ARIC Manuscript Proposal # 1690

PC Reviewed: 7/12/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of polymorphisms in C-reactive protein and plasma CRP with cancer risk in the ARIC cohort

b. Abbreviated Title (Length 26 characters): Plasma CRP, CRP SNPs and cancer

2. Writing Group:

Writing group members: Anna Prizment, James Pankow, Aaron Folsom, Kristin Anderson, Kala Visvanathan, Corinne Joshu, Elizabeth Platz

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:

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Recently, my colleagues and I examined associations of inflammatory markers with colorectal cancer (proposal #1429) and found associations between C-reactive protein (CRP), fibrinogen and a combined inflammatory score with colorectal cancer incidence in the ARIC study (1). Several other, but not all, studies also reported positive relations between circulating CRP and all-site, breast, lung, prostate, and some other cancers (2-5).

In proposal #1429, we said that we also planned to examine associations of the inflammatory markers with the risk of three most common cancers (breast, lung, and prostate) and total cancer in ARIC. We briefly examined the associations of CRP with the risk of those cancers and observed statistically significant positive associations of CRP with breast and lung cancer risks.

The data on the associations of CRP genotypes and cancer risk are scarce and inconsistent (5, 6-8). 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 (6). 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 (8).

We are suggesting a different approach to studying associations between CRP polymorphisms and cancers. Five GWAS studies have been published that altogether reported more than 30 SNPs associated with CRP levels (9-13). They included SNPs located in the CRP gene, as well as SNPs in approximately 20 other genes – IL6R, LEPR, APOE and etc. The most recent among these GWAS studies, by Delhgan et al [2011] (9), also reported on a replication study; 18 SNPs were replicated and a weighted genetic CRP risk score was developed, which was strongly associated with CRP levels and explained ~5% of the trait variance.

Almost all of those SNPs have been genotyped in ARIC – either on Affymetrix (imputed SNPs) or on IBS. Also, all 18 replicated SNPs have been genotyped in ARIC. For Whites in ARIC, we are planning to create a weighted CRP genetic score as a sum of risk alleles for each person using parameter estimates from the above-mentioned replication study and examine associations of this genetic score with total, breast, lung, colorectal, and prostate cancers. Using the CRP genetic score, we will have increased power and avoid multiple comparisons.

Assuming incidence rate of 0.002 for CRC and 0.01 for total cancer and annual loss to follow-up of 0.5% among 8700 Caucasians in ARIC, we will have 80% power to detect RR=1.32 for CRC and RR=1.12 for total cancer (two-sided α=0.05) for CRP genotypic score, dichotomized at median [Power program, Kaiser Permanente].

Recently, a study has been published that examined associations of each CRP variants reported in the two earliest GWAS studies (12,13) with total cancer and four common cancers in three Finnish cohorts (total number of cancers is N=1559: N=153 for CRC , N=122 for lung, and N=328 for breast, and N=263 for prostate cancer) (14). That study reported associations of several individual SNPs with total and lung cancer. The

advantages of our study are 1) more CRP SNPs have been established and replicated for plasma CRP at this time and 2) the ARIC study has larger numbers of cancers: among Whites, there are 1928 cases of total cancers, 205 CRCs, 274 lung, 371 breast, and 394 prostate cancers.

Our proposed goals for the analysis of CRP variants and cancer are:

1) to examine associations of total and each of the cancers with the CRP genetic score. Our preliminary data shows an increased risk of CRC with an increasing CRP genetic score.

2) to reproduce the Finnish analysis in the ARIC cohort.

References

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12. Reiner AP, Barber MJ, Guan Y, Ridker PM, Lange LA, Chasman DI, et al. Polymorphisms of the HNF1A gene encoding hepatocyte nuclear factor-1 alpha are associated with C-reactive protein. Am J Hum Genet 2008;82:1193-201.
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14. Heikkila K, Silander K, Salomaa V, Jousilahti P, Koskinen S, Pukkala E, et al. C-reactive protein-associated genetic variants and cancer risk: Findings from FINRISK 1992, FINRISK 1997 and health 2000 studies. Eur J Cancer 2011;47:404-12.

5. Main Hypothesis/Study Questions:

- Examine associations of plasma CRP with the risk of total cancer as well as of specific cancers: breast, prostate, lung cancers.
- Examine associations of genetic score based on CRP variants with plasma CRP level and with the risk of total, colorectal, breast, prostate, and lung cancers among white participants;
- Assess reproducibility of associations of CRP polymorphisms reported in Heikkila et al (14) with the risk of total, colorectal, breast, prostate, and lung cancers among white participants.

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=205), breast (N=371), prostate (N=394), and lung cancers lung (N=274), and total cancer (N=1928) are available through 2006 for White participants. Plasma CRP levels were measured for all participants at Visit 4 (1996-98).

Independent variables: plasma CRP level, CRP variants established in GWAS studies and genetic score based on CRP polymorphisms.

Covariates:
For genetic analysis, 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.
For the analysis of CRP levels and cancers, covariates measured at visit 4 will be used.

Analysis plan: All analyses examining genotypes will be conducted for Whites only because of the potential population stratification and low power for Blacks. For each directly genotyped SNP, Hardy Weinberg equilibrium (HWE) will be calculated and genotypes not in HWE will be excluded. For genetic score, only SNPs not in linkage disequilibrium will be included.
We will use Cox proportional hazards regression to examine associations of CRP polymorphisms, as well the associations of plasma CRP levels with the risk of cancer. We will utilize linear regression to explore the association of CRP polymorphisms with its plasma level.
An additive genetic model will be used with SNPs coded as 0, 1, or 2, where 2 will designate a risk allele. Genetic score will be derived as a sum of risk allele for each person. The score will be weighted (using estimates from GWAS studies) and rescaled. For the analysis of SNPs and plasma CRP levels, log transformation of CRP will be used because of skewness of CRP distribution. For the analysis of plasma CRP with cancers, CRP 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 plasma 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 CRP, 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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
__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

_x__ 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.