivors (those diagnosed with cancer between baseline and before visit 4 attendance), overall and by common cancer site? These subjects will be stratified by gender and time between cancer diagnosis, and date of visit 4 and visit 5. There are 545 individuals diagnosed with cancer between time of enrollment and visit 4, excluding non-melanoma skin cancer, with the greatest subgroups including 160 prostate, 140 breast and 50 colon cancers. By visit 5, there are 4107 individuals with cancer with subgroups of highest numbers including 887 prostate, 748 lung, 696 breast. Of note, there is some preliminary unpublished data in ARIC regarding cTnT at visit 5 and association with cancer status (now submitted for publication), however, it will be important for the present study to evaluate cTnT at visit 4, as well as characterize NT-proBNP and galectin-3 levels.

1. Are cTnT, NT-pro BNP and galectin-3 at visit 4, associated with incident cardiovascular events in cancer survivors (those diagnosed with cancer between baseline and before V5 attendance)? If so, how do they compare with non-cancer survivors?
2. Among cancer survivors, are cTnT, NT-pro BNP and galectin-3 at visit 4 associated with global longitudinal strain at visit 5?

![Cancer Diagnosis and CV Events Timeline]

Figure 1: study time course

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).

ARIC visit 4 (1996–98) will serve as the baseline visit for the analysis. Variables of interest include age, gender, race, physical activity, body mass index, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, smoking status by pack-years, alcohol use, hypertension, diabetes, chronic kidney disease status, cardiovascular medications used (aspirin, statin, etc.), and diagnosis of atrial fibrillation. Biomarkers measured will include high sensitivity troponin T (cTnT), NT-pro brain natriuretic peptide (NT-proBNP) and galectin-3.

After traditional ARIC exclusions (races that are neither White or Black, center based exclusions) and excluding individuals with prevalent CVD (CAD, HF, ischemic stroke), all subjects with available information on the above variables will be eligible for the analysis. Subjects will be classified as those with any history of cancer (as previously determined by adjudication teams in Joshu et al. 2017, via cancer registries, self-report, ICD code on discharge summary, or death certificate) excluding patients with non-melanoma skin cancer, and those without cancer. Subjects with incident cancer diagnosis between visit 4 and 5 will also be included in the study. Distribution of the biomarkers in those with cancer will be compared to those without. The primary outcome will be incident cardiovascular event (all cause mortality, heart failure admission, myocardial infarction, or stroke).

Using Cox proportional hazards models, we will describe the association between cTnT, NT-proBNP, galectin-3, and incident cardiovascular events stratified by cancer status. If associations are present, we will assess the performance of these biomarkers individually, in concert (lab model including: age, race cTnT, NT-proBNP, as per Nambi et al., 2013) and in addition to traditional risk factors for its ability to predict cardiovascular events among cancer patients using traditional metrics including area under the receiver operator (ROC) curve (AUC), IDI, reclassification and NRI.
Subsequently, logistic regression will be done using global longitudinal strain (GLS) as the outcome measure of interest. Statistical power for CV events may be a concern, therefore in the present study we would like to also use strain as a surrogate for incident HF. After understanding the distribution of GLS/normalizing we will evaluate the association of the biomarkers with GLS after adjustment for traditional CVD risk factors.

Some challenges and limitations of the study include achieving adequate power for the incident CVD outcome. Based on preliminary calculations, by visit 4 there are 545 individuals diagnosed with cancer, excluding non-melanoma skin cancer with the greatest subgroups including 160 prostate, 140 breast and 50 colon cancers. Assuming a 14% event rate for heart failure in controls, the minimum detectable association between heart failure events between control and cancer subjects assuming power 0.8 and two-sided alpha 0.05, would be a hazard ratio of 1.45 for total cancer, 1.8 for breast cancer, 1.7 for prostate cancer, and 3.0 for colorectal cancer, which we feel is reasonable. Since we will also be including individuals diagnosed with cancer between visit 4 and 5, the numbers in each group will be higher, thus the ability to detect true differences is likely underestimated here. While it will be ideal to evaluate by cancer sub-type and by CVD event sub-type the power may be lacking- hence we will combine the cancers and the incident CVD events for the main analysis. Given the importance of incident HF as an outcome we will study this separately and further strengthen this analysis by evaluating incident GLS as well. Other limitations inherent in the study design include attrition and survival bias.

Finally, we do not yet have data including the chemotherapy treatments for each subject. We would expect greater events in patients treated with certain classes of chemotherapy than those treated surgically, however understanding a risk of developing CV events in cancer patients also necessitates understanding the risk for cancer patients as a larger group. Chemotherapy treatment data is currently being collected by adjudication teams and could allow for future studies to examine how specific chemotherapy regimens may be associated with CV events.

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 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

    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)?

ARIC Proposals: #2912 Subclinical Myocardial Damage Among Cancer Survivors in ARIC; #3013 Association of high-sensitivity cardiac troponin T and natriuretic peptide with cancer risk and mortality in the community-based cohort; 3038 Cancer risk in persons with clinical cardiovascular disease.

Publications as below:

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 * #2008.10; 2011.07; 1995.04
  ___ _ 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

References:

1. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments. Nat Rev Cardiol. 2015;12:547-558

2. Chang, HM, Moudgil R, Scarabelli T, Okwuosa TM, and Yeh EH. Cardiovascular Complications of Cancer Therapy. JACC. 2017;70(20):2536-2565


