1.a. Full Title: Adherence to WCRF/AICR recommendations and risk of colorectal cancer (CRC) in Whites and African-Americans in the Atherosclerosis Risk in Communities (ARIC) study.

b. Abbreviated Title (Length 26 characters): WCRF/AICR score and CRC risk

2. Writing Group:
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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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3. Timeline:
   Analysis will begin as soon as the proposal has been approved. Completion of the analysis is expected to be summer 2016 with a draft of the manuscript by fall 2016.

4. Rationale:
   In 2007, the World Cancer Research Fund (WCRF) and the American Institute of Cancer Research (AICR) published recommendations on diet, weight, and physical activity for cancer
prevention. Adherence to individual recommendations has been linked to decreased incidence, mortality and better quality of life after a breast, prostate colorectal, bladder, uterine, or skin melanoma cancer diagnosis, as well as reduced aggressiveness of disease in many but not all studies [1-7]. Several groups later operationalized the recommendations into a composite measure (hereafter, called WCRF/AICR score) adherence scores to evaluate the association between recommendation adherence and cancer incidence or outcomes [1-2, 5-7, 12]. This composite measure may better explain the etiology of cancer, and the findings using this approach may be more easily translated into strategies aimed at reducing the cancer burden than each of individual components [9].

The table below presents variables that were included in the WCRF/AICR score in the cancer studies in the Iowa Women’s Health Study (IWHS) and The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort [5, 12]. Each variable/recommendation contributed half or whole point to the overall adherence score, depending on how well each individual adhered to the specific guideline (Table 1):

Table 1. WCRF/AICR recommendations for cancer prevention* and operationalization of the WCRF/AICR score in the IWHS [12] and EPIC study [5].

<table>
<thead>
<tr>
<th>WCRF/AICR Recommendation</th>
<th>Variable</th>
<th>Operationalization [5,12] *</th>
<th>Score</th>
</tr>
</thead>
</table>
| Be as lean as possible without becoming underweight | BMI | 18 - <25 kg/m²  
25 - <30 kg/m²  
≥30 or < 18.5 kg/m² | 1  
0.5  
0 |
| Be physically active for at least 30 minutes every day. Limit sedentary habits. | Physical activity level | High  
Moderate  
Low | 1  
0.5  
0 |
| (1) Limit consumption of energy-dense foods.  
(2) Avoid sugary drinks. | (1) Not included  
(2) High sugar beverage intake | --  
0 g/day  
<250 g/day  
≥250 g/day | 1  
0.5  
0 |
| Eat more of a variety of vegetables, fruits, whole grains and legumes such as beans. | (1) Total fruit and vegetable intake frequency  
(2) Daily dietary fiber intake | ≥5 servings/day  
3 - <5 servings/day  
<3 servings/day  
≥ 25 g/day  
12.5 - <25 g/day  
<12.5 g/day | 1  
0.5  
0 |
| Limit consumption of red meats and avoid processed meats | Total red and processed (RP) and processed (P) meat intake (g/wk) | <500 g/day RP and <3 g/day P  
<500 g/day RP and 3-<50 g/day P  
≥500 g/day RP or ≥50 g/day P | 1  
0.5  
0 |
| If consumed at all, limit alcoholic drinks to 2 for | Weekly alcohol intake | <20 g/d (men)  
<10 g/d (women) | 1 |
men and 1 for women/day

<table>
<thead>
<tr>
<th>Daily sodium intake</th>
<th>≤1,500 mg/day</th>
<th>&gt;1,500-2,400 mg/day</th>
<th>&gt;2,400 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–30 g/d (men)</td>
<td>0.5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10–20 g/d (women)</td>
<td>0.5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>&gt;30 g/d (men)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>&gt;20 g/d (women)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*The table was adapted from the table in the IWHS study [12]. The table was supplemented by including different categories for alcohol intake in men [5].

Following the individual components of the WCRF/AICR guidelines has been associated with lower risk of colorectal cancer (CRC) [1, 7-9], as well as to the lower risk of colorectal polyps, a precursor for colon cancer [10]. Two studies conducted within the EPIC cohort have found that adherence to the WCRF/AICR score is associated with decreased CRC incidence and mortality [5, 7]. In the study of 386,355 healthy people at baseline in the EPIC cohort (3880 CRC cases), the HR (95% CI) for CRC incidence was 1, 0.91 (0.84, 1.00), 0.77 (0.70, 0.84), and 0.73 (0.65, 0.81) for the first, second, third, and fourth categories of the WCRF/AICR score, respectively, (p-trend < 0.0001) [5]. A similar trend was observed for CRC-specific mortality among 3,292 CRC patients: HRs (95% CI) were 0.8 (0.72, 1.06), 0.74 (0.61, 0.90), and 0.70 (0.56, 0.89) for the second, third, and fourth categories, respectively, when compared to participants with the lowest adherence to recommendations (p-trend < 0.0001) [7].

