ARIC Manuscript Proposal # 3038

PC Reviewed: 09/12/17  Status: _____  Priority: 2
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1.a. Full Title: Cancer risk in persons with clinical cardiovascular disease

b. Abbreviated Title (Length 26 characters): Clinical CVD and cancer risk

2. Writing Group:
   Writing group members: Yejin Mok, Roberta Florido, Elizabeth Selvin, Anna Prizment, Corinne Joshu, Elizabeth A. 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:
   Improvements in management and treatment have led to an increase in a number of adults with a history of cardiovascular disease (CVD). Indeed, 92.1 million US adults are estimated to live with cardiovascular disease (CVD) [1]. The risk of CVD mortality is relatively high during the first few years after incident CVD, but, after that, the risk of non-CVD mortality starts to increase [2, 3]. In addition, hospitalizations due to non-CVD causes are common among patients with CVD, and cancer is a leading non-CVD cause [4]. However, the clinical management of patients with CVD has been mainly focusing on preventing recurrence of CVD outcomes, and
the risk of non-CVD outcomes, particularly cancer, in this clinical population has not been rigorously investigated.

In this context, a few recent epidemiologic studies have reported increased cancer risk among patients with CVD [3, 5-12]. For example, a Danish study reported only an increase in smoking-related cancer (cancers of the lung, larynx, oral cavity, tongue, pharynx, esophagus, pancreas, kidney, and urinary bladder) among those with CVD [8]. Subsequent studies showed a marginal increase in the risk of non-smoking-related cancer such as digestive cancer in this clinical population [3, 9, 12].

There are a few plausible pathophysiologic mechanisms behind potentially elevated cancer risk among CVD patients. Shared risk factors such as smoking, alcohol intake and diabetes may contribute to promote the risk of both cardiovascular disease and cancer. Inflammation may be another potential link since it plays a major role in the progression of CVD and cancer [13-15]. More specifically, inflammation is associated with malignant transformation with an influence on proliferation of cell, stimulating angio-neogenesis and apoptosis [15]. Also, some medications for CVD patients may alter cancer risk [16].

Nonetheless, there are several limitations in those previous epidemiological studies. First, these studies used different definitions of CVD (self-reported CVD [5], overall vascular disease even including its risk factors such as hypertension, dyslipidemia or diabetes [6], ischemic stroke [11], heart failure [7, 10], heart failure after myocardial infarction [MI] [3], cardiac revascularization [9], and atherosclerosis [8]), it is hard to derive definite conclusions. Second, site-specific cancers are yet to be intensively and comprehensively explored.

To overcome those caveats, using data from the Atherosclerosis Risk in Communities (ARIC) study, we will comprehensively investigate whether patients who developed clinical CVD (coronary disease, stroke, and heart failure) have a higher risk of overall and site-specific cancer incidence and mortality compared to those who did not. This investigation will have a few public health and clinical implications. For example, persons with CVD could be further encouraged for behavioral modification (e.g., smoking and alcohol intake), aiming for the risk of both cardiovascular disease and cancer. Also, recommendations for established screening programs such as colorectal cancer (aged ≥50 years) and lung cancer (current or former smokers ages 55-74 years in good health with at least a 30 pack-y history) [17] do not necessarily involve any considerations for CVD status. Individuals eligible for cancer screening programs with prior CVD should be particularly encouraged to adhere to those established screening programs.

5. Main Hypothesis/Study Questions:

- Persons with clinical CVD defined as MI, heart failure or stroke have increased risk of cancer incidence and mortality compared to those without clinical CVD.
- The increased cancer risk in those with CVD could be due to shared risk factors for CVD and cancer and reduced uptake of cancer screening in those with CVD.
- Alternatively, cancer risk might be attenuated by the use of medications used to treat CVD and associated conditions, such as statin and antiplatelet.

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).
Study design:
- Matched-cohort study
  - We will primarily conduct a matched-cohort study using incidence density sampling without replacement of controls. We will match participants who developed CVD by age (± 5 years) to 2 non-exposed persons randomly selected from participants who were alive and actively followed at least for the same period (time to incident CVD) but did not develop CVD or cancer during that time [18].
  - If feasible, we will match the exposed (CVD) and unexposed groups (no CVD) on other potentially confounding factors (sex, race, heart rate, smoking status, physical activity, the presence of hypertension and diabetes, and the use of cardiovascular medications [e.g., statin]).

