The Association of Systemic inflammation with Cognitive Decline and Incident Dementia in Older Adult Cancer Survivors.

**b. Abbreviated Title (Length 26 characters):**

Inflammation and Cognition

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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:**

Cancer-related cognitive impairment (CRCI), characterized by decreased abilities in memory, attention, executive function, and processing speed, is now well-recognized as a long-lasting, highly debilitating adverse outcome in cancer patients, even among those who are post-treatment and in remission\(^1-6\). A cross-sectional study using data from a national survey showed that cancer survivors were 40 percent more likely to self-report memory problems compared to persons with no cancer history\(^7\). In another study, 75 percent of cancer patients reported cognitive impairments during treatment which persisted in 35 percent of cancer survivors, years after cancer treatment\(^1,2,8\). CRCI affects daily functioning and imposes additional layers of functional, psychosocial and financial burden on survivors and their caregivers. Consequently, there is growing concern about cognitive impairment and related degenerative outcomes among the growing cancer survivor population in the U.S.\(^9\).

Although cognitive impairment is reported in both survivors of adult and childhood cancers\(^10\), the effect may be more profound in older adult cancer survivors. Given that normal aging is associated with some changes in cognitive performance, a history of cancer may exacerbate cognitive impairment in older adults. With more than half of all newly diagnosed cancer cases and two-thirds of
cancer survivors being above 65 years\textsuperscript{11-13}, cancer survivors are a growing proportion of the U.S. older adult population with implications for health services delivery. But research on cancer-related cognitive impairment and its long-term sequelae in this population is limited and evidence to support cognitive trajectory is mixed. For instance, there is mixed evidence on the risk of dementia in older adult cancer survivors. Despite reports of long-term cognitive impairment, even decades after cancer treatment, a number of studies, including three population-based studies, report an overall lower risk of dementia or Alzheimer’s disease (AD) in cancer survivors\textsuperscript{14-16}. Conversely, other studies showed higher risk of AD in prostate cancer survivors\textsuperscript{17,18} and dementia in colorectal cancer survivors\textsuperscript{19}. Taken together, these studies suggest that as cancer survivors age, it is unclear whether cognitive deterioration progresses at higher, the same, or lower rates in cancer survivors compared to individuals with no cancer history.

The burden of cognitive impairment is huge, and the implications are far-reaching, yet, the underlying mechanisms, especially in older adult cancer survivors are poorly understood\textsuperscript{20}. There is significant evidence from research of heightened inflammation in cancer survivors prior to treatment\textsuperscript{21}, during chemotherapy\textsuperscript{6,22}, and after chemotherapy\textsuperscript{5,23-25}. Although the role of inflammation in cancer etiology is well-understood, knowledge gaps persist regarding the role of inflammation in the etiology of neurocognitive impairment in cancer survivors. We posit that cellular stress due to the index cancer, cancer treatments, past and continued exposure to pro-inflammatory cancer risk factors, may cause inflammation to increase and persist, contributing to neurocognitive deficits in cancer survivors. However, prospectively designed studies to characterize inflammation and its temporal contribution to neurocognitive outcomes in older adult survivors of different cancers are lacking\textsuperscript{26}. The vast majority of studies of inflammation in cancer survivors are performed in heterogenous populations and utilize few and different combinations of cytokines which challenges comparability and systematic characterization of trends\textsuperscript{9}. Prior studies have also been cross-sectional, largely focused on female breast cancer, or had short duration of post-treatment follow up, limiting interpretation, utility, and extrapolation of findings from prior studies. Furthermore, most of the studies are conducted in clinical cohorts that lack adequate pre- and peri-diagnostic information required for adequate etiologic inquiries.

