ARIC Manuscript Proposal #4064

PC Reviewed: 7/12/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Role of Obesity and Cardiovascular Disease in Cancer Development in ARIC-Cancer Participants with Cardiovascular Disease

b. Abbreviated Title (Length 26 characters): Obesity in CVD as a risk for cancer

2. Writing Group:

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

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3. Timeline:

Analysis completed within 3 months of approval of manuscript proposal, with manuscript drafted approximately 6 months later (December 2022).

4. Rationale:

Cardiovascular disease (CVD) and cancer often occur in the same patients, in part because of shared risk factors such as obesity (Koene et al). As compared with Caucasians, the prevalence

of obesity is higher in African Americans (AA), who in turn suffer from a higher burden of CVD and cancer-related mortality (Stocks et al, Frieden et al). Socioeconomic disparities due to systemic racism, chronic psychosocial stress, and lack of access to high-quality food and healthcare may promote obesity, thus exacerbating hypertension and other risk factors. The resulting pro-inflammatory milieu is potentially a significant risk factor for CVD and cancer. Population studies have reported associations between CVD and cancer risk (de Boers et al, Malmborg et al). In the general population, there is evidence of obesity itself increasing the risk of cancer (Gallagher et al). However, it is not known how modifiable risk factors such as obesity mediate the risk of development of cancer in those with CVD, especially among AAs who are at a higher risk of obesity. Investigating this risk can help influence care plans and recommendations for patients at a more individualized level.

Thus, we propose studying the role of obesity as a risk factor for cancer development in patients with CVD. We hypothesize that similar to the non-CVD population, obesity is a risk factor for the development of cancer in CVD patients. In addition, we hypothesize that this risk may be different in AAs vs European Americans (EAs),

5. Main Hypothesis/Study Questions:

Aim 1: Determine the association of a) obesity with the risk of cancer, especially obesity-associated cancers, in participants with CVD.
The analysis will be adjusted for covariates including demographic factors (e.g., age, sex, race), shared modifiable risk factors for cancer (apart from obesity) and CVD, hypertension, diabetes, and life-course socioeconomic status (SES), and other disparity-specific social determinants of health.

Sub-aim 1: Determine the association between obesity and risk of cancer, especially obesity-associated cancers, separately in AAs and EAs participants with CVD.

Sub-aim 2: We will specifically focus this aim on atherosclerotic cardiovascular disease (ASCVD), with the rest of the analysis being similar to aim 1 and sub-aim 1.

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:
In the analytic study population, we will include ARIC participants who were diagnosed with CVD after Visit 1 and who were followed for cancer incidence through 2015. We will use the prospective cohort study design. Analyses will be performed separately for AA and EAs participants in Aim 1.

We will define CVD as 1) heart failure (HF), 2) a definite or probable stroke, 3) coronary heart disease (CHD), defined as a definite or probable MI or definite fatal CHD, or 4) peripheral artery disease.

We will define ASCVD as 1) a definite or probable stroke, 2) coronary heart disease (CHD), defined as a definite or probable MI or definite fatal CHD, or 3) peripheral artery disease.

Exclusions: We will exclude participants at Visit 1 who already had a diagnosis of cancer as indicated by the 2015 ARIC cancer dataset. Participants will enter follow-up at the date of CVD diagnosis if diagnosed after visit 1. Participants with CVD at Visit 1 are not excluded and will be categorized as having baseline CVD. Participants will be followed until cancer diagnosis, death, or the end of follow-up, whichever comes first.

Exposures: Obesity – Obesity will be defined based on measured body mass index (BMI), waist circumference (WC), and waist to hip ratio (WHR). We will utilize obesity as a time-independent variable at the start of follow-up (i.e., the first visit after a CVD diagnosis). We will use measures of obesity from the first visit after the date of CVD diagnosis. BMI will be categorized into normal weight (18.5 to <25 kg/m2), overweight (25 to <30 kg/m2), and obese (≥30 kg/m2) groups.

Outcomes of interest:

1. Primary outcomes: Cancer risk. We will use the 2015 cancer case file.
2. In secondary analyses, we will evaluate obesity-associated cancers only. We will define obesity-specific cancers as the 14 from WHO-IARC list (Lauby-Secretan et al): gallbladder and other biliary, pancreas, stomach cardia, thyroid, kidney and renal pelvis, esophageal adenocarcinoma, colon and rectum, corpus and uterus, breast, ovary, multiple myeloma, liver, and intrahepatic bile duct.

Ascertainment of cancer cases

In ARIC, cancer diagnoses were ascertained between 1987 and 2015 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.

Covariate assessment (assessed at the same time as CVD):

1. age
2. gender (Visit 1)
3. race (Visit 1)
4. field center
5. attained education (Visit 1)
6. cigarette smoking status (each visit) and cumulative cigarette/years
7. alcohol use (each visit)
8. diabetes if they self-reported a physician diagnosis, used a pharmacologic treatment for diabetes, having fasting glucose ≥126 mg/dL or non-fasting glucose ≥200 mg/dL
9. total cholesterol concentration (each visit)

10. hypertension defined as ≥140/90 or taking antihypertensive medication,
11. life-course socioeconomic status (SES) (Visit 4) - occupation, number in household, and income
12. health insurance status, type of health insurance; frequency of routine exams (Visit 1)

Statistical analysis

Aim 1

1. We will perform univariate comparisons of baseline characteristics between the groups of patients with CVD stratified by the three categories of BMI (or waist or WHR). Our sample size for analysis after exclusions and missingness is n = 1498.

2. We will use Fine Gray competing risk regression models to estimate the subdistribution hazard ratios (HR) of cancer risk for participants with CVD divided among the three categories of BMI while considering the competing risk of mortality

3. We will repeat the same with the tertiles of WHR and WC. We will use the following progressive adjustment approach to identify sources of confounding.

    4. Model 1: Adjusted for age, sex, and center

    5. Model 2: Model 1 + smoking status, cumulative pack-years, alcohol use, diabetes, hypertension, and total cholesterol.

    6. Model 3: Model 2 + life-course SES

7. Generate cubic splines to depict nonlinear associations of adjusted HR in model 3 vs. the three measures of obesity using them as continuous variables. Knots to be determined at a later time point.

8. Repeat the above restricting to the combination of the 14 obesity-associated cancers. We will censor participants at the date of their diagnosis of cancer not thought to be obesity-associated.

Sub-aim 1: Repeat Aim 1a) separately in AA and EA participants

Sub-aim 2: Repeat all Aim 1 analyses using the analytic cohort participants with ASCVD.

Sensitivity analyses:

Repeat the above analysis separately by sex given some obesity-associated cancers are sex-specific.

Limitations and challenges:

- Possibility of residual confounding as with any observational study
- Limited power for analyses of cancer subtype, stage, and in analyses of other subgroups
- The long gap between Visits 4 and 5 will result in a delay between the time of CVD assessment and the time of cancer diagnosis for some patients, during with time unmeasured

changes in BMI may have occurred. However, since we will also be getting data from annual phone follow-up visits, this will be somewhat mitigated.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? __X__ 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/aric/mantrack/maintain/search/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)?

3028 Cardiovascular Risk Among Cancer Survivors in the ARIC study
3038 Cancer risk in persons with clinical cardiovascular disease
Other manuscripts with obesity and cancer risk
#4002, #3152, #1792, #1766

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* 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 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.

References

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6. Lauby-Secretan, B., Scoccianti, C., Loomis, D., Grosse, Y., Bianchini, F., & Straif, K. (2016). Body fatness and cancer—viewpoint of the IARC Working Group. New England Journal of Medicine, 375(8), 794-798.