ARIC Manuscript Proposal # 3028

PC Reviewed: 8/8/17	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Cardiovascular Risk Among Cancer Survivors in the ARIC Study

b. Abbreviated Title (Length 26 characters): CVD and Cancer

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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:

Early detection and improvements in treatment have lead to dramatic increases in cancer survivorship, highlighting the importance of non-cancer health-related issues of this population. Survivors of cancer are increasingly recognized as a population at increased risk for cardiovascular disease (CVD). Accumulating evidence suggests CVD is the leading cause of morbidity and mortality in survivors of certain malignancies (1,2). Excess cardiovascular risk beyond 50 years of age has been well characterized among survivors of childhood cancer (2). Among women diagnosed with breast cancer in adulthood, death from CVD surpasses death from cancer approximately 5-10 years after cancer diagnosis (1). CVD mortality is particularly common among older women with a history of breast cancer and those with local disease at the time of diagnosis (3).

Several factors may converge to increase CVD risk among survivors of cancer. Cancer and CVD share several risk factors, including obesity and diabetes, suggesting a common biology. Retrospective data have yielded conflicting results regarding the burden of CVD risk factors at the time of cancer diagnosis likely reflecting differences in the underlying populations at risk for various malignancies (4,5). However, it is well established that following diagnosis and treatment of cancer, patients are prone to decreases in physical activity and weight gain, with high incidence of hypertension and metabolic abnormalities (6-9). Additionally, several cancer therapies are associated with cardiovascular toxicities. Traditional cancer treatments such as radiation and anthracycline-based chemotherapy are known to cause cardiovascular complications such as coronary artery disease, cardiac dysfunction and heart failure (10). Additionally, novel targeted therapies are being increasingly associated with adverse cardiac effects through a combination of on- and off-target mechanisms (10,11). Lastly, CVD may be associated with worse outcomes in this population with unique characteristics. For example, cardiac dysfunction from anthracycline is associated with 3.5 times higher mortality compared to idiopathic cardiomyopathy and 2-year mortality rates as high as 60%(12).

Data from large prospective cohort studies are needed to rigorously understand the full burden of CVD after a cancer diagnosis. The Atherosclerosis Risk in Communities (ARIC) Study offers a unique opportunity to prospectively evaluate the associations of cancer with various types of CVD and CVD mortality. The current proposal aims to investigate the rates of CVD events among ARIC participants with a history of cancer, and test the hypothesis that these patients have increased risk of CVD events compared to ARIC participants without a history of malignancy.

5. Main Hypothesis/Study Questions:

Aim:

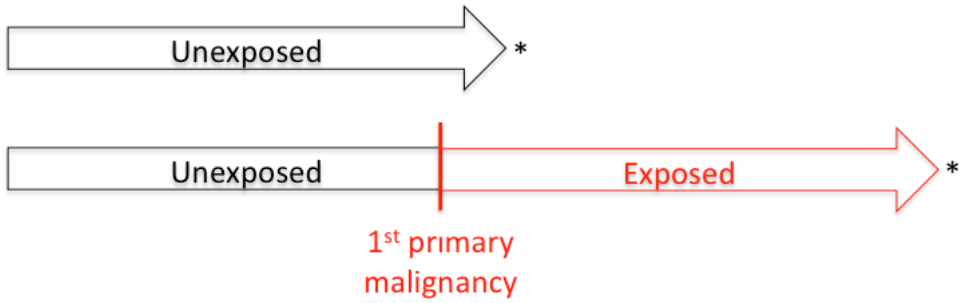
1. To estimate the risk of incident CVD following a first primary diagnosis of cancer

2. To compare the risk of incident CVD following a first primary diagnosis of cancer to the risk of incident CVD among persons without a cancer diagnosis

   a) Cancer of any site
   b) Common cancers (lung, breast, prostate, or colorectum)
   c) Cancer diagnosed at a local or regional/distant stage

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 conduct a prospective cohort study (Figure). Participants without a history of CVD or cancer will be followed from Visit 1. Individuals will contribute person-time into the "unexposed" group until the development of: a) CVD event; b) 1st primary malignancy; or c) end of study follow up. Participants will be censored at the time of CVD event or end of study follow up. If a participant develops a 1st primary malignancy prior to censoring, they will be continued to be followed and contribute person-time after the malignancy into the "exposed" group until development of CVD event or end of study follow up.



* Censoring at: a) CVD event; or b) end of follow up

Exclusions: We will exclude participants with a history of CVD (CHD, HF or stroke) or cancer at baseline and participants missing data on covariates of interest.

Exposures: The main exposure is a diagnosis of a first primary cancer, which is a time-varying exposure. Participants will contribute person-time at risk to the "no cancer" exposure category until a) the time that they are diagnosed with CVD (and then censored as an event), die, or reach the end of follow-up in 2012, or b) the time that they are diagnosed with a first primary cancer, at which point they will begin to contribute person-time at risk to the "cancer" exposure category until they are diagnosed with CVD, die, or reach the end of follow-up in 2012.

A similar approach will be used for site-specific cancers and cancer stage. Persons diagnosed with a cancer other than those of interest or a particular stage will contribute person-time at risk to the no cancer exposure group, and then if the person did not have CVD, die, or reach the end of follow-up, at the time of diagnosis of

another cancer or other stage, that person will be censored as not being at risk of a first primary cancer of that type or that stage.

