A comparison of the inflammatory proteome in cancer survivors and individuals with no cancer history.

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

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

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3. Timeline: 6 – 18 months; manuscript submission in Fall 2020

4. Rationale:

Introduction

Inflammation is a major pathophysiologic mechanism that underlies many adverse outcomes faced by cancer survivors. There is significant evidence from research, of heightened inflammation in cancer survivors prior to treatment, during chemotherapy, and after chemotherapy, and inflammation has been associated with cardiovascular disease, cognitive decline, fatigue, depression and mortality in cancer survivors. Although the role of inflammation in cancer etiology is well-understood, significant knowledge gaps persist in the characterization of the inflammatory proteome, its roles and effects in long-term cancer survivors, especially as they age.

In normal physiologic states, inflammation is a coordinated response to cellular assaults and is well-regulated. The inflammatory response involves progressive release of mediators and recruitment of leukocytes in circulation. These mediators and leukocytes are activated at the inflammatory site and in turn release further mediators. To check and clear inflammatory cells, anti-inflammatory cytokines and intracellular negative regulatory factors are released. Chronic inflammatory states disrupt anti-inflammatory regulatory mechanisms resulting in heightened inflammation.
In cancer survivors, cellular stress due to past and continuing exposure to cancer risk factors, the cancer itself, and cancer treatments among other known and unknown factors that cause DNA damage may persistently activate the inflammatory response, resulting in chronic inflammation. For instance, chemotherapy-related cognitive impairment (CRCI) is thought to result from chronic inflammatory processes in the brain. Although they do not cross the blood-brain barrier (BBB), most chemotherapeutic agents are known to be reactive oxygen species (ROS) generating\(^2\). Thus, they induce metabolic changes that disrupt the BBB, enhancing its permeability to pro-inflammatory cytokines and orchestrating neuron-damaging chronic inflammatory processes that triggers CRCI\(^2\). The nuclear factor-kappa beta (NF-κB) pathway\(^20\) is known to play a central role in inflammation through the regulation of genes that encode pro-inflammatory cytokines, adhesion molecules, chemokines, growth factors, and inducible enzymes like cyclooxygenase 2\(^20-23\). Cellular stress activates the NF-κB pathway through cellular senescence\(^24\), production of ROS, tumor necrosis factor (TNF-α) and other upstream pro-inflammatory proteins.

Inflammation is amenable to treatment, but successful therapeutic approaches would require identification of specific therapeutic targets such as protein receptors and pathways. Prior studies have shown higher levels of commonly measured pro-inflammatory markers such as interleukin-6, TNF receptor, IL-1, platelet-to-lymphocyte ratio (PLR) and granulocyte-to-lymphocyte ratio (GLR), in cancer survivors compared to persons with no history of cancer\(^3\). However, these studies are limited by the inclusion of only a small number of candidate proteins. Additionally, majority of these studies have been cross-sectional, precluding determination of pre-diagnostic levels of inflammation. Therefore, to date, no study has comprehensively characterized the inflammatory proteome and pathways in cancer survivors, pre- and post-cancer diagnosis, especially in comparison with persons with no cancer history.

The characterization of the inflammatory proteome in large populations requires high-throughput technology. With the emergence of high sensitivity, high-throughput multiplex aptamer-based assay methods, it is now possible to efficiently measure an extensive array of circulating proteins in plasma. Given that most inflammatory proteins are in circulation (Ferrucci and Fabbri 2018), hundreds of proteins, including cytokines, chemokines and their receptors, involved in upstream and downstream inflammatory regulation and immune activation are measurable by multiplex proteomics assay technology. A comprehensive analysis of the distribution and levels of inflammatory proteins in a cohort of cancer survivors and cancer free individuals may provide insight into the peculiarities of the inflammatory proteome in cancer survivors and pathways that may be targeted for preventive or therapeutic interventions.

