

## ARIC Manuscript Proposal # 1429

PC Reviewed: 10/14/08  
SC Reviewed: \_\_\_\_\_

Status: A  
Status: \_\_\_\_\_

Priority: 2  
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, Kala Visvanathan, 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**]

**First author: Anna Prizment**

Address: Division of Epidemiology and Community Health  
1300 South 2nd St., Suite 300  
Minneapolis, MN 55454

Phone: 612-626-0250

Fax: 612-624-0315

E-mail: prizm001@umn.edu

**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).

Name: **Aaron Folsom**

Address: Division of Epidemiology and Community Health  
1300 South 2nd St., Suite 300  
Minneapolis, MN 55454

Phone: 612 626-8862

Fax: 612-624-0315

E-mail: folso001@umn.edu

### 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 (CRP) - 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 CRP, 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 other than CRP 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 CRP, 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 CRP, 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:** WBC, fibrinogen, albumin, VWF, and factor VIII (all from Visit 1), CRP from Visit IV (all categorized into quartiles and continuous per 1 SD), and eosinophil count from Visit I (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?  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 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  
 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.csc.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)?**

**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?**  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.csc.unc.edu/atic/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

1. Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002;420(6917):860-7.
2. Chan AT, Giovannucci EL, Schernhammer ES, Colditz GA, Hunter DJ, Willett WC, et al. A prospective study of aspirin use and the risk for colorectal adenoma. *Ann Intern Med*. 2004;140(3):157-66.
3. Lamont EB, Dias LE, Lauderdale DS. NSAIDs and colorectal cancer risk: Do administrative data support a chemopreventive effect? *J Gen Intern Med*. 2007;22(8):1166-71.
4. Erlinger TP, Platz EA, Rifai N, Helzlsouer KJ. C-reactive protein and the risk of incident colorectal cancer. *JAMA*. 2004;291(5):585-90.
5. Ito Y, Suzuki K, Tamakoshi K, Wakai K, Kojima M, Ozasa K, et al. Colorectal cancer and serum C-reactive protein levels: A case-control study nested in the JACC study. *J Epidemiol*. 2005;15 Suppl 2:S185-9.

6. Gunter MJ, Stolzenberg-Solomon R, Cross AJ, Leitzmann MF, Weinstein S, Wood RJ, et al. A prospective study of serum C-reactive protein and colorectal cancer risk in men. *Cancer Res.* 2006;66(4):2483-7.
7. Shankar A, Mitchell P, Rochtchina E, Tan J, Wang JJ. Association between circulating white blood cell count and long-term incidence of age-related macular degeneration: The blue mountains eye study. *Am J Epidemiol.* 2007;165(4):375-82.
8. Yano K, Grove JS, Chen R, Rodriguez BL, Curb JD, Tracy RP. Plasma fibrinogen as a predictor of total and cause-specific mortality in elderly japanese-american men. *Arterioscler Thromb Vasc Biol.* 2001;21(6):1065-70.
9. Shankar A, Wang JJ, Rochtchina E, Yu MC, Kefford R, Mitchell P. Association between circulating white blood cell count and cancer mortality: A population-based cohort study. *Arch Intern Med.* 2006;166(2):188-94.
10. Erlinger TP, Muntner P, Helzlsouer KJ. WBC count and the risk of cancer mortality in a national sample of U.S. adults: Results from the second national health and nutrition examination survey mortality study. *Cancer Epidemiol Biomarkers Prev.* 2004;13(6):1052-6.
11. Grimm RH, Jr, Neaton JD, Ludwig W. Prognostic importance of the white blood cell count for coronary, cancer, and all-cause mortality. *JAMA.* 1985;254(14):1932-7.
12. Friedman GD, Fireman BH. The leukocyte count and cancer mortality. *Am J Epidemiol.* 1991;133(4):376-80.
13. Lee YJ, Lee HR, Nam CM, Hwang UK, Jee SH. White blood cell count and the risk of colon cancer. *Yonsei Med J.* 2006;47(5):646-56.
14. Margolis KL, Rodabough RJ, Thomson CA, Lopez AM, McTiernan A, Women's Health Initiative Research Group. Prospective study of leukocyte count as a predictor of incident breast, colorectal, endometrial, and lung cancer and mortality in postmenopausal women. *Arch Intern Med.* 2007;167(17):1837-44.
15. Ko WF, Helzlsouer KJ, Comstock GW. Serum albumin, bilirubin, and uric acid and the anatomic site-specific incidence of colon cancer. *J Natl Cancer Inst.* 1994 Dec 21;86(24):1874-5.
16. Gleich GJ. Mechanisms of eosinophil-associated inflammation. *J Allergy Clin Immunol.* 2000;105(4):651-63.
17. Munitz A, Levi-Schaffer F. Eosinophils: 'new' roles for 'old' cells. *Allergy.* 2004;59(3):268-75.
18. Nielsen HJ, Hansen U, Christensen IJ, Reimert CM, Brunner N, Moesgaard F. Independent prognostic value of eosinophil and mast cell infiltration in colorectal cancer tissue. *J Pathol.* 1999;189(4):487-95.
19. Pretlow TP, Keith EF, Cryar AK, Bartolucci AA, Pitts AM, Pretlow TG, 2nd, et al. Eosinophil infiltration of human colonic carcinomas as a prognostic indicator. *Cancer Res.* 1983;43(6):2997-3000.
20. Yamada H, Izutani R, Chihara J, Yudate T, Matsukura M, Tezuka T. RANTES mRNA expression in skin and colon of patients with atopic dermatitis. *Int Arch Allergy Immunol.* 1996;111 Suppl 1:19-21.
21. Prizment AE, Folsom AR, Cerhan JR, Flood A, Ross JA, Anderson KE. History of allergy and reduced incidence of colorectal cancer, Iowa Women's Health study. *Cancer Epidemiol Biomarkers Prev.* 2007;16(11):2357-62.