In the proposed study, we will determine the prospective association of systemic inflammation with cognitive decline and also incident dementia in long-term survivors of the most common survivable cancers, by evaluating the association of each inflammatory protein, as well as a proteomic measure of inflammation with each outcome. We will then identify specific inflammatory proteins that are independently associated with these outcomes in cancer survivors. We will analyze data from ~633 ≥5-year survivors of the most survivable cancers - prostate, breast, colorectal, endometrial and bladder, who attended visit 5 (2011-2013), in the Atherosclerosis Risk in Communities (ARIC) Study. In the ARIC study, ~5,000 proteins, including ~350 inflammatory proteins, were recently assayed in plasma collected at 2 timepoints 18 years apart, using a state-of-the-art, highly sensitive, high throughput aptamer-based protein profiling (SOMAscan® Platform). We will identify cognitive changes at visit 6 and incident dementia from visit 5 (2011-2013) till December 2017.

5. Main Hypothesis/Study Questions:

**Aim 1:** In long-term cancer survivors, determine whether levels of circulating inflammatory proteins are associated with cognitive decline and incident dementia.

Hypothesis 1: In long-term cancer survivors, higher levels of pro-inflammatory proteins and lower levels of anti-inflammatory proteins are associated with steeper cognitive decline and incident dementia.

**Aim 2:** In long-term cancer survivors, determine whether a higher systemic inflammation score (“I-Score”) is associated with cognitive decline and incident dementia. I-Score, a proteomic measure of systemic inflammation, will be constructed using exploratory factor analysis.
Hypothesis 2: In long-term cancer survivors, higher I-Score is associated with cognitive decline and incident dementia.

Aim 3: In long-term cancer survivors, determine whether the association of the circulating inflammatory proteins identified in Aim 1 and I-Score with cognitive decline and incident dementia varies by a) major cancer site (prostate and breast), b) sex (for non-sex specific cancers), and c) race.

Hypothesis 3: In long-term cancer survivors, the association of the circulating inflammatory proteins identified in Aim 1 and I-Score with cognitive decline and incident dementia differs by major cancer site, sex and race.

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:**

**ARIC** is an ongoing population-based, prospective, cohort study, which from 1987 to 1989 enrolled 15,792 adults (Fig. 1) between the ages of 45 and 65 years, from communities within the U.S: Washington County, MD; Forsyth County, NC; northwestern suburbs of Minneapolis, MN; and Jackson, MS. 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 cancer registries, was used to 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.

**Study participants**

**Inclusion criteria:** All participants who attended Visit 5 (2011 – 2013) and had inflammatory proteins measured in SOMALogic will be eligible for inclusion in the study. Our study sample will be drawn from visit 5 as the baseline for the proposed study. For cancer survivors however, 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 the Visit 5 study visit. This inclusion criteria minimizes the likelihood of including survivors who still have active disease. At visit 5 (2011-2013), 1138 (18%) of 6461 participants still alive had a history of cancer after enrollment in ARIC, of whom 883 were ≥5 years post-diagnosis (Fig 1). However, of these 883, only 633 are survivors of the more commonly survivable cancers. However, these numbers are based on the cancer case files through 2012. As cancer case files have recently been updated through 2015, we expect some increase in the population of survivors eligible for our study.
**Exclusion criteria:** We will exclude participants who have no measurements of inflammatory proteins at Visit 5 using the aptamer-based SOMAscan assay, participants who are diagnosed with less commonly survivable cancers (such as cancers of the lung and pancreas), and participants who are <5 years post-cancer diagnosis. Additionally, for the dementia analysis, we will exclude participants who have had a prior diagnosis of dementia as at visit 5 (study baseline).

**Exposure:** Our primary exposure is plasma concentrations of inflammatory proteins. We will interrogate an extensive array of ~350 inflammatory measured at visits 3 and 5 (Fig. 1). These proteins include all known inflammatory proteins in literature, including most of the 194 proteins used in a prior study of inflammation in end stage renal disease\(^{29}\), inflammatory proteins that are involved in, or by-products of the nuclear factor kappa beta (NF-κB) pathway, and proteins previously studied in relation to aging-associated outcomes in general populations typically by ELISA\(^{30}\). We will model inflammation in four ways; we will examine a) the absolute measure of individual proteins, b) the change in inflammatory proteins in 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); c) a proteomic inflammatory score (I-Score) that is based on inflammatory protein levels at visit 5 and d) change in I-Score between visit 3 and 5. Visit 3 represents a pre-diagnostic time point at which 99% of the cohort were cancer-free. At Visit 5, there were ~633 ≥5-year survivors of the 5 cancers of interest.