We had previously proposed to study the association of circulating inflammatory proteins and EFA-based inflammatory scores (I-Scores) with neurocognitive outcomes – cognitive decline and dementia (MP#3444) and mortality from causes other than the index cancer (MP#3445) in the Atherosclerosis Risk in Communities (ARIC) study. In the proposed study, we will characterize and compare the inflammatory proteome in ~633 ≥5-year older adult survivors of the most survivable cancers - prostate, breast, colorectal, endometrial and bladder; and 5323 individuals with no cancer history, who attended visit 5 (2011-2013), using ~400 inflammatory proteins measured using the SOMAscan® Multiplexed Proteomic technology in ARIC – a large 30-year, ongoing prospective cohort study of biracial community-dwelling adults. We will examine and compare levels of inflammatory proteins at two visits, 18 years apart: Visit 3 (during which >90% of the cohort were cancer free) and Visit 5 (at which time >1100 surviving participants had a confirmed history of cancer). We will then explore the effect of a cancer history on the inflammatory proteome, adjusting for age, race/ethnicity, sex and shared cancer/cardiovascular disease (CVD) risk factors. In this discovery phase, we will identify specific inflammatory proteins that are associated with a cancer history which will be validated in future in a replication cohort. Thus, while inflammatory proteins are the exposures of interest in previous proposals, the current proposal evaluates the association of a cancer history (as the exposure) on inflammation (as the outcome).
Specifically, we will:

5. Main Hypothesis/Study Questions:

Aim 1: Determine whether a history of cancer is associated with elevated or reduced levels of circulating inflammatory proteins at visit 5

**Hypothesis 1:** Inflammatory proteins measured at Visit 5 will be significantly different (higher pro-inflammatory proteins and lower anti-inflammatory proteins) in cancer survivors compared to individuals with no cancer history who share similar age, sex, race and cancer risk factors (by propensity score matching).

i. We will evaluate and compare the distribution of ~400 inflammatory proteins (Table 1) at Visit 5 in cancer survivors and individuals with no cancer history

ii. Using regression techniques, we will evaluate the association between a history of cancer and levels of each of ~400 inflammatory proteins conditioned on age, sex, race and known cancer/CVD risk factors by propensity score matching; Depending on the distribution of the log-transformed proteins, we may use linear, generalized gamma or quantile regression techniques to test if the effect of a cancer history on inflammation differs by levels or quantiles circulating inflammatory proteins.

iii. Using pathway analysis, we will identify inflammatory protein signatures or networks that may be significantly altered (upregulated or downregulated) in cancer survivors.

Aim 2: Determine whether a history of cancer is associated with higher levels of a protein-based measure of inflammation at Visit 5.

**Hypothesis 2:** A proteomic measure of inflammation constructed with a combination of pro- and anti-inflammatory proteins measured at ARIC study visit 5 (I-Scores) will be significantly higher in cancer survivors compared to persons with no cancer history who share similar age, sex, race and cancer risk factors.

i. We will construct a proteomic measure of systemic inflammation (I-Score) for all study participants using inflammatory proteins measured at Visit 5.

ii. We will compare the distribution of I-Scores derived at Visit 5 in cancer survivors and individuals with no cancer history

iii. Using linear and/or Quantile regression, we will test the effect of a cancer history on the I-Scores

Aim 3: Determine from analysis of paired samples collected ~18 years apart (ARIC study visits 3 and 5), whether the interval change in inflammatory proteins or I-Scores differs by visit 5 cancer status. Specifically, we will determine whether the change in inflammatory proteins or I-Scores over the 18-year period differs between long-term (≥5 years) survivors of cancers diagnosed between visit 3 and 5 versus participants with no cancer history at visit 5 (Illustration on Fig 3.)

**Hypothesis 3:** Compared to participants who remain cancer-free, participants with no history of cancer at ARIC study visit 3 who become diagnosed with cancer will have steeper changes in inflammatory proteins and I-Scores in the ~18-year period between ARIC study visits 3 and 5. We hypothesize that a diagnosis of cancer in the 18 year interval will be associated with steeper increases in proinflammatory proteins and declines in anti-inflammatory proteins compared to participants who remained cancer free.

i. We will evaluate and compare the distribution of ~400 inflammatory proteins and I-Scores at Visit 5 in cancer survivors and individuals with no cancer history;
ii. We will compare ~18-year changes (Visit 3 to 5) in inflammatory proteins and *I-Scores* in cancer survivors and individuals with no cancer history;

iii. Using appropriate regression techniques, we will evaluate the association of a history of ≥5-year cancer survival, with 18-year change in ~400 inflammatory proteins and *I-Scores*, accounting for differences conditioned on age, sex, race and known cancer/CVD risk factors by propensity score matching;

iv. Identify inflammatory proteins or network of proteins that are significantly altered over time in cancer survivors