The aims of this study are to determine whether a combination of those lifestyle behaviors is associated with the risk of CRC development and mortality in the whole cohort and, specifically, in Whites and African-Americans. In the United States, CRC incidence and mortality rates are higher in African-Americans compared to Whites, but it has not been established whether this difference may be attributed to differences in genetic backgrounds, environmental factors, such as diet and smoking, or to differences in utilization of healthcare between races [11]. To our knowledge, no study has investigated the relations between adherence to the WCRF/AICR score and CRC risk after stratification by race. We expect that we will have sufficient number of CRC cases among African-American to study this association after the new cancer cases (up to 2011) are ascertained in the ARIC study. The ARIC dataset will provide all the necessary information about factors included in the WCRF/AICR recommendations for cancer prevention: lifestyle behaviors, including dietary intake, alcohol consumption, physical activity, and BMI. ARIC also has information about potential confounders that were collected at baseline.

5. Main Hypothesis/Study Questions:

**Primary Hypothesis**

Adherence to the WCRF/AICR recommendations for cancer prevention is inversely associated with incident CRC risk in the whole cohort, and separately among Whites and African-Americans.

**Secondary Hypothesis:** Adherence to the WCRF/AICR recommendations for cancer prevention is inversely associated with mortality from CRC as an underlying cause of death.
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).

This will be a prospective cohort study of the risk of CRC development and mortality from CRC in people free of any type of cancer (except non-melanoma skin cancer) at baseline.

**Inclusion/Exclusion:** *Inclusion:* All ARIC participants with no history of cancer (except non-melanoma skin cancer) at Visit 1; *Exclusion:* participants with missing race, sex, ethnicity, BMI, physical activity, alcohol, or dietary data. Those with implausibly high or low total energy intake (<600 or >5,000 kcal/d) dietary data will be also excluded.

**Independent variables:** The score will be a sum of the following baseline variables: BMI, physical activity, vegetable and fruit consumption, fiber, alcohol, intake of red and processed meat [13], sugary drinks [14], and sodium. All variables were ascertained at Visit 1 and will be operationalized as presented in Table 1. Sport index (1-5) will be used as a measure of physical activity [15, 16] and will be categorized into three groups. Intake of sugar-sweetened beverages will be used as a surrogate for the intake of energy dense foods.

**Dependent variables:** Incident CRC up to 2006 (N~340) and mortality with CRC (N~90) as the underlying cause of death up to 2011. After the new cancer counts become available, we will update the analysis with cancer incidence for the follow-up until 2011.

**Confounders:** Age, sex, race-center, smoking status and pack years, education, aspirin use, calcium intake, use of hormone replacement therapy (among women).

**Analysis plan:** The WCRF/AICR adherence score will be presented as quartiles. We will determine the percent of the ARIC population and, separately, the percent of African-American and Whites who adhere to the individual recommendations and WCRF/AICR adherence score (highest quartile). Demographic and lifestyle characteristics will be compared across the quartiles of the score using linear models or chi-square for continuous and categorical variables, respectively.

We will use Cox proportional hazard regression to estimate HR (95% CI) of CRC for each individual recommendation and the score in the model adjusted for age, center, sex, and race. Further, we will calculate the risk of incident CRC and mortality in relation to the score after further adjusting for other confounders associated with the score and CRC risk and mortality. We will also study the associations with the score separately in African-American and Whites, but the power to test the interaction could be low. In addition, we will calculate the population attributable risk (PAR) to estimate the proportion of CRC cases and mortality that would have been avoidable if the entire cohort had adhered to the WCRF/AICR score (top quartile).

Also, we will conduct several sensitivity analyses:
- We will stratify by CRC subsite and examine the association with the score for colon cancer only. We will not have a sufficient number of rectal cancer cases to study the association in a separate analysis.
● We will stratify the association between the score and CRC risk by CRC screening for those diagnosed after Visit 4, since the screening information was available at Visit 4 only.
● We will repeat the analysis for the score and CRC risk by using the variables assessed at Visit 3 to create the WCRF/AICR score (for those diagnosed after Visit 3).

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 ICTDER 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

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)?

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/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes ____ No.

References
16. Folsom AR, Yatsuya H, Nettleton JA. Community Prevalence of Ideal Cardiovascular Health, by the AHA Definition, and Relation to Cardiovascular Disease Incidence