**Cancer survivor status:** A cancer survivor at study baseline (Visit 5) is defined as a participant who has a history of cancer and is at least 5 years post diagnosis at visit 5.

**Outcomes:**

**a) Cognition:** Global and test-specific cognitive function was measured at five time points (Fig 2) using three standardized measures. These measures include the Delayed Word Recall Test (DWRT), Digit Symbol Substitution Test (DSST), and Word Fluency Test (WFT). At visits 5 and 6, a neuropsychology test battery, logical memory immediate and delayed recall, the mini-mental state examination (MMSE), incidental learning from the Wechsler Memory Scale-III, trail making test parts A and B, WAIS-R digits span backward, Boston naming test, and animal naming were additionally administered.

**b) Incident dementia:** Among participants who were alive at visit 5, we will examine all cases of dementia or mild cognitive impairment (MCI) occurring after visit 5. Participants who attended visit 5 underwent evaluation for dementia in-person. Participants who were unable or unwilling to attend visit 5 were offered evaluations at homes or their care facilities. To assess dementia among participants who were alive but declined any kind of in-person visits, a telephone assessment using a modified telephonic instrument of cognitive status (TICS-m). Among those for whom TICS-m was not possible, informant interviews and ICD-9 hospital discharge codes were used to assess dementia status. Subsequently, incident dementia was actively ascertained in-between visits using these remote methods. In this analysis, participants diagnosed mild cognitive impairment (MCI) will be classified as having dementia. The detailed procedure for ascertainment of dementia prior to, and after visit 5 has been described elsewhere.\(^{31,32}\)

**Other covariates:** 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. Apolipoprotein ε4 and other genotyping were also done at baseline. Additionally, laboratory and physiologic data, including systolic and diastolic blood pressures, total/high density lipoprotein cholesterol, triglycerides and waist circumference will be extracted from all study visit for which they were collected. Cancer diagnosis, shared cancer and cardiovascular disease risk factors, such as cigarette, alcohol use/intake, physical activity, and diabetes, and other disease information (such as cardiovascular disease, hypertension, coronary heart disease, heart failure), and medication use will also be extracted from Visits 1, 2, 4, 5 and 6. Information about chronic inflammatory disease
diagnoses (i.e., lupus, gout, and arthritis) will be extracted from Visit 4. Information about liver function will be determined by liver function tests. We will adjust for age, sex, race, and education as confounders of the association between inflammation and neurocognitive outcomes. Given that cognitive reserve – defined as innate and developed cognitive capacity, influenced by various factors, including genetics, education, occupational attainment, and lifestyle – may affect the cognitive change trajectory, we will account for cognitive reserve by adjusting for education in our analyses. Additionally, given the increased susceptibility of carriers of the $APOE \varepsilon 4$ allele to neurocognitive deficits\textsuperscript{33}, we will adjust for the $APOE \varepsilon 4$ allele in our analysis.

### Statistical Analysis

**Aim 1:** *In long-term cancer survivors, determine whether levels of circulating inflammatory proteins are associated with cognitive decline and incident dementia.*

