ARIC Manuscript Proposal #4103

PC Reviewed: 8/9/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Peripheral artery disease and subsequent risk of cancer: the Atherosclerosis Risk in Communities (ARIC) Study

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

2. Writing Group:
Writing group members: Shoichiro Nohara, Yejin Mok, Jeremy Van't Hof, Maya Salameh, Corinne E Joshu, Elizabeth A Platz, Roberta Florido, Kunihiro Matsushita, Others welcome

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

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3. Timeline: Analysis will begin following proposal approval and completion of visit 1 data cleaning. A manuscript will be completed within 6 months after for the approval of this proposal.

4. Rationale:
Cardiovascular disease (CVD) and cancer share common risk factors such as smoking and obesity (1-5). Moreover, several studies have reported shared pathophysiological pathways (e.g., oxidative stress, chronic inflammation, and angiogenesis) for the onset and progression of both

CVD and cancer (6-10). Indeed, several studies have shown elevated risk of CVD among patients with cancer (11-13) and increased risk of cancer among patients with CVD such as myocardial infarction and heart failure (14-19).

Lower extremity peripheral artery disease (PAD) is another CVD subtype, which affects over 200 million people worldwide (20, 21). Prior studies have indicated potentially increased risk of cancer in persons with PAD (22-27). For example, a large Danish cohort reported that patients with PAD defined by the presence of intermittent claudication had a higher risk of cancer, particularly tobacco-related cancers (e.g., lung cancer), compared to the general population (24). However, there are several important limitations in the published literature. Specifically, most of these studies did not adjust for some important confounders such as smoking and diabetes (24-27) and had relatively short follow-up period (e.g., <10 years) (23-26). Moreover, all studies included only Whites or did not report race-specific results (22-27) while cancer epidemiology varies considerably across racial groups (28, 29).

To overcome these caveats, we will quantify the association of PAD with cancer incidence and mortality using data from the Atherosclerosis Risk in Communities (ARIC) Study, a biracial community-based cohort with follow-up over 30 years. ARIC will allow us to explore different definitions of PAD, e.g., symptomatic PAD, asymptomatic PAD according to ankle-brachial index (ABI), and hospitalization-based PAD.

5. Main Hypothesis/Study Questions:

- PAD is associated with cancer incidence and mortality.
- The association is particularly evident in tobacco-related cancer (e.g., lung cancer) but remains significant even after adjustment for smoking status and cumulative tobacco exposure (cigarette-years).

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 population:
ARIC participants at Visit 1 (1987-89) (Aged 45-64)

Inclusions: All Black and White ARIC participants with data of baseline ABI at visit1

Exclusions:
Race other than Black or White
Individuals with self-reported history of cancer at visit 1
Individuals with no ABI data
Participants with missing data on covariates of interest

Exposure: PAD

1. Time-fixed exposure at visit 1

Symptomatic PAD will be defined as the self-reported intermittent claudication or a history of lower extremity revascularization at visit 1.

Asymptomatic PAD will be defined as ≤0.9 ABI, the ratio of blood pressure of the ankle to the upper arm.

2. Time-varying exposure during follow-up

We will also model incident PAD as a time-varying exposure. Specifically, participants without prevalent PAD and cancer will be followed from visit 1. They will contribute person-time into the "non-PAD" category until cancer diagnosis, death, loss to follow-up, or the end of study follow-up (December 31, 2015), whichever came first. If participants develop PAD prior to censoring (incidence cancer or death), they will begin contributing person-time to the "PAD" category until cancer diagnosis, death, loss to follow-up, or the end of study follow-up. Incident PAD will be defined by hospitalization with PAD based on International Classification of Diseases Code, Ninth Revision (ICD-9); 440.20, 440.21, 440.22, 440.23, 440.24, 440.29, 440.3, 440.4, 38.18, 39.25, 39.29, 39.50 and its corresponding ICD-10 codes as done in previous ARIC studies (30, 31).

Outcomes

Cancer incidence will be defined as the first primary invasive cancer (excluding non-melanoma skin cancer) diagnosis or death of cancer during ARIC follow-up periods. Data of cancer were collected from the linkage of the ARIC study with four state cancer registries (Minnesota, North Carolina, Maryland, and Mississippi). These data were complemented by the information from participants or their families directly, hospital discharge summary, and confirmation of medical records. Also, some site-specific cancer (i.e., bladder, breast, colorectal, liver, lung, pancreatic, and prostate cancer) were adjudicated by ARIC expert panels (32-34).

