ARIC Manuscript Proposal # 957

PC Reviewed: 09/10/03	**Status: A**	**Priority: 2**
SC Reviewed: 09/11/03	**Status: A**	**Priority: 2**

1.a. Full Title:
Physical activity and the metabolic syndrome: risk for colon and rectal cancer in the Atherosclerosis Risk In Communities (ARIC) cohort

b. Abbreviated Title (Length 26 characters):
Colorectal cancer risk in ARIC

2. Writing Group (list individual with lead responsibility first):

Lead: **Rehana Ahmed**
Address: Division of Epidemiology
1300 S 2nd St, Suite 300
Minneapolis, MN 55454
Phone: 612-624-7349 Fax: 612-624-0315
E-mail: ahmed_r@epi.umn.edu

Writing group members:
Dr. Aaron Folsom, Dr. Kathryn Schmitz, Dr. Kristin Anderson,…

3. Timeline:
September 2003-June 2004

4. Rationale:
Colon and rectal cancers (CRC) are the 4th most common cause of cancer and cancer death in the US, with an estimated 105,500 cases to occur in 2003.[1] Epidemiological observational studies provide increasing evidence that physical activity decreases risk for certain cancers of hormonally related etiology – the evidence is strongest for colon cancer.[2,3] There is also evidence that excess weight, in particular abdominal obesity, is associated with increased risk for hormonally related cancers, such as colon and rectal cancers.[4] Mechanisms by which physical activity and weight control may protect against these cancers include decreases in the availability of hormones that promote cellular growth as well as decreases in inflammation that lead to increased cellular turnover. Interestingly, elevated body fat and insulin resistance are both associated with elevated levels of cellular growth factors and inflammatory markers. Exercise leads to preferential fat loss from intraabdominal stores.[5] Fat loss may be associated with decreases in the availability of hormones that promote cellular growth as well as decreases in inflammatory markers.

Physical activity has been shown to be protective for colon cancer in several prospective observational studies. Of 51 studies conducted to date on colon and colorectal cancer, 43 demonstrate a reduced risk of cancer, ranging from 40-70% among the most physically active male and female participants (for a review please see Friedenreich and Orenstein, 2002).[15] 25 of 29 studies found a trend in the association between physical activity and decreased cancer risk, such that those who are more physically active experience the greatest benefit.[15] Current evidence indicates that insulin resistance is associated with cancer of the colon and possibly

rectum. In addition, while there is a strong association between physical activity and protection for colon cancer, there does not seem to be an association with rectal cancer.[15]

It is fairly well established that physical activity is associated with reduced risk for colon cancer. However, the mechanisms for this association are not yet clear and further research is needed to elucidate the mechanisms. Obesity, hyperinsulinemia, and diabetes have been linked to both colon and rectal cancers in some but not all studies.[4] Physical activity may be protective for colon cancer through improvements in obesity, hyperinsulinemia, and diabetes. In the ARIC study data has been collected to allow us to determine obesity by waist circumference >40 inches in men or >35 inches in women, hyperinsulinemia as fasting insulin ≥ 20 uU/ml, and fasting glucose ≥ 110 mg/dL. We propose to use the ARIC data set to assess the association of physical activity and colon cancer risk, the association of insulin, glucose, and obesity with colon cancer risk, and the potential for insulin, glucose, and obesity to mediate the association of physical activity and cancer. We also propose to examine these associations with colorectal cancer risk as a secondary outcome.

The metabolic syndrome is gaining attention as a model to examine risk for colon and rectal cancers;[9] physical activity may be protective of colon cancer through improvement in physiological processes that lead to the metabolic syndrome as well as pathologic sequelae. The metabolic syndrome is defined by the presence of three or more of the following: abdominal obesity (waist circumference >40 inches in men or >35 inches in women); triglycerides ≥150 mg/dL; HDL cholesterol <40 mg/dL in men or <50 mg/dL in women; blood pressure ≥130/≥85 mmHg; and fasting glucose ≥110 mg/dL.[6] Some, but not all epidemiologic studies link elements of the metabolic syndrome to risk for colon and rectal cancer.[9] Physical activity leads to improvements in body fat as well as insulin sensitivity, and is thought to impact the metabolic syndrome (e.g. Irwin et al, 2002).[16] Change in metabolic syndrome related physiologic parameters may be a mechanism through which physical activity reduces risk for colon cancer – we propose to examine this potential association in secondary analyses using ARIC data.

Markers of the metabolic syndrome and physical inactivity have been examined in prospective observational studies. Obesity has been strongly linked with risk for CRC in prospective observational studies.[7] Hardman (2001)[8] reviews evidence that a high BMI may be associated with an increased risk of CRC in sedentary men, but not in physically-active men. Insulin resistance has been examined in several populations in relation to colon and rectal cancers (e.g. reviewed in Chang and Ulrich, 2003)[9] In a cohort of diabetic patients, there was increased incidence of both colon cancer and rectal cancer.[10] In cohort studies in the general population, biomarkers of insulin resistance increased risk for CRC. For example, in the Cardiovascular Health Study, 2-hour post-challenge glucose concentration was a significant risk factor for CRC.[11] A case-control study nested within the Nurses' Health Study found that elevated blood insulin concentration and HbA1C levels did not significantly increase risk for CRC; however, it was associated with increased risk for advanced CRC.[12] "X syndrome", also described as the metabolic syndrome, was associated with a three-fold increased risk of CRC mortality in a cohort of men and women.[13] A limitation of this study was the examination of CRC mortality as opposed to incidence, however data on the relation between metabolic syndrome and CRC incidence are sparse. Familial aggregation of diabetes (OR parents: 2.4 (1.2,4.8) OR siblings: 5.8 (2.6,13.3)) and hypertension (OR: 1.7 (1.1,2.6) were each positively associated with colorectal neoplasia in a recent colonoscopy-based case-control study.[14] There are no consistent data for a differential association between insulin resistance and CRC by either gender or