**Incident dementia:** Using complementary log-log (cloglog) regression models, we will evaluate the association of systemic inflammation and incident dementia *in cancer survivors*. Cloglog models will account for the non-continuous ascertainment of dementia in our study. Our study baseline is visit 5. Therefore, visit 5 is considered time zero or the time origin, and time since visit 5 as time scale (*Fig. 2*). Participants will be followed from Visit 5 till a diagnosis of dementia or MCI, or till the end of our study follow up in December 2017. Deaths occurring during follow-up will be treated as competing risks (*Fig. 2*). Thus, all regression models will evaluate the cause-specific risk of death due to causes other than the index cancer. We will fit a number of models to examine the association of systemic inflammation with our outcome(s). The primary exposure - systemic inflammation will be evaluated in 2 ways: a) *Specific inflammatory proteins measured at Visit 5,* and
b) 18-year Change in inflammatory proteins from visit 3 to visit 5. (Figs. 1, 2). Thus, for Models 1a – 7a (Table 1), we will fit cloglog models among eligible cancer survivors using log-transformed inflammatory proteins measured at Visit 5 and modelled as continuous variables. For Models 1b – 7b, we will fit cloglog models among a smaller sub-group of cancer survivors who were cancer free at visit 3 (Fig. 1). We will model the risk of dementia between visit 5 (our study baseline) and the end of follow up (Dec 2017) as a function of 18-year change in each systemic inflammation protein between visit 3 (1993-95), during which participants were mostly mid-life and cancer-free; and visit 5 (2011-2013) when they were at least 5 years post cancer diagnosis (Figs. 1, 2).

In Models 1a-b, we will adjust for age, sex, race-center (Maryland white; Minnesota white; North Carolina white; North Carolina African American; Mississippi African American), APOE ε4 genotype status (0 or ≥1 ε4 alleles), education (less than high school; high school/vocational school; or any college) and time since cancer diagnosis; Models 2a-b will be extensions of Model 1, additionally adjusted for shared cardiovascular and cancer risk factors. We will test the validity of the proportional hazards assumption using statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals. If we find that the hazards are not proportional, we will fit non-proportional hazards or generalized gamma models. We will evaluate model fit using likelihood ratio tests and Akaike Information Criteria (AIC). To account for multiple comparisons, we will apply false discovery rate (FDR) methods. Inflammatory proteins that are significantly associated with our outcomes at the FDR/Bonferroni-corrected level of significance will constitute the neurocognitive inflammatory signature in cancer survivors and we will use volcano plots to visually depict these proteins.

To estimate whether inflammatory proteins are associated with faster time to dementia, we will identify quartiles (minimum – 25th, 25th – 50th, 50th – 75th and 75th – maximum) of log-transformed distributions of each inflammatory protein identified as critical to dementia. We will then create Kaplan-Meier plots that compare time to dementia in survivors in the highest and lowest quartiles. We may also compare time to dementia between survivors who remained in the lower quartiles of inflammation at visits 3 and 5, and those who remained in the higher quartile or transitioned from lower to higher quartiles over the 18-month period.

Cognitive decline: Among cancer survivors, we will evaluate the association between measures of inflammatory proteins described above (Visit 5 absolute values and 18-year change) and 5-year cognitive change between visits 5 and 6 by fitting linear mixed effects models with robust variance and unstructured correlation to account for within-person correlation. Model building for cognitive decline will be similar to the models for the dementia outcome above. We will evaluate changes in global cognitive scores as well as domain-specific changes with a focus on memory and executive function/processing speed – domains in which the greatest deficits have been reported in cancer survivors.

**Aim 2:** In long-term cancer survivors, determine whether a higher systemic inflammation score (“I-Score”) is associated with cognitive decline and incident dementia.

### Table 1: Regression Models for inflammatory proteins

<table>
<thead>
<tr>
<th>Models*</th>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Models 1a-b</td>
<td>Age, sex, race-center, education, APOE ε4, time since cancer diagnosis</td>
</tr>
<tr>
<td>Models 2a-b</td>
<td>Age, sex, race-center, education, APOE ε4, time since cancer diagnosis, cancer/CVD risk factors</td>
</tr>
<tr>
<td>Models 3a-b</td>
<td>Age, sex, race-center, education, APOE ε4, time since cancer diagnosis, Inflammatory marker*race interaction term</td>
</tr>
<tr>
<td>Models 4a-b</td>
<td>Age, sex, race-center, education, APOE ε4, time since cancer diagnosis, Inflammatory marker*sex interaction term</td>
</tr>
<tr>
<td>Models 5a-b (Prostate Ca)</td>
<td>Age, race-center, education, APOE ε4 genotype, time since cancer diagnosis, cancer/CVD risk factors</td>
</tr>
<tr>
<td>Models 6a-b (Breast Ca)</td>
<td>Age, race-center, education, APOE ε4 genotype, time since cancer diagnosis, cancer/CVD risk factors</td>
</tr>
</tbody>
</table>

