1.a. Full Title: Weight change and cancer risk: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Weight Change and Cancer

2. Writing Group:
   Writing group members:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **XH** [please confirm with your initials electronically or in writing]

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3. **Timeline:**
Analyses will begin once the manuscript proposal is approved.

4. **Rationale:**
In the U.S., cancer has been the leading killer among people aged younger than 85 years since 1999 [1]. It is estimated that approximately 100,500 (~20%) cases of cancer are caused by obesity every year in the U.S. [2] Excess body fat has been strongly linked to risks of postmenopausal breast, endometrial, colorectal, kidney, pancreas, and esophageal cancers [2]. The effect of weight change during life on cancer risk is less clear. Gaining weight as an adult is associated with postmenopausal breast cancer [3] Limited evidence also suggests a link between adult weight gain and increased risk of colon cancer in men [4]. There are few studies on weight change and risk of other cancers. The association between weight gain and cancer risk is biologically plausible because gaining excess adipose tissue through life can increase levels of estrogen and insulin, suppress immune response, induce chronic inflammation, and promote angiogenesis [5], which all contribute to tumorigenesis and tumor progression.

The role of weight loss on cancer risk is more complicated. Conventional wisdom argues that intentional weight loss may improve health and perhaps reduce cancer risks, and two recent studies did show a relationship between bariatric surgery and reduced cancer risk among obese people [6, 7]. However, epidemiological studies have observed that individuals who lose weight have an increased risk of total mortality compared with those who maintained a stable body weight [8, 9]. Unexplained weight loss may also be a marker of unknown illness such as a subclinical cancer.

In the proposed study we seek to examine the effect of long-term weight change from age 25 to mid-adulthood and short-term recent weight change on several cancer outcomes: incidence of cancer overall, the combined incidence of cancer types that have evidence linking them to obesity, and the most common cancer types separately: breast cancer, colorectal cancer, prostate cancer, lung cancer, as well as endometrial cancer and bladder cancer.

This study will be patterned after the study by Stevens et al. (ARIC MS #710) that examining association of weight change with coronary heart disease and ischemic stroke incidence.

5. **Main Hypothesis/Study Questions:**
Study question 1: What are the associations between long-term weight change and risk of our cancer outcomes? We hypothesize that long-term weight gain will be associated with increased risk of obesity-related cancers.

Study question 2: What are the associations between short-term weight change and risk of our cancer outcomes? We hypothesize that short-term weight loss will be associated with increased risk of most types of cancer.
Study question 3: How do the relationships between weight change and cancer risk differ by cancer types? We hypothesize that long-term weight change will have a stronger effect on obesity-related cancers than other cancer, and the association between short-term weight change and cancer risks will be more prominent for the patients with deadlier cancer types.

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. For study question 1, long-term weight change is defined as body weight at clinic visit 1 minus weight at age 25, and follow-up is from clinic visit 1 until December 31, 2005. For study question 2, short-term weight change is defined as weight change between two consecutive clinic visits, and follow-up is 3 years following the weight change intervals.

Inclusion/Exclusion Criteria: Participants with previous cancer diagnosis at enrollment of the cohort (visit 1) will be excluded. For study question 1 on long-term weight change, participants with missing weights at visit 1 or at age 25 will be excluded, and cancer incidences that occurred in the three years following the first examination will be excluded to avoid or reduce inclusion of participants with unintentional weight loss caused by disease. For study question 2 on short-term weight change, the subjects with missing information on short-term weight change are excluded. Moreover, since the earliest follow-up for question 2 starts at visit 2, those who lost to follow-up, deceased or had a cancer incidence before visit 2 will be excluded as well.

Outcome variables: incident any type of cancer, obesity-related cancers (cancers of breast in postmenopausal women, endometrium, colorectum, kidney, esophagus and pancreas), incident non-obesity-related cancers (other cancer than the above), premenopausal breast cancer, postmenopausal breast cancer, colorectal cancer, prostate cancer, endometrial cancer, bladder cancer and lung cancer.

Exposure variables: weight at age 25, weights at each visit, BMI at age 25, and BMI at each visit.

Covariates: age, sex, center, race, education, height, smoking, waist-to-hip ratio (or waist circumference), physical activity, alcohol drinking, family history of cancer, total energy intake, where appropriate, age at menarche, age at first birth, number of live births, menopausal status, age at menopause, use of hormone replacement therapy, meat intake, vegetable and fruit intake, fat intake, diabetes.

Data analysis: We will use Cox proportional hazard models to estimate the multivariate adjusted risks of cancer in relation to long-term weight change and short-term weight change.
Long-term weight change and short-term weight change will be categorized as <-3% (weight loss), >=-3 to <=3% (weight maintenance; reference group), >3% (weight gain) and hazard ratios (HRs) and 95% confidence intervals (CIs) will be estimated for weight loss and weight gain.

Weight change will also be analyzed in the continuous form. First quadratic spline regression models [10] will be used to examine the shape of the effect of continuous weight change variables on risks of cancer. Models with appropriate knots will be used when linear models are not sufficient for the analysis. HRs and CIs per 1% weight change will be estimated using the appropriate models.

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”?  ____ 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 #710: Associations between changes in anthropometric variables and mortality. The purpose of the proposal was to examine independently the associations of long- and short-term weight change and incident coronary heart disease and ischemic stroke. We will use the same approach to examine the associations of long- and short-term weight
change and risk of cancers. Dr. June Stevens and Dr. Kimberly Truesdale of that proposal are members of our writing group.

MS #1722: Associations of height and leg length with risk of breast and colorectal cancers in the Atherosclerosis Risk in Community study. This study examined the association between another two anthropometric measurements (height and leg length) and breast and colorectal cancers. Breast cancer and colorectal cancer are two common cancers that have strong evidence linking them to obesity. There is no overlap with our proposed manuscript.

MS# 957: Physical activity and the metabolic syndrome: risk for colon and rectal cancer in the Atherosclerosis Risk In Communities (ARIC) cohort. There is no overlap with our proposed manuscript.

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* __________)

___ 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/](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.