We will evaluate overall cancer first, and then explore by the group based on their primary risk factors of cancer because cancers are caused various risk factors such as environment factor (infection, smoking, alcohol, food, lifestyle, and radiation) and genetic factor. We are particularly interested in tobacco-related cancer, such as lung cancer, since smoking is one of the most potent risk factors of PAD. We will treat breast, ovarian, and colon cancer as a separate group because they have strong genetic risk factor (35, 36). Also, hepatocellular carcinoma, gastric, and cervical cancer are known to be associated with specific viruses or bacteria (37) and are treated as a separate group. We will exclude skin cancer from the outcome that is caused specific environmental exposure (ultraviolet rays exposure) (38). We will also assess cancer mortality.

Other variables of interest and covariates:

- Sociodemographics: age, gender, race, center, education level
- Lifestyle: smoking status, total cigarette-years of smoking, alcohol drinking status
- Physical information: diabetes mellitus, blood pressure, body mass index, lipid levels (total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride)
- history of other CVD subtypes (i.e., coronary heart disease, heart failure, or stroke)

Use of anti-hypertensive medications, cholesterol-lowering medications, and aspirin

Analysis plan:

・In this study, we will perform analyses defining PAD as two types of exposure; 1. Time-fixed exposure at visit 1 and 2. Time-varying exposure during follow-up.

・First, we will compare baseline characteristics at Visit 1 across categories of symptomatic PAD, asymptomatic PAD (ABI ≤0.9), and five other ABI categories (>0.9-1.0, >1.0-1.1, >1.1-1.2, >1.2-1.3, and > 1.3).

・We describe continuous variables as mean (SD) or as median with interquartile interval (IQI) and categorical variables are presented as numbers and ratios (%). We will compare the statistical difference among these category groups using the analysis of variance for continuous variables and the chi-squared test for categorical variables.

・We will examine the cumulative incidence of cancer incidence and mortality by PAD status at Visit 1 (i.e., symptomatic PAD, asymptomatic PAD, and other ABI categories) using the Kaplan-Meier method.

・We will run Cox proportional hazards models to estimate the hazard ratios and corresponding 95% CIs for cancer incidence and mortality according to PAD status accounting for potential confounders.

a. Model 1: adjusted for age, sex, race, center, and education level

b. Model 2: additionally adjusted for drinking status, systolic blood pressure, antihypertensive medication use, BMI, total and HDL cholesterol levels

c. Model 3: further adjusted for smoking status (never, former, and current), smoking pack years, and diabetes mellitus (two major risk factors of PAD)

・We will perform linear spline model among participants without symptomatic PAD to characterized the continuous association between ABI and the hazard ratio after fully-adjusted Cox model across the range of ABI values.

・We will also perform Cox proportional hazards models with incident PAD as a time-varying exposure.

・We will conduct a few sensitivity analyses: First, we will repeat the analysis excluding persons with prevalent CVD as this will likely be significantly more prevalent in the PAD group. Second, we will perform subgroup analysis according to age, gender, race, smoking status, and clinical conditions (e.g., the presence and absence of obesity, diabetes, and history of CVD). We will evaluate statistical interaction by comparing models with and without relevant interaction terms. Third, we will conduct competing-risk analysis using Fine and Gray' methods with non-cancer mortality as a competing event (39).

Limitations:

・Only Black and White populations.

・Defining incident PAD based on ICD diagnostic codes.

・As with any observational study, we will not be able to rule out the possibility of residual confounding.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes ____ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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/aricproposals/dtSearch.html

___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)?

#MP2022: Peripheral arterial disease and risk of incident heart failure in the Atherosclerosis Risk in Communities Study
#MP2248: Peripheral Arterial Disease as an Indicator of Enlarged Abdominal Aorta Diameters
#MP3028: Cardiovascular Risk Among Cancer Survivors in the ARIC Study
#MP3038: Cancer risk in persons with clinical cardiovascular disease
#MP3310: Ankle-brachial index and subsequent risk of infectious disease in older individual
#MP3244: Peripheral artery disease and its association with use of cigars, pipes and smokeless tobacco in the Atherosclerosis Risk in Communities 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
___ A. primarily the result of an ancillary study (list number* __ 2011.07 and 2014.05_____)
___ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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.

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