*Models 1 – 2 apply to Aim 1  
*Models 3 – 6 apply to Aim 3  
*Model 4 will be limited to survivors of non-sex specific cancers  
a-models: Inflammatory proteins at visit 5  
b-models: Change in inflammatory proteins between visit 3 and 5
Table 2: I-Score Regression Models

<table>
<thead>
<tr>
<th>Models*</th>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Models 1c-d</td>
<td>Age, sex, race-center, education, APOE ε4, time since cancer diagnosis</td>
</tr>
<tr>
<td>Models 2c-d</td>
<td>Age, sex, race-center, education, APOE ε4, time since cancer diagnosis, cancer/CVD risk factors</td>
</tr>
<tr>
<td>Models 3c-d</td>
<td>Age, sex, race-center, education, APOE ε4, time since cancer diagnosis, cancer/CVD risk factors, Inflammatory marker*race interaction term</td>
</tr>
<tr>
<td>Models 4c-d</td>
<td>Age, sex, race-center, education, APOE ε4, time since cancer diagnosis, cancer/CVD risk factors, Inflammatory marker*sex interaction term</td>
</tr>
<tr>
<td>Models 5c-d (Prostate Ca)</td>
<td>Age, race-center, education, APOE ε4 genotype, time since cancer diagnosis, cancer/CVD risk factors</td>
</tr>
<tr>
<td>Models 6c-d (Breast Ca)</td>
<td>Age, race-center, education, APOE ε4 genotype, time since cancer diagnosis, cancer/CVD risk factors</td>
</tr>
</tbody>
</table>

*Models 1 – 2 apply to Aim 2
*Models 3 – 6 apply to Aim 3
*a-models: Inflammatory proteins at visit 5
*b-models: Change in inflammatory proteins between visit 3 and 5

Inflammatory scores will be constructed using Exploratory Factor Analysis (EFA). We will perform EFA to find combinations of inflammatory markers at each visit that explain a significant proportion of the variance in the inflammatory proteins. 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. We will estimate separate inflammatory scores (I-scores) for visits 3 and 5. An individual’s inflammatory score (I-score) at each visit will be equivalent to factor scores for the individual, derived as the of weighted inflammatory proteins at that visit, where the weights are the loadings for significant component(s) from EFA. To determine whether higher levels of I-Scores are associated with cognitive decline and incident dementia, we will evaluate the effect of absolute I-Scores at visit 5 (c), and 18-year change in I-Scores between visits 3 and 5 (d). We will then construct the same models as in Aim 1 above. As done in Aim 1, we will identify quartiles of the I-Score distribution and create Kaplan-Meier plots estimating time to dementia for cancer survivors who have the highest and lowest quartiles of I-Scores.

Aim 3: In long-term cancer survivors, determine whether the association of the circulating inflammatory proteins identified in Aim 1 and I-Score with cognitive decline and incident dementia varies by a) major cancer site (prostate and breast), b) sex (for non-sex specific cancers), and c) race.

To evaluate potential differences by race and sex in the association of specific inflammatory proteins on dementia, we will extend Models 2a-b to include inflammatory protein and race interaction terms (Models 3a-b), and inflammatory proteins and sex interaction term (Model 4a-b), performing the analysis for each inflammatory protein. To determine whether the association of systemic inflammation with incident dementia in cancer survivors varies by major cancer site ~ prostate and breast, we will perform sub-group analyses in ~276 prostate cancer (Models 5a-b) and 189 breast cancer survivors (Models 6a-b), excluding the sex term in the adjustment covariates. Similarly, to evaluate potential differences by race and sex in the association of the I-Scores on dementia, we will apply similar methods described for the specific inflammatory proteins. We will fit Models 3c-d (Table 2) by extending Models 2c-d to include an I-Score and race interaction term, and an I-Score and sex interaction term (Model 4c-d).

