1.a. Full Title: Adiponectin (ADIPOQ) and adiponectin receptor (ADIPOR1, and ADIPOR2) SNPs and the incidence of cancer: Atherosclerosis Risk in Communities (ARIC) study

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

2. Writing Group:
   Writing group members: Laura Rasmussen-Torvik, James Pankow, Anna Prizment, Aaron Folsom. Wayne Rosamond and Eric Boerwinkle have been invited to participate but have not yet responded to our request.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __LJRT___ [please confirm with your initials electronically or in writing]

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3. Timeline:

   Analyses will begin when CARe SNP data is made available in the ARIC cohort and when cancer cases are added after the new linkage to cancer registries (up to 2006). We anticipate the manuscript will be completed within 1 year.
4. **Rationale:**

Adiponectin is a protein, secreted only by adipocytes, that is inversely associated with both measures of adiposity and insulin resistance in epidemiologic studies (1-4). Low adiponectin has been associated prospectively with an increased risk of diabetes, after adjustment for BMI (5, 6). Recently, it has been hypothesized that adiponectin may also play a role in the development and progression of several types of cancer.

Three different studies have shown that the adiponectin protein inhibits growth and proliferation of prostate cancer, breast cancer, and colon epithelial cells in vitro (7-9). Additionally, it has been shown that serum or plasma adiponectin is lower in breast cancer cases and prostate cancer cases than in controls (10, 11), and that low plasma adiponectin levels predict colon cancer in men (12). Finally, the associations of SNPs in the Adiponectin (ADIPOQ) and Adiponectin receptor 1 (ADIPOR1) gene with breast cancer and with colon cancer were recently reported. In a case-control study including women from New York city, two SNPs in adiponectin were significantly associated with breast cancer risk (rs1501299 GG OR – 1.80, rs2241766 GG OR - .63) as was one SNP in ADIPOR1 (rs7539542 CC OR .51) (13). In a second study, one ADIPOQ SNP (rs266729 GG/CG OR - .73) was significantly associated with colon cancer risk in two case-control studies which enrolled subjects in New York City and Chicago (14).

The ARIC dataset provides and excellent opportunity to replicate and expand upon the results from the two recently published SNP studies. As part of the CARE consortium, ARIC participants are being genotyped on 22 SNPs in ADIPOQ, 15 SNPs in ADIPOR1, and 35 SNPs in ADIPOR2. All four of the significant SNPs reported in the two Kaklamani et al. papers are included in this set of SNPs. Additionally, the CARE consortium picked tagging SNPs which are designed to capture much of the known variation in a given gene.

Data from the ARIC ancillary Cancer study, newly updated to include cases through 2006, is expected to provide almost 300 incident cases of colorectal cancer and over 550 cases of breast and prostate cancers for this analysis.

Therefore, with this proposed analysis we can

- Replicate, or not, reported significant associations between ADIPOQ and ADIPOR1 SNPs and Breast and colon cancer in whites
- Report novel associations
  - between prostate cancer and ADIPOQ/ ADIPOR1 SNPs in whites
  - between breast, colon, and prostate cancer and ADIPOR2 SNPs in whites
  - between breast, colon, and prostate cancer in ADIPOQ/ADIPOR1/ADIPOR2 SNPs in African Americans
- Examine how obesity and insulin resistance may prospectively interact or mediate with ADIPOQ, ADIPOR1, and ADIPOR2 SNPs to increase risk of breast, colon, and prostate cancer
5. **Main Hypothesis/Study Questions:**

A) SNPs in ADIPOQ/ADIPOR1/ADIPOR2 are related to risk of colon cancer  
B) SNPs in ADIPOQ/ADIPOR1/ADIPOR2 are related to risk of breast cancer  
C) SNPs in ADIPOQ/ADIPOR1/ADIPOR2 are related to risk of prostate cancer

In addition we will investigate interactions between obesity and insulin resistance and ADIPOQ/ADIPOR1/ADIPOR2 SNPs on risk of incident cancer.

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 colon cancer, incident breast cancer (stratified on pre/post menopausal breast cancer in supplemental analyses), incident prostate cancer. Currently, 2014 cancer cases (1895 people) are available through 2000. Ms. Prizment and Dr. Folsom are updating cancer cases through 2006 and expect to have 284 colorectal, 552 breast, and 584 prostate cancer cases after the updates.

**Independent variables**: 22 SNPs in ADIPOQ, 15 SNPs in ADIPOR1, and 35 SNPs in ADIPOR2 (being typed in the IBC chip as part of the CARe consortium)

**Covariates**: Because this is a genetic analysis, confounding is not anticipated, but we will consider confounding by major cancer risk factors such as age, sex, smoking, BMI, alcohol, physical activity etc. (and NSAID use, hormone replacement use, age at menarche, and age at menopause for specific cancers)—measured at visit 1. Interactions with BMI and fasting insulin (measured at visit 1) will be considered for significant SNP / cancer associations.

**Analysis plan**: All analyses will take place stratified by self-identified race in recognition of the potential for population stratification. In cases where patterns of association are similar across races, race-combined analyses may be undertaken, controlled for self-identified race. For each genotype, Hardy Weinberg equilibrium will be calculated and those genotypes not in HWE will be excluded.

We will use a model-free approach to modeling the genotypes using 2 d.f. statistical tests (or 1 d.f. tests if small numbers of homozygous recessives merit the combination of heterozygous and homozygous recessive genotype groups). To replicate the significant results in the Kaklamani papers, a dominant model may also be used in some instances. We will use a proportional hazards model to estimate the adjusted risk of incident colon,
breast, or prostate cancer in relation to genotype. If we find significant genotype/cancer associations we will use interaction terms in the proportional hazards models to determine if these associations vary by BMI or fasting insulin at baseline.

Because of the number of SNPs included in the analysis, the p-value threshold for significance must be corrected. A p-value less than .001 will be considered significant in this analysis, but all p-values less than .05 will be reported in the paper, in recognition of the fact that our correction is likely too conservative, given the expected correlation between SNPs in the same gene.

Inclusion/Exclusion: inclusion: all ARIC visit 1 participants free of cancer; exclusion: participants with missing genotype information, and any ARIC participants who did not agree to participant in nonCVD or genetic research.

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.csec.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)?

#1227 TCF7L2 variants and cancer risk. Dr. Folsom, the first author of this paper, will participate in the writing group

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

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


