ARIC Manuscript Proposal # 1690

PC Reviewed: 9/14/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of polymorphisms in C-reactive protein and fibrinogen genes with cancer risk: Atherosclerosis Risk in Communities (ARIC) study

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

2. Writing Group:

Writing group members: Anna Prizment, James Pankow, Aaron Folsom, Kristin Anderson, Kala Visvanathan

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __AP___ **[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 will begin after the ARIC Committee approves the proposal. We anticipate the manuscript will be completed within 1 year.

4. Rationale:

We propose to examine associations between C-reactive protein (CRP) and fibrinogen gene polymorphisms, measured in CARe, and risk of breast, lung, colorectal, and prostate cancers in the Atherosclerosis Risk in Communities (ARIC) study.

Recently, we examined associations of circulating levels of two acute phase reactants –hs-CRP and fibrinogen – with risk of colorectal cancer in ARIC and detected positive associations[1]. The results for CRP and colorectal cancer are in general agreement with findings from several studies [2-4]. Several other studies also reported positive relations between circulating CRP and all-site, lung, prostate, and some other cancers [4-7]. However, not all studies reported consistent results, and it is not clear whether or not the observed associations are causal.

To our knowledge, no other study examined fibrinogen in relation to incident cancer. A large meta-analysis of prospective studies reported a positive association between fibrinogen levels and mortality from smoking-related cancers, cancers of colorectum and other digestive organs [8]. There is also a biologic evidence that fibrinogen contributes to colorectal carcinogenesis [9].

A potential approach to examining the link of CRP and fibrinogen with incident cancers is gene-association studies, which use the principles of Mendelian randomization. As gene variants are randomly allocated at conception, associations of genetic polymorphisms and cancer outcomes are not affected by confounders or reverse causality [10]. The data on the associations of CRP genotypes and cancer are scarce and inconsistent [7,11-13]. A prospective study from Denmark found that genetic variants in the CRP gene were associated with increased plasma CRP but not with colorectal cancer risk [11]. In contrast, the prospective CLUE II cohort study detected a statistically significant positive association of two CRP haplotypes and two individual SNPs with colorectal cancer risk[13].

ARIC provides an excellent opportunity to analyze CRP and fibrinogen genotypes in relation to cancer, because 28 CRP SNPs and up to 30 SNPs in each of three fibrinogen genes (FGA, FGB, FGG) have been genotyped in CARe including candidate and tagging SNPs [7, 11-13,14]. An additional advantage of our study is the availability of data about circulating fibrinogen and CRP for all ARIC participants measured at Visit 1(1987-89) and Visit 4 (1996-98), respectively.

References

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2. Heikkila K, Ebrahim S, Lawlor DA. A systematic review of the association between circulating concentrations of C reactive protein and cancer. J Epidemiol Community Health. 2007;61(9):824-833.
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13. Tsilidis KK, Helzlsouer KJ, Smith MW, et al. Association of common polymorphisms in IL10, and in other genes related to inflammatory response and obesity with colorectal cancer. Cancer Causes Control. 2009;20(9):1739-1751.
14. Carty C, Cushman M, Jones D, Lange L, Hindorff L, Rice K, Jenny N, Durda JP, Walston J, Carlson C, Nickerson D, Tracy R, et al. Associations between common fibrinogen gene polymorphisms and cardiovascular disease in older adults. The Cardiovascular Health Study. Thromb Haemost 2008;99:388-95

5. Main Hypothesis/Study Questions:

- Associations of CRP and fibrinogen polymorphisms with the risk of colorectal, breast, prostate, and lung cancers;
- Associations of circulatory CRP and fibrinogen levels with the risk of colorectal, breast, prostate, and lung cancers;
- Associations of CRP and fibrinogen polymorphisms with blood CRP and fibrinogen levels, respectively.

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: Prospective cohort study

Dependent variables: Incident colorectal (N~346), breast (N~570), prostate (N~684), and lung cancers (N~476) are available through 2006. CRP levels were measured for all participants at Visit 4 (1996-98)

Independent variables: up to 28 SNPs in CRP gene and 78 SNPs in three fibrinogen genes

Covariates:
Because our main analysis is genetic, confounding is not expected, but we will consider confounding by major risk factors such as age, sex, center, smoking, BMI, pack-years, education, alcohol, aspirin use, hormone therapy use, and diabetes, measured at visit 1.

Interactions with sex, smoking, and NSAIDs (measured at visit 1) will be examined for SNP /cancer associations.
For the analysis of CRP levels and cancers, covariates measured at visit 4 will be used.

Analysis plan: All analyses will be stratified by race because of the potential for population stratification. For each genotype, Hardy Weinberg equilibrium (HWE) will be calculated and genotypes not in HWE will be excluded.
We will use Cox proportional hazards regression to examine associations of biomarker (CRP, fibrinogen) polymorphisms, as well the associations of circulatory biomarker levels with the risk of colorectal, breast, prostate, and lung cancers. We will utilize linear regression to explore the association of each biomarker polymorphisms with its blood level. An additive genetic model will be used with SNPs coded as 0, 1, or 2, indicating the number of minor alleles. Given that we are evaluating many SNPs for each biomarker, we will correct for multiple comparisons. If we find significant genotype/cancer associations, we will examine interaction terms to determine if these associations vary by sex, smoking, and NSAIDs.
For the analysis of SNPs and circulatory CRP levels, log transformation of CRP will be used because of skewness of the CRP distribution. For the analysis of circulatory CRP and fibrinogen with cancers, CRP and fibrinogen levels will be presented as continuous variables and as quartiles.

Inclusion/Exclusion: *inclusion*: all ARIC visit 1 participants free of cancer; *exclusion*: participants with missing genotype information, and those who did not give consent to participate in cancer studies.
For the analysis of circulatory CRP and cancer, participants, who had prevalent cancer at visit 4 or did not give consent to participate in cancer studies, or had missing information about the biomarkers under study, will be excluded from the analyses.

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 ____ No
(This file ICTDER03 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? __x__ 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"?
__x__ 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)?

#1429 Inflammatory and allergy markers as predictors of colorectal cancer risk (CRC): Atherosclerosis Risk in Communities (ARIC) study. Dr. Prizment, the first author and all coauthors of this paper, will participate in the writing group.

Dr. Leslie Lange and other members of blood biomarkers working group for CARe were contacted to avoid any potential conflict with any CARe IBC papers and they did not have objections to our project.

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* _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 at http://www.cscc.unc.edu/aric/forms/

12. 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.