To determine whether the association of the EFA-based proteomic measure (I-Scores) with incident dementia in cancer survivors varies by major cancer site ~ prostate and breast (Aim 3), we will perform sub-group analyses in ~276 prostate cancer survivors (Model 5c-d) and 189 breast cancer survivors (Model 6c-d), excluding the sex term in the adjustment covariates.

With linkages to CMS data for a subset of ARIC participants enrolled in Medicaid at the time of their cancer diagnosis, we may be able to evaluate the effect of treatment in this subset of cancer survivors. However, given our sample size, we may have insufficient power to detect significant differences by treatment type. If this happens, we will interpret findings with caution and plan to explore treatment effect in future other cohorts sufficiently powered for determination of treatment effect.

Additional analysis: To see if our data supports higher or lower incidence of dementia in older adult cancer survivors compared to those who have no history of cancer, we may fit complementary log-log models with a cancer history as the exposure, adjusted for age, race and sex. We will estimate and
compare the crude and age, race, sex-adjusted cumulative incidence of dementia, by cancer history. The time origin will be time since age 45 and a cancer diagnosis will be considered a time-varying absorbent state. We will also estimate and compare cognitive change or the rate of cognitive decline between visits 5 and 6, in cancer survivors and persons with no cancer history adjusting for age, race and sex.

**Incident dementia: \( h[t] = h_0(t) \exp(\beta_1 \times \text{Cancer history}) \)**

Where;

\( \exp(\beta_1) = \) Hazard ratio of dementia in cancer survivors compared to persons with no cancer history who are of similar age, race and sex.

**Cognitive decline: \( E(Y) = \beta_0 + \beta_1 \times \text{Cancer history} \)**

Where;

\( Y = \) Cognitive change between visits 5 and 6 (in Z-scores)

\( \beta_0 = \) Average change in global or domain-specific cognitive scores for persons with no cancer history (Cancer history = 0)

\( \beta_0 + \beta_1 = \) Average change in global or domain-specific cognitive scores for cancer survivors (Cancer history = 1)

\( \beta_1 = \) Difference in the average change in global or domain-specific cognitive scores in cancer survivors compared to persons with no cancer history who are of similar age, race and sex

**Potential Pitfalls and Mitigation strategies:**

**Effect of attrition:** >40% of the participants at visit 5 did not return for visit 6. Participants who suffer severe cognitive impairments are more likely to miss clinic visits. Although active surveillance methods have been applied to the ascertainment of outcomes among participants who missed visit 6, a significant proportion are still missing outcomes. To mitigate this problem, advanced multiple imputation techniques have been applied to determining missing visit 6 neurocognitive outcomes in the ARIC, with detailed sensitivity analyses to minimize error.

**Power for sub-group analyses:** Given differences in cancer site and treatment approaches, testing effect of treatment is ideal. However, we have limited treatment information, and even with that, we may have insufficient power to detect significant differences in sub-groups of treatment classes. For analyses for which we have insufficient power, we will test for interactions on the additive scale and as part of follow-on studies, plan to test hypotheses of these interactions within sufficiently powered cohorts of cancer survivors.

**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.

Our study has several strengths. To the best of our knowledge, this is the first prospective study in an adult cancer cohort, to utilize an extensive array of inflammatory proteins, prospectively collected at more than one time point, to characterize inflammation, its risk factors and its temporally-determined effects on mortality in the same individuals over time. Using a broad range of inflammatory proteins, we will be able to identify critical inflammatory proteins and the inflammatory signature that drives non-index cancer mortality in cancer survivors – a potentially important step in the search for innovative therapies to reduce life-threatening 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# 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)* __________ __________ __________)

*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

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


