ARIC Manuscript Proposal # 1429

PC Reviewed: 10/14/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Inflammatory and allergy markers as predictors of colorectal cancer risk (CRC): Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): **Biomarkers and CRC risk**

2. Writing Group:

Writing group members: Anna E Prizment, Kristin E Anderson, Wayne D Rosamond, Aaron R Folsom

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __AEP___ **[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:

Analysis to begin upon approval of the proposal with spring 2009 as completion date.
Draft of manuscript– summer 2009

4. Rationale: Chronic inflammation has been previously linked to the etiology of cancer [1]. The evidence is strongest for colorectal cancer (CRC), the second most common cause of cancer death in adult Americans. It was shown that colonic inflammatory bowel disease, especially ulcerative colitis, is associated with increased risk for CRC whereas nonsteroidal anti-inflammatory drugs reduce the risk for colorectal cancer [2, 3]. Moreover, epidemiological studies observed positive associations between C-reactive protein - non-specific marker of inflammation in the body and risk of CRC [4-6]. Finally, several studies investigated associations of other acute phase reactants such as white blood count (WBC), fibrinogen, and albumin with CRC incidence and mortality.

Acute phase reactants markedly change their concentration in response to acute and chronic inflammation. When inflammation occurs, the levels of positive reactants, such as WBC, fibrinogen, Von Willebrand factor (VWF), and factor VIII increase, whereas concentration of albumin (negative reactant) decreases. Several epidemiological studies found that high WBC and fibrinogen are positively associated with all-site and cancer-specific mortality [7-12]. Few studies examined acute phase reactants in relation to incident CRC. Two of them reported an increased risk of CRC related to high WBC [13, 14] and one study observed an inverse association between serum albumin concentrations and incident CRC [15].

The ARIC dataset gives a great opportunity to prospectively examine inflammatory markers in relation to cancer because data about these biomarkers as well as information about potential confounders (aspirin, BMI, and smoking) were collected for all participants before cancer diagnoses. Our first aim is to investigate whether markers of systemic inflammatory response including WBC, fibrinogen, VWF, factor VIII, and albumin are associated with CRC.

Our second aim is to examine whether high eosinophil count usually caused by allergic reactions is related to incident CRC. Several studies demonstrated that eosinophils are tumor-cytotoxic [16,17] and are correlated with better survival in CRC patients [18,19]. Upregulation of cytokines that stimulate eosinophilic infiltration has been observed in colon tissue of patients with atopic dermatitis [20]. Recently, we found an inverse association between history of allergies and risk of colorectal cancer among elderly women in Iowa Women's Health Study [21]. So, we speculate that eosinophil count, which is an allergy marker, will be inversely associated with incident CRC.

We also plan to examine associations of the inflammatory markers and eosinophil count with incident breast, lung, and prostate cancers.

5. Main Hypothesis/Study Questions:

1) Incident CRC is associated with positive acute phase reactants such as WBC, fibrinogen, VWF, and factor VIII, and is inversely associated with albumin – a negative acute-phase protein.

2) Risk of CRC is inversely associated with eosinophil count.

In addition, we will investigate relations of these biomarkers with breast, lung, and prostate cancers.

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).
Independent variables: Visit 1 values of WBC, fibrinogen, albumin, VWF, factor VIII (all categorized into quartiles and continuous per 1 SD), eosinophil count (dichotomized at median).
Dependent Variables: Incident colorectal cancer up to 2006, as well as incident breast, lung, and prostate cancers. Currently, 2014 cancer cases (1895 people) are available through 2000 including 194 colorectal, 378 breast, 282 lung, and 400 prostate cancer. Now we are contacting cancer registries to perform linkage to update cases through 2006. After the update, we expect to have 284 colorectal, 552 breast, 411 lung, and 584 prostate cancers.
Confounders: age, sex, cigarette smoking, alcohol, family history of colorectal cancer, postmenopausal hormone use, aspirin/NSAID use, diabetes, hyperglycemia (fasting glucose 110 mg/dL), BMI, waist circumference, physical activity.
Analysis Plan: Prospective cohort. We propose to use proportional hazard model to estimate the multivariate adjusted risk of incident CRC and other cancers in relation to inflammatory markers and eosinophil count and investigate whether these associations vary across smoking status, BMI, and NSAID use. In the analysis of eosinophil count, relative risks will be adjusted for total leukocyte count.

Inclusion/Exclusion: *inclusion*: all ARIC visit 1 participants free of cancer; *exclusion:* participants with missing values of biomarkers

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? ____ 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 file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
____ 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?
____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)?

MS #694 Association of Coagulation factors and albumin with cancer incidence (1999). This was withdrawn.

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.

References

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