ARIC Manuscript Proposal # 1722

PC Reviewed: 12/14/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Associations of height and leg length with risk of breast and colorectal cancers in the Atherosclerosis Risk in Communities study

b. Abbreviated Title (Length 26 characters): Leg length and cancer

2. Writing Group:

Writing group members: Anna E Prizment, Pam L Lutsey, Kristin E Anderson, Elizabeth Platz, Corinne Joshu, Aaron R Folsom (Welcome suggestions for other members)

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 to begin upon approval of the proposal with spring 2011 as completion date. Draft of manuscript– summer 2011. Coauthors' review and revision –fall 2011.

4. Rationale:

The risk of adult cancer is affected by exposures in childhood, adolescence, and young adulthood. However, only a few studies have measurements of childhood exposures (such as diet) and sufficient follow-up to allow examining the link between childhood nutritional status and cancer. Adult height may be considered as a marker for nutritional and hormonal factors in pre-adult life (1-3). Numerous studies examined associations between adult height and cancer risks and positive associations have been consistently established for breast and colorectal cancer with the strongest evidence for breast cancer (2, 4, 5). There is weak evidence that there are associations of height with pancreatic, ovarian and endometrial cancers. The components of height – leg and trunk– are poorly correlated with each other and may be differently associated with cancer risk (4). Calorie intake in childhood and growth-promoting hormones particularly affect leg length and may increase the risk of breast and colorectal cancers, whereas high life-time exposure to estrogen may lead to a larger trunk and may potentially increase breast cancer risk and decrease CRC risk (2, 4, 5).
There is some evidence to suggest that leg length is the component of height that determines observed associations of height with breast and colorectal cancer (2). However, among the few studies that examined the associations of leg and trunk with the risk of these cancers, one was cross-sectional (4) and others had low power (1, 6). It is important to investigate differential associations of trunk and leg length with breast and colorectal cancers since this may provide indirect evidence of the potential causes of these cancers and determine the periods of life critical for cancer development.

5. Main Hypothesis/Study Questions:

We hypothesize that

1) height and leg length are positively associated with breast and colorectal cancer, and the associations are stronger for breast cancer.
2) If the associations with leg length exist, they will be independent from any association with trunk length.

We propose to investigate whether race and gender (for colorectal cancer) modify the associations of height and leg length with 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).

Study design. Prospective cohort. All ARIC visit 1 participants free of cancer at baseline will be included. Participants with missing values for seated height will be excluded.

Independent variables: Leg length, trunk length, and height. At baseline, height, and seated height were measured. Seated height will approximate trunk length. Leg length will be computed as total height minus seated height.

Dependent Variables: Incident colorectal cancer (N~346) and breast cancer (N~570) up to 2006.

Potential confounding and mediating factors: age, sex, center, race, cigarette smoking, education, waist-to hip ratio (or waist circumference), physical activity, diabetes. Models for breast cancer will be additionally adjusted for age at menarche, number of livebirths, menopausal status and age of menopause for post-menopausal women. In a sensitivity analysis, we will also test adjusting for birth weight, parental education and parental homeownership, about which the participants were queried at Visit 4.

Analysis plan
We will use a proportional hazard model to estimate the multivariate adjusted risk of incident breast and colorectal cancers in relation to height, leg, and trunk length.

1) Height, leg, and trunk length will be modeled as quartiles and as continuous variables. Hazard ratios per 1 standard deviation of the continuous measures will be calculated. Each measure will be entered in the Cox model individually and then two of these anthropometric measures will be entered simultaneously into the model to examine whether the association with each variable changes after adjustment for another one.
2) Since leg, trunk and height are correlated, to further examine associations of cancers with these anthropometric measures, we will use the residual method. This method will calculate leg and trunk adjusted for height (from the linear regression model). Thus we will examine the associations of leg and trunk independent of height.

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? ____ 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)?

For the analysis, we will use an approach suggested by Pam Lutsey in the "Leg length and incident venous thromboembolism: The Longitudinal Study of Thromboembolism Etiology (LITE)". Pam Lutsey and Aaron Folsom (senior author in that proposal) are members of our 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

1. Whitley E, Martin RM, Smith GD, Holly JM, Gunnell D. Childhood stature and adult cancer risk: The boyd orr cohort. Cancer Causes Control 2009;20:243-51.
2. World cancer research Fund/American institute for cancer research. food, nutrition, physical activity and the prevention of cancer: A global; perspective, washington DC: AICR. In: ; 2007. p. 39.
3. Okasha M, McCarron P, Gunnell D, Smith GD. Exposures in childhood, adolescence and early adulthood and breast cancer risk: A systematic review of the literature. Breast Cancer Res Treat 2003;78:223-76.
4. Lawlor DA, Okasha M, Gunnell D, Smith GD, Ebrahim S. Associations of adult measures of childhood growth with breast cancer: Findings from the british women's heart and health study. Br J Cancer 2003;89:81-7.
5. Gunnell D, Okasha M, Smith GD, Oliver SE, Sandhu J, Holly JM. Height, leg length, and cancer risk: A systematic review. Epidemiol Rev 2001;23:313-42.
6. Gunnell D, May M, Ben-Shlomo Y, Yarnell J, Smith GD. Height, leg length, and cancer: The caerphilly study. Nutr Cancer 2003;47:34-9.