ARIC Manuscript Proposal # 3017

PC Reviewed: 7/11/2017 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: The role of physical activity and sedentary behaviors in life expectancy and cancer-free life expectancy

b. Abbreviated Title (Length 26 characters): **Physical activity and cancer-free life expectancy**

2. Writing Group:

Writing group members: Carmen Cuthbertson, Kelly Evenson, Gerardo Heiss, Anna Kucharska-Newton, Hazel Nichols, Xianming Tan, Corinne Joshu, Elizabeth Platz

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

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3. Timeline: This is part of my doctoral dissertation. I plan to defend my proposal August 2017 and conduct analysis and paper write-up until Summer 2018.

4. Rationale:

Chronic diseases such as cancer and cardiovascular disease (CVD) are the leading causes of death, premature mortality, and years lived with disability[1, 2]. Although mortality rates have declined and life expectancy has increased, many adults are living longer, but not necessarily in good health [2]. In 2010, the average US life expectancy at birth was 78.2 years but adults could expect to live at least 10 years with illness and disability[2]. By 2030, Americans aged 65 and older will account for 20% of the US population and currently two out of three Americans in this age group have multiple chronic health conditions[3]. Given the high burden of chronic disease and the projected increase in the aging population[4], it is important to identify modifiable risk factors that can extend the number of years spent in good health.

The benefits of physical activity are well known for the prevention of certain cancers[5-7], improvement in many risk factors for cancer[8-10], and extended life expectancy[11, 12]. Walking is the most commonly reported physical activity by adults[13] and is linked to a lower risk of breast cancer [14], colon cancer [15, 16], and all-cause mortality[17, 18]. Physical activity is also linked to reduced risk of CVD and new evidence suggests adults who engage in physical activity at mid-life can expect to live more years free of CVD[19-21]. For example, men in the Framingham cohort who engaged in high levels of leisure-time physical activity could expect at age 50 a life expectancy of 29.9 years (95% confidence interval (CI) 29.0-31.0) with 22.8 years (95% CI 21.6-23.9) as CVD-free. By comparison, men who engaged in low levels of leisure-time physical activity could expect a life expectancy of 26.2 years (95% CI 25.4-27.1) with 19.7 years (95% CI 18.7-20.6) as CVD-free - a difference of 3.2 more years (95% CI 1.9, 4.3) spent CVD-free for men who engaged in high levels of activity[19]. These types of studies are informative for understanding how physical activity extends disease-free years, but have not considered cancer outcomes and have been limited to primarily Caucasian populations.

In contrast to physical activity, greater amount of time spent in sedentary behaviors is linked to development of cancer[22, 23] and risk factors for cancer[24, 25], even among adults who are physically active. Sedentary behavior is distinct from physical activity – sedentary behaviors are any waking behaviors that expend little energy expenditure ($\leq$ 1.5 metabolic equivalent of task (METs)) while in a sitting or reclining posture[26]. Physical activities are often classified into three intensity levels – light (1.6 – 2.9 METs), moderate (3.0 – 5.9 METs), and vigorous ($\geq$ 6.0 METs)[27]. On average, Americans spend 8 hours per day in sedentary behaviors with older adults spending close to 9 hours per day sedentary[28]. Associations with adverse health outcomes are observed across different measures of sedentary behavior including overall sitting time[23] and time spent television viewing[23, 25, 29]. Sedentary behaviors are recognized as an independent risk factor for many adverse health outcomes, yet few studies have examined life expectancy or years lived free of cancer according to sedentary behaviors.

As the number of older Americans is projected to increase substantially, identifying behaviors that can extend healthy years is a priority to promote healthy aging for millions of Americans. This project will contribute new knowledge, specifically estimates of life expectancy and disease-free years by physical activity and sedentary behaviors. This research will be the first to 1) assess years spent free of three of the leading incident cancers (breast, colorectal, and prostate), 2) examine how sedentary behaviors influence disease-free life expectancy, and 3) provide disease-free life expectancy estimates specific to African Americans.

5. Main Hypothesis/Study Questions:

Aim 1: To estimate life expectancy and breast cancer-free (women only), colorectal cancer-free, and prostate cancer-free (men only) life expectancy at age 50 by mid-life leisure-time physical activity behaviors.