Table 1: Summary of ~400 inflammatory proteins measured in the proteomic platform (SOMAscan) that will be investigated

<table>
<thead>
<tr>
<th>Class of protein</th>
<th>Somalogic ID</th>
<th>No.</th>
<th>Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Necrosis Factor ligands (TNFL)</td>
<td>4838 – 4852</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>TNF–receptor super-family (TNF-RSF)</td>
<td>4853 – 4884</td>
<td>32</td>
<td>TNF-RSF3, 4, 6b, 8, 9, 10a, 11a, 11b, etc</td>
</tr>
<tr>
<td>Interleukins (ILEU)</td>
<td>2343 – 2426</td>
<td>84</td>
<td>IL-1A, IL-1B, 2, 3, 4, 5, 6, 7, 10, etc</td>
</tr>
<tr>
<td>Interleukin receptors (ILEUR)</td>
<td></td>
<td></td>
<td>IL-1R, 2RA, 4R, 5RA, 6R, etc</td>
</tr>
<tr>
<td>Interferons (IFN)</td>
<td>2312 – 2342</td>
<td>31</td>
<td>IF-Gamma, IFNL1</td>
</tr>
<tr>
<td>C-Reactive Protein</td>
<td>10971</td>
<td></td>
<td>CRP</td>
</tr>
<tr>
<td>Chemokine ligands (CHK)</td>
<td>1142 – 1151</td>
<td>10</td>
<td>CCL1, 2, 3, 3L1, 4, 5, 7, 8, 11, 13, 16, etc. 28, CXCCL1, 2, 3, 5, 6, 6gfr</td>
</tr>
<tr>
<td>Chemokine receptors CHKR</td>
<td>1225 - 1230</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Complement proteins and factors</td>
<td>1027 – 1067</td>
<td>41</td>
<td>C1, 2, 3, 4, 5, 6, 7, 8, 9, etc</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CFB, CFD, CFH, CFHRS, CFI</td>
</tr>
<tr>
<td>Cell surface or CD molecules</td>
<td>837 – 862</td>
<td>26</td>
<td>CD350, 209, 4, 48, 84 etc</td>
</tr>
<tr>
<td>Colony stimulating factors (CSF)</td>
<td>1960 – 1963</td>
<td>5</td>
<td>Granulocyte and Macrophage CSFs, CSF1, 2, 3, etc</td>
</tr>
<tr>
<td>Transforming Growth Factors</td>
<td>4719 – 4725</td>
<td>7</td>
<td>TGFα, TGFβ</td>
</tr>
<tr>
<td>Transmembrane proteins</td>
<td>4751 – 4787</td>
<td>37</td>
<td>TMEM105, 106A, 106B, etc</td>
</tr>
<tr>
<td>Adhesion molecules</td>
<td>467</td>
<td>33</td>
<td>Basal cell adhesion molecule</td>
</tr>
<tr>
<td></td>
<td>749-756</td>
<td></td>
<td>Carcinoembryonic antigen-related cell adhesion molecule</td>
</tr>
<tr>
<td></td>
<td>863 – 867</td>
<td></td>
<td>Cellular adhesion molecules</td>
</tr>
<tr>
<td></td>
<td>1614</td>
<td></td>
<td>E-Selectin</td>
</tr>
<tr>
<td></td>
<td>2306 – 2311</td>
<td></td>
<td>Intra-cellular adhesion molecules</td>
</tr>
<tr>
<td></td>
<td>2452 – 2454</td>
<td></td>
<td>Junctional adhesion molecules</td>
</tr>
<tr>
<td></td>
<td>2919</td>
<td></td>
<td>Mucosal addressin adhesion molecule</td>
</tr>
<tr>
<td></td>
<td>3034 – 3038</td>
<td></td>
<td>Neural cell adhesion molecules</td>
</tr>
<tr>
<td></td>
<td>3082</td>
<td></td>
<td>Neuronal cell adhesion molecule</td>
</tr>
<tr>
<td></td>
<td>3412</td>
<td></td>
<td>Platelet cell endothelial adhesion molecule</td>
</tr>
<tr>
<td></td>
<td>5075</td>
<td></td>
<td>Vascular cell adhesion molecules (VCAM1)</td>
</tr>
<tr>
<td>Other proteins of the NFkB pathway</td>
<td>2116-2121</td>
<td>7</td>
<td>HMGP – High Mobility Group Proteins</td>
</tr>
<tr>
<td>Other inflammatory proteins (unclassified)</td>
<td>3168</td>
<td></td>
<td>NFKB1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>KLRK, LAG, LTA4H, LY9, MIF, SLAM, LTb, PPBP, PDCD, NCR, FASLG, FCER2, GRN, ICOS, CRTAM, CRLF, A1F1, HAVCR2</td>
</tr>
</tbody>
</table>