Figure. Matched-cohort study design with incidence density sampling in which unexposed persons (no CVD) are selected at each time a person becomes exposed (developed incident clinical CVD) occurs

- Incident CVD as a time-varying covariate
  - Secondarily, we will model incident CVD as a time-varying exposure in the entire cohorts and quantify whether it is associated with cancer risk accounting for time-fixed and time-varying covariates.
Inclusions:
- All ARIC participants without a history of a diagnosis of CVD or cancer at Visit 1.

Exclusions:
- Individuals self-reported with CVD diagnosis (coronary heart disease, heart failure or stroke) or cancer prior to baseline (Visit 1)
- Participants with prevalent cancer at baseline
- Race other than White and Black
- Participants missing data on covariates of interest

Exposures:
- The main exposure is a non-fatal incident CVD event (MI, heart failure and stroke). MI will be defined as definite or probable non-fatal MI cases adjudicated by the ARIC physician panel. Heart failure will be defined as a hospitalization having in any position a ICD-9 code 428 or ICD-10 code I50 for heart failure diagnosis. Stroke will be defined as definite or probable stroke, ischemic or hemorrhagic stroke.

Covariates:
Covariates of interest: socio-demographic characteristics (age, race, gender, education), alcohol intake, smoking status, body mass index, family history of cancer (Visit 3), hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, use of antihypertensive medication), diabetes (fasting blood glucose ≥126 mg/dl, non-fasting glucose ≥200 mg/dl, reported diagnosis of diabetes, or use of diabetes medication), lipid parameters (total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride), statin use, and antiplatelet use. We are going to use the updated covariates over time.

Outcomes:
- Cancer incidence (first primary invasive)
- Cancer mortality
- 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])
  - Post-menopausal breast (women)
  - Bladder
  - Endometrial (women)
  - Colon/rectum*
  - Kidney/other urinary
  - Lung*
  - Pancreas*
  - Prostate* (men)
Statistical Analysis:

1. We will summarize [if decide that the main analysis will use the cohort design: age-adjusted (or age-standardized)] characteristics at Visit 1 as well as at the time of matching by participants with/without incident CVD during the follow-up, overall, and by sex and by race.

2. The cumulative incidence rate of overall and site-specific cancer will be examined by those with incident CVD and without. We will also compare the ranking of cancer types between these two groups.

3. To describe the observed risk of cancer incidence and mortality in those with and without CVD, we will use Kaplan-Meier method, overall, by age group (5 year bins) separately by sex, separately by race, and separately by joint categories of sex and race.

4. We will quantify the association of incident CVD with cancer incidence (total, system-specific, site-specific) and mortality using two multivariable models: Cox proportional hazard models and Gray piecewise constant time-varying coefficients model to estimate the hazard ratios and 95% CI. Those models will adjust for covariates listed above.
   a. Cox proportional hazards model: we will construct a Cox model without consideration of potential non-proportional hazards.
   b. Gray piecewise constant time-varying coefficients model [19, 20]: Gray model which is extension of Cox model assumes time-variant effects of exposure and estimates the hazards to change over different time intervals.

5. We will repeat the analyses above for individual CVD subtypes (MI, heart failure, and stroke).

6. We will conduct a few sensitivity analyses.
   a. To explore the contributions of CVD to overall and site-specific cancer risk is due to shared risk factors, we will perform subgroup analysis according to age, gender, race, smoking status, alcohol intake, and clinical conditions (diabetes, hypertension, obesity, and chronic kidney disease). Statistical interaction between CVD and those variables will be assessed by likelihood ratio tests.
   b. To explore increased risk of cancer are due to opportunity for screening for cancer, we will adjust for uptake of medical care (annual exam) and access to medical care (health insurance) as a surrogate for opportunity for screening for cancer. Also, since most of the increased health demands of CVD patients tends to occur early (during the first year of diagnosis) we will confirm cumulative incidence by years after incident CVD.
   c. To explore whether overall and site-specific cancer are attenuated by medications to treat CVD, we will perform subgroup analysis by statin use and antiplatelet use among patients with CVD.
   d. We will do competing risk analyses using Fine and Gray’s method to determine effect estimates in the presence of a competing risk [21]. Since cardiac mortality is relatively high during the first few months after incident CVD, after that, it falls considerably in CVD patient who survive, we will conduct competing risk analysis with death before cancer incidence as a competing event.

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  _ x _ 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)?
   #2795: Atrial fibrillation and the Risk of Cancer: the ARIC Study
   #3013: Association of high-sensitivity cardiac troponin T and natriuretic peptide with cancer risk and mortality in the community-based cohort

These proposals have a similar concept, but no actual overlap is recognized.

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

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