Hypothesis 1.1: Participants who engage in high levels of leisure-time moderate-to-vigorous physical activity (MVPA) will have a longer life expectancy at age 50 and longer breast cancer-free, colorectal cancer-free, and prostate cancer-free life expectancy than participants who engage in low levels of leisure-time MVPA.

Hypothesis 1.2: Participants who engage in high levels of leisure-time walking will have a longer life expectancy at age 50 and longer breast cancer-free, colorectal cancer-free, and prostate cancer-free life expectancy than participants who engage in low levels of leisure-time walking.

Aim 2: To estimate life expectancy and breast cancer-free (women only), colorectal cancer-free, and prostate cancer-free (men only) life expectancy at age 50 by mid-life sedentary behaviors.

Hypothesis 2.1: Participants who engage in low levels of TV viewing time will have a longer life expectancy at age 50 and longer breast cancer-free, colorectal cancer-free, and prostate cancer-free life expectancy than participants who engage in high levels of TV viewing time.

Hypothesis 2.2: Among participants who are employed, participants who engage in low levels of sitting time at work will have a longer life expectancy at age 50 and longer breast cancer-free, colorectal cancer-free, and prostate cancer-free life expectancy than participants who engage in high levels of sitting time.

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: We will use baseline measures of physical activity and sedentary behavior and will ascertain cancer outcomes after baseline (1987-89) through 2012.

Study population

We will include men and women of all ages at baseline.

Exclusions

We will exclude participants with any type of prevalent cancer (except for non-melanoma skin cancers) at Visit 1 and those missing information on physical activity, sedentary behavior, and for any of the covariates used in our analyses. We will exclude the small number of participants who are not Caucasian or African American. We will also exclude participants with mobility issues who cannot walk without assistance.

Exposures

1) Physical activity is measured at visit 1 with the Baecke questionnaire by asking participants to list up to four leisure-time activities they participated in the past year, along with the number of hours/week (duration) and months/year (frequency) that they participated in each of the 4

activities. Using this information, we will calculate MET-hours per week of MVPA and categorize it into distribution-based quantiles or tertiles, determined after exploratory analyses. We will also consider leisure-time light activity if enough participants report these activities
2) Time spent walking is measured at visit 1 for the participants who listed walking as one of the four leisure-time activities. Data collected on frequency and duration of walking will be used to estimate hours per week spent walking.
3) We will also consider additional analyses categorizing participants as meeting the 2008 US physical activity aerobic guidelines (at least 150 minutes per week of moderate intensity or 75 minutes of vigorous activity, or the equivalent combination)[30].
3) At visit 1, participants were asked how often they view TV and how often they sit at work. Responses include never, seldom, sometimes, often, or very often. Based on exploratory analyses, we will either examine TV viewing and sitting at work as an ordinal variable based on the responses above or grouped into fewer categories.

Outcomes

The outcomes include incident first primary breast, colorectal, and prostate cancer. We will further consider lethal breast and prostate cancers. The cancer outcomes were ascertained by linkage to cancer registries in the states in which the ARIC study is conducted (North Carolina, Maryland, Minnesota, Mississippi) and supplemented with review of hospital discharge summaries, participant contact, and medical record review.

Covariates

Potential covariates common to all models (both physical activity and sedentary and across all cancer types) include age, gender, race, field center, education, smoking, comorbidity at baseline (diabetes, cardiovascular disease), alcohol intake, socio-economic status, and health insurance. For breast and prostate cancer we will consider controlling for healthy diet. The healthy diet score will be created based on the 5 components used for the AHA Life's Simple 7 definition (fruits and vegetables, fish, whole grains, sodium, sugar-sweetened beverages)[31]. For colorectal cancer we will control for individual components of diet (see below). For all three types of cancer we would like to control for cancer screening behavior (mammography for breast cancer screening; colonoscopy for colorectal cancer; and prostate-specific antigen for prostate cancer) but these data are not available. Instead we will control for frequency of having an annual physical exam as a proxy for uptake of cancer screening behaviors.

For all three types of cancer we will conduct stratified analyses by an adiposity measure (BMI, waist circumference, or waist-hip ratio).