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 participants**

**Inclusion criteria:** All participants who attended ARIC study Visit 5 (2011 – 2013) and had inflammatory proteins measured in SomaLogic will be eligible for inclusion in the study. However, for cancer survivors, we will include only survivors of the more survivable common cancers – prostate, breast, colorectal, endometrial and bladder cancers who are at least 5 years
post-diagnosis at study Visit 5. This inclusion criteria minimizes the likelihood of including survivors who still have active disease in the study.

**Exclusion criteria:** We will exclude participants who had a cancer diagnosis 5 or less years before Visit 5, a primary cancer diagnosis other than the 5 common and survivable cancers of interest and participants who have no measurements of inflammatory proteins at Visit 5 using the SOMAscan assay.

**Outcome variable: Proteomic measurement:** Inflammatory proteins measured in plasma collected from ARIC study participants at visit 3 (1993 – 95) and visit 5 (2011 – 2013) using a Slow Off-rate Modified Aptamer (SOMAmer)-based capture array (SomaLogic, Inc, Boulder, Colorado). We identified ~400 proteins that include all proteins that are known to be involved in the process of inflammation and immune activation (Coussens 2002, Hanahan and Weinberg 2011), including 194 proteins used in a prior study of inflammation in end stage renal disease, and other known inflammatory proteins and proteins of the nuclear factor kappa beta (NF-κB) pathway (Table 1). These proteins also include those previously studied in relation to aging-associated outcomes in general populations typically by ELISA. We will model inflammation in four ways; we will examine a) the absolute levels of individual proteins at Visit 5 (Aim 1), b) a proteomic inflammatory score (I-Score) that is based on inflammatory protein levels at visit 5 (Aim 2), c) the change in inflammatory protein levels and I-Scores at two critical timepoints 18 years apart - Study visit 3: 1993-95, during which >99% of the cohort had no cancer history; and visit 5, 2011-13, during which >1,000 participants had survived a cancer experience (Aim 3);

**Exposure variable:** A history of > 5 – year survival of cancer of the prostate, breast, colon, rectum, endometrium or bladder. The focus of this analysis is on long term older adult cancer survivors. Therefore, we describe a cancer survivor at study baseline (Visit 5), as a participant who has a history of cancer and is at least 5 years post diagnosis at visit 5. In 2012, the ARIC study infrastructure was enhanced to become a full-fledged cancer epidemiology cohort. 15,641 ARIC participants (99% of the total cohort) consented to research on non-CVD outcomes such as cancer (Fig 1). Among them, information from medical records and state ascertain and adjudicate incident cancer cases. Mortality case files since inception of ARIC in 1987 were generated and updated annually. By 2012, 4743 incident cancers among 4107 participants with up to 25 years of follow-up, were ascertained and characterized; and 1660 cancer-related deaths.

**Other covariates of interest:** Demographic and clinical variables of interest such as age, sex, race, education, body mass index (BMI), collected at baseline and updated as needed during follow-up will be extracted. Shared cancer and cardiovascular disease risk factors, such as cigarette, alcohol use/intake, physical activity, and diabetes will also be extracted from Visits 1, 2, 4, 5 and 6. Information about a history of lupus, measures of liver and kidney function will also be extracted.
**Statistical Analysis**

The overall strategy for this analysis is to apply exploratory analysis and regression methods to describe and quantify potential differences in the patterns, levels, distribution and changes in circulating inflammatory proteins in cancer survivors and persons with no cancer history.

**Circulating inflammatory proteins associated with a cancer history:** Inflammatory proteins will be natural log-transformed to reduce skewness. We will also assess differences in visit 5 distribution of each log-transformed inflammatory protein in cancer survivors and cancer-free individuals using nonparametric Kruskal–Wallis tests. This test evaluates normality and equal variance assumptions of the biomarkers across both groups. We will compare means and quantiles of inflammatory proteins (separately for visits 3 and 5) and 18-year interval change of inflammatory proteins (visit 3 to 5) in both populations. We will, evaluate, compare and describe demographic and clinical characteristics, as well as cancer risk factors in cancer survivors and persons with no cancer history. Specifically, we will examine differences in age, sex, race, BMI, waist circumference, cigarette smoking, pack-years, alcohol use, physical inactivity and diabetes. Potential differences will inform variables to be included in propensity score weighting methods to ensure covariate balance across both groups.

Using linear regression (or other appropriate regression techniques mentioned), we will evaluate the association between a history of any long-term cancer (the exposure) and levels of each ~400 inflammatory proteins at Visit 5, accounting for differences in age, sex, race, and known cancer/CVD risk factors by propensity score matching or weighting methods. Depending on the distribution of the proteins, we may utilize quantile regression techniques to test if the effect of a cancer history on inflammation differs across quantiles of circulating inflammatory proteins. Quantile regression methods are useful for non-normally distributed outcomes as observed with inflammatory proteins and allow for the detection of the effect of an exposure on distinct quantiles of the outcome, especially in the highest and lowest tails of the distribution of the outcome. This method has the additional advantage of being more robust to the effect of outliers in the outcome measurement and allows assessment of the effect of an exposure on across specific quantiles of the outcome measure which cannot be estimated by linear regression methods. We will determine how a history of cancer affects varying percentiles of inflammatory proteins. Models will be adjusted for age, sex, race/ethnicity, and shared cancer/CVD risk factors using propensity score matching. We will then identify specific inflammatory proteins that are significantly elevated in cancer survivors and perform further analysis to identify pathways/networks. To determine if the inflammatory protein signature associated with a history of cancer differs by cancer type, we will repeat these analyses in subgroups of a) prostate cancer survivors and age and race–matched cancer-free men, and b) female breast cancer survivors and age and race–matched cancer-free women.

**Association of a cancer history with proteomic measure of inflammation (I-Scores):** We will explore correlation between all inflammatory proteins. Informed by results from correlation analysis and analysis of specific proteins in Aim 1, we will use exploratory factor analysis (EFA) methods to construct a visit-specific proteomic measure of systemic inflammation (I-Score).
using inflammatory proteins measured at Visits 3 and 5. EFA is a mathematical data reduction procedure that uses the linear relationships among variables to find a smaller set of factors that explain most of the variance in the original variables and depict the underlying structure of the phenomena (in this case, inflammation). We will select inflammatory proteins to be included in the EFA based on the variability of each protein in cancer survivors and the correlation of proteins within the same class. EFA assumes that linear intercorrelations between measured variables reflect a smaller number of latent processes, which can be described by a weighted linear combination of the original variables. Weights from each component represent the magnitude and direction of the relationship between each protein and inflammation. We will decide on component(s) to retain based on eigen values, scree plots and parallel analysis. In parallel analysis, eigenvalues from our data set will be compared with those from a matrix of random values of the same dimensionality and components as our data. Factors with eigenvalues greater than those from the corresponding random data will be retained.

We will compare the mean and distribution of Visit 5 I-Scores derived in cancer survivors and individuals with no cancer history. Using linear and/or Quantile regression, we will test the effect of a cancer history on the I-Scores ensuring covariate balance by propensity score matching or weighting methods. As in Aim 1, we will determine if the inflammatory protein signature associated with a history of cancer differs by cancer type by repeating these analyses in subgroups of prostate and breast cancer survivors and age, sex and race – matched cancer-free men and women respectively.

Interval change differences in systemic inflammation by cancer status: We will evaluate and compare the distribution of ~400 inflammatory proteins and I-Scores at measured in Visit 3 plasma samples in cancer survivors and individuals with no cancer history; We will compute ~18-year (Visit 3 to 5) changes in each inflammatory protein and I-Scores. Using linear regression, we will evaluate the association of a history of ≥5-year cancer survival, with 18-year changes in each of ~350 inflammatory proteins and I-Scores, accounting for differences in age, sex, race, CVD and known cancer/CVD risk factors in cancer survivors and cancer-free individuals by propensity score matching. Given that cancers (our exposure of interest) were diagnosed after visit 3 measurement of inflammatory proteins, we will also explore models that test if a cancer history mediates the association between Visit 3 inflammatory proteins (as exposure) and Visit 5 inflammatory proteins (as the outcome). We will compare proteins which are found to significantly change in cancer survivors over the 18-year period, with those identified to be abnormally elevated or reduced at Visit 5 (Aim 2).

Potential Pitfalls and Mitigation strategies:
Selection bias: To be eligible for our study, cancer survivors have to survive until Visit 5. Selection bias may occur if there are informative differences between cancer survivors in our study and cancer cases who died before our study. To investigate this, we will compare the characteristics of ≥5-year survivors of our cancers of interest (prostate, breast, colorectal,
endometrial and bladder cancers) who died before Visit 5 with 633 ≥5-year survivors who were alive at Visit 5 and will be included in our study. If there are informative differences, we will correct for this by either applying inverse probability of selection weights to our analyses or performing sensitivity analyses to examine how much impact these differences are likely to have on our study findings.

Other sensitivity analyses:
Given the role of the liver and kidney in the synthesis and regulation of circulating inflammatory proteins, participants with compromised liver or kidney function may have altered levels of inflammatory proteins independent of other causes. We will determine the sensitivity of our findings to compromised liver and kidney function by excluding participants with a history of liver/kidney disease and repeating the analysis in a smaller subset of cancer survivors who have no history of liver or kidney disease. We will also adjust for markers of liver and/or kidney function and evaluate the robustness of findings before and after these adjustments.

Given the inflammatory effects of autoimmune diseases like lupus, we will identify and exclude participants with a history of lupus. We do not anticipate that there will be many participants with lupus in our study. However, we will perform sensitivity analysis to test the robustness of our findings to the inclusion versus exclusion of participants with a history of lupus.

Our study has several strengths. First, this is the first comprehensive evaluation of the inflammatory proteome in long-term cancer survivors, particularly in comparison to individuals with no history of cancer. Additionally, the prospective measurement of inflammatory proteins at two time points overcomes the limitations of cross-sectional studies and provides insight as to how levels of inflammation change pre- and post-cancer diagnosis. Using a broad range of inflammatory proteins, we may be able to identify an inflammatory signature that contributes to adverse health outcomes in cancer survivors – a potentially important step in the search for innovative therapies to curb inflammation in cancer survivors.

7.a. Will the data be used for non-CVD analysis in this manuscript? _✓_ 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? ____ 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   _✓_ 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

   _✓_ 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)?

- MP#3444. The Association of Systemic inflammation with Cognitive Decline and Incident Dementia in Older Adult Cancer Survivors.
- MP#3445. The Association of Systemic inflammation with Mortality Due to Non-Index Cancer in Older Adult Cancer Survivors
- MP# 3327. A proteomic analysis of incident dementia: The ARIC Study
- MP# 3051. The association of middle and late-life blood pressure with conversion to MCI and dementia: The ARIC Study
- MP# 3058. The association of late-life glycemia status with 3-year late-life cognitive decline and incident MCI/dementia: The ARIC Study
- MP# 3903. Multi-omic data integration using systems approaches for mechanistic understanding of disease in the Atherosclerosis Risk in Communities (ARIC) Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __√__ Yes    ____ No

11.b. If yes, is the proposal

- NO_ A. primarily the result of an ancillary study (list number* _________)
- YES_ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

2019.06: The contribution of systemic inflammation to neurocognitive outcomes and mortality in long-term cancer survivors
2017.27 Proteomic longitudinal ARIC study: SOMA scan of multiple visits
2011.07 Enhancing ARIC Infrastructure to Yield a New Cancer Epidemiology Cohort
1995.04 Cancer Study 2017.27 Proteomic longitudinal ARIC study: SOMA scan of multiple visits
2011.07 Enhancing ARIC Infrastructure to Yield a New Cancer Epidemiology Cohort
1995.04 Cancer Study

*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 _____ No.
References