In ARIC, cancer diagnoses were ascertained between 1987 and 2012 via linkage with state registries in MN, NC, MD, and MS. Additional information was obtained from medical records and hospital discharge codes. Participants who self-reported a diagnosis of cancer on one of the follow-up telephone calls were later contacted to provide additional information and had medical records reviewed. For bladder, breast, colorectal, liver, lung, pancreas, and prostate cancers not previously identified by registry linkage, cancer-related hospitalizations were included as cases after review of medical records. Information about deaths from cancer was obtained from death certificates where cancer was listed as the underlying cause of death.

Outcomes:

1. Primary outcomes: Incident CVD defined as incident fatal or non-fatal CHD, HF or stroke. CHD will be defined as definite or probable myocardial infarction, or definite coronary death; HF defined as death from HF or first HF-related hospitalization; or stroke as definite or probable stroke, ischemic or hemorrhagic.
2. In secondary analyses, we will evaluate each of the CVD outcomes (CHD, HF, or stroke) separately.

Covariates: Demographic variables: age, sex, race-center and education level. CVD risk factors: smoking status, total cigarette-years of smoking, alcohol use, BMI, LDL and HDL-cholesterol, triglycerides, use of lipid lowering medications, systolic blood pressure, use of anti-hypertensive medications, diabetes, estimated GFR, NSAID use (including ASA), and hormone replacement therapy.

Main Analyses:

1) We will perform univariate comparisons of demographics and cardiovascular risk factors at Visit 1 between "exposed" and "unexposed" participants (i.e., those persons who subsequently develop cancer vs. those who do not).
2) We will use Poisson regression to estimate the age, sex, and race-center adjusted incidence rates of CVD events among individuals classified as "exposed" and "unexposed" [see Exposure definition].
3) We will use Cox proportional hazards regression models to estimate the hazard ratios and corresponding 95% CIs for incident CVD comparing the "exposed" and "unexposed" groups.
4) We will repeat the analyses above stratified by cancer subtype: lung, post-menopausal (female) breast, colorectal, prostate, and persons with multiple primary malignancies.
5) Adjustment models:
    a. Model 1: Adjusted for age, race-center, sex, educational level
    b. Model 2: Model 1 + BMI, LDL-C and HDL-C, triglycerides, use of lipid lowering medications, systolic blood pressure, use of anti-hypertensive medications, diabetes, estimated GFR.
    c. Model 3: Model 2 + NSAID use and hormone replacement therapy use

Sensitivity Analyses:

1) We will repeat analyses above using CHD, HF and stroke as separate outcomes.

Limitations:

- We will likely have limited power for analyses of cancer subtype, stage, and in analyses of other subgroups
- Lack of information on cancer treatments, which may have difference cardiac toxicities.
- As with any observational study, there is the likelihood of residual confounding

7.a. Will the data be used for non-CVD analysis in this manuscript?
_X (cancer)___ 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 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:

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.

Kubota Y, Evenson KR, Maclehose RF, Roetker NS, Joshu CE, Folsom AR. Physical Activity and Lifetime Risk of Cardiovascular Disease and Cancer. Med Sci Sports Exerc. 2017 Aug;49(8):1599-1605.

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

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 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 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:

1. Bradshaw PT, Stevens J, Khankari N, Teitelbaum SL, Neugut AI, Gammon MD. Cardiovascular Disease Mortality Among Breast Cancer Survivors. Epidemiology 2016;27:6-13.
2. Fidler MM, Reulen RC, Henson KE et al. Population-Based Long-Term Cardiac-Specific Mortality Among 34,489 Five-Year Survivors of Childhood Cancer in Great Britain. Circulation 2017.
3. Abdel-Qadir H, Austin PC, Lee DS et al. A Population-Based Study of Cardiovascular Mortality Following Early-Stage Breast Cancer. JAMA Cardiol 2016.
4. Danese MD, O'Malley C, Lindquist K, Gleeson M, Griffiths RI. An observational study of the prevalence and incidence of comorbid conditions in older women with breast cancer. Ann Oncol 2012;23:1756-65.
5. Al-Kindi SG, Oliveira GH. Prevalence of Preexisting Cardiovascular Disease in Patients With Different Types of Cancer: The Unmet Need for Onco-Cardiology. Mayo Clin Proc 2016;91:81-3.
6. Gross AL, May BJ, Axilbund JE, Armstrong DK, Roden RB, Visvanathan K. Weight change in breast cancer survivors compared to cancer-free women: a prospective study in women at familial risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2015;24:1262-9.
7. Vance V, Mourtzakis M, McCargar L, Hanning R. Weight gain in breast cancer survivors: prevalence, pattern and health consequences. Obes Rev 2011;12:282-94.
8. Cardinale D, Bacchiani G, Beggiato M, Colombo A, Cipolla CM. Strategies to prevent and treat cardiovascular risk in cancer patients. Semin Oncol 2013;40:186-98.
9. Weaver KE, Foraker RE, Alfano CM et al. Cardiovascular risk factors among long-term survivors of breast, prostate, colorectal, and gynecologic cancers: a gap in survivorship care? J Cancer Surviv 2013;7:253-61.
10. Moslehi JJ. Cardiovascular Toxic Effects of Targeted Cancer Therapies. N Engl J Med 2016;375:1457-1467.
11. Hahn VS, Lenihan DJ, Ky B. Cancer therapy-induced cardiotoxicity: basic mechanisms and potential cardioprotective therapies. J Am Heart Assoc 2014;3:e000665.
12. Cardinale D, Colombo A, Lamantia G et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol 2010;55:213-20.