For the leisure-time physical activity analyses, we will control for sedentary behavior and for the sedentary behavior analyses we will control for physical activity. We will also consider an analysis of the joint effects of physical activity and sedentary behavior with outcomes.

To examine the independent effect of walking, we will control for engagement in types of physical activities other than walking. This will be accomplished by specifying a variable either for 1) engagement in activities other than walking or 2) MET hours contributed by participation in activities other than walking

Breast cancer
For the breast cancer analysis we will restrict to post-menopausal women and consider these additional covariates: postmenopausal hormone therapy use, past oral contraceptive use, age at menarche, age at menopause (age groups for when menopause began (40-44,45-49, 50-54, 55+), and parity. We also will stratify by estrogen receptor positive and negative (ER+, ER-) status for the women in which this data is available.

Colorectal cancer
For the colorectal cancer analysis both men and women will be included and in addition to the previously mentioned variables we will consider adjusting for specific components of diet (energy adjusted intake from red meat, calcium, dietary fiber, folate intake, total energy intake), post-menopausal hormone therapy use (women only), aspirin use, and nonsteroidal anti-inflammatory drug (NSAID) use.

Prostate cancer
For the prostate cancer analysis we will include only men and control for the previously mentioned variables (age, race, field center, smoking, diabetes, BMI, education, SES, health insurance, regularity of annual physical exam).

Statistical analysis
Given that life expectancy has increased but the years gained may not be in good health, summary measures like health expectancies have been developed that combine morbidity and mortality information to reflect the average number of years a person can expect to live in full health free of disease/morbidity [32-35]. Total life expectancy can be partitioned into life expectancy with disease and without disease. For this analysis we will use a continuous-time multi-state survival model that estimates transition probabilities of moving between states which are used to calculate life expectancies in the different states [36]. Specifically, we will use a non-recoverable three state illness-death model where participants start free of disease and can move to one of three states: 1) from free of disease to developing a disease, 2) from free of disease to death from any cause, or 3) from disease to death. A multi-state survival model accounts for death as a competing risk because the model allows for participants to move to a death state at any time during follow-up. We will estimate the model using the R package msm and estimate life expectancies using the R ELECT package[36, 37]. For the time scale of the survival model we will create a time dependent age variable which will be baseline age + time on study. This time dependent variable will be a covariate in the models. The data will be set up so that each participant has a row for each year they are in the study. In this row variables will include an id, a time dependent age variable, a variable that indicates if they are in states 1, 2, 3 or censored, and time fixed covariates. Life expectancy in different states is estimated for a specific age conditional on reaching that age. Our primary analysis is to estimate life expectancy at age 50. But we will conduct sensitivity analyses to see how life expectancy estimates differ for a range of baseline ages.

All analyses will be race-gender specific, where we have sufficient sample size. We plan to conduct race-gender specific analyses because disparities in life expectancy are observed across race-gender subgroups. For example, in 2014, at age 50 white females had the longest life

expectancy (33.4 years) followed by black females (31.5 years), white males (29.9 years), and black males (27.1 years)[38].

All analyses will be conducted separately for each outcome.

Limitations

Limitations include measurement error due to self-report of physical activity and lack of information on specific time spent in sedentary behaviors. Physical activity is assessed with the Baecke questionnaire, which asks questions about leisure time physical activity. This questionnaire has high short-term reliability, shows moderate validity compared with physical activity logs (with strongest agreement for vigorous activities), and is similar in reliability and validity as other physical activity questionnaires [39, 40]. The questions used to ascertain sedentary behaviors from the Baecke questionnaire have not been validated; however, other validation and reliability studies of sedentary questions suggest reliability is high but validity varies for domain-specific sedentary behavior (TV viewing, sitting at work)[41, 42]. Other limitations include using only baseline measures of these behaviors, which may change as participants age.

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)?

MS# 2711 led by Yasuhiko Kubota "Physical Activity and Lifetime Risk of Incident Cardiovascular Disease, and Cancer: the ARIC Study"
Please note we talked with Dr. Platz, Dr. Joshu, and Dr. Folsom about the potential overlap of the MS #2711 proposal/published paper and my current manuscript proposal. They all agreed my outcomes of life expectancy were different from the lifetime risk of CVD and cancer that Dr. Kubota and Dr. Folsom estimated.