location on the colon/rectum,.[9] The lack of consistent data regarding associations among components of the metabolic syndrome and location of tumorigenesis on the colorectal track speak to the need to further examine the metabolic syndrome, insulin resistance, obesity, and physical inactivity and their relation to CRC as well as colon cancer alone.

We have recently updated colon and rectal cancer cases in the ARIC cohort through 2000 by linkage to the state cancer registries. There are 134 incident colon and 49 incident rectal cancer cases; additionally, there are 6 colon and 5 rectum cases that have been identified by CEL-only – we plan to have these cases validated. We plan to conduct analyses using the colon cancer cases alone as well as the combined colon and rectal cases.

1. American Cancer Society, Cancer Facts and Figures, www.nih.gov
2. Friedenreich, CM *Ca Epi, Biomarker, & Prev* 2001; 10:287-301
3. McTiernan A, et al. *Ca Epi* 1999;8(3): 201-207
4. Folsom AR, et al. *Am J Epi* 1990;131:794 (17)
5. Ross, R, Janssen I *Med Sci Sports Med* 1999; 31:S568-S572
6. NHLBI website: http://www.nhlbi.nih.gov/guidelines/cholesterol/atp_iii.html
7. Murphy TK, C. E., Rodriguez C, Kahn HS, Thun MJ *Am J Epi* 2000; 152(9): 847-854
8. Hardman, A. *Proceedings of the Nutrition Society*, 2001; 60(1): 107-113.
9. Chang CK, Ulrich CM. *Diabetologica* 2003; 46: 595-607.
10. Weiderpass E, Gridley G, et al. *J Natl Cancer Inst*, 1997; 89: 660-661
11. Schoen RE, Tangen CM, et al *J Natl Cancer Inst*, 1999; 91: 1147-1154
12. Platz EA, Hankinson SE, et al. *Cancer Causes Control*, 1999; 10: 379-386
13. Trevisan M, Liu J, et al. *Cancer Epi Biomarkers and Prev*, 2001; 10: 937-941
14. Brauer PM, McKeown-Eyssen, et al. *Am Jnl Epidemiology* 156(8): 702-713
15.Friedenreich CM, Orenstein MR. *J Nutrition*, 2002; 132: 3456S-3464S
16, Irwin ML, Ainsworth BE, et al. *Obesity Research*, 2002 10(10): 1030-1037

5. Main Hypothesis/Study Questions:
The primary aim is to examine whether there is a relation of incident colon cancer with physical activity, elevated waist circumference, insulin resistance and elevated fasting glucose. Secondarily we will examine whether there is a relation of incident colon and colorectal cancer (CRC) with physical activity and the metabolic syndrome. We hypothesize the presence of elevated BMI, insulin resistance or the metabolic syndrome increase risk for CRC, whereas physical activity is protective.

6. Data (variables, time window, source, inclusions/exclusions):
Inclusion/Exclusion: *inclusion*: all ARIC visit 1 participants free of cancer; *exclusion:* type I diabetics
Independent Variables: physical activity level from survey; BMI; hyperinsulinemia (fasting insulin ≥ 20uU/ml), and hyperglycemia (fasting glucose ≥ 110 mg/dL); the metabolic syndrome (defined as the presence of 3 or more: abdominal obesity (waist circumference >40 inches in men or >35 inches in women); triglycerides ≥150 mg/dL; HDL cholesterol <40 mg/dL in men or <50 mg/dL in women; blood pressure ≥130/≥85 mmHg; fasting glucose ≥110 mg/dL and/or insulin resistance, fasting insulin ≥ 20uU/mL). (We realize there are several other ARIC papers on definitions of the metabolic syndrome and we will consider these as well.)
Dependent Variables: colon and colorectal cancer incidence through 2000
Possible covariates: age, cigarette smoking, family history of colorectal cancer, postmenopausal hormone use, Aspirin or NSAID use, intake of red meat and alcohol consumption, calcium,

vitamin D, treatments for diabetes/insulin resistance (sulfonyl ureas, meglitinide, biguanides, thiazolidinediones, alpha-glucosidase inhibitors)

Analysis Plan: Prospective analysis. Data description will consist of presenting means together with numbers, standard deviations, minima and maxima. We propose to conduct Cox Proportional Regression Analyses with the above variables/covariates. The detectable RR for colorectal cancer is 1.54; for colon cancer alone, 1.69.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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/pub.phtml

____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)?

This will be the first paper on colon and colorectal cancer in ARIC, so there is no overlap. The most relevant paper is:

Mink PJ, Shahar E, Rosamond WD, Alberg AJ, Folsom AR Am J Epidemiol 2002; 156:349-352. Serum insulin and glucose levels and breast cancer incidence levels: The Atherosclerosis Risk in Communities Study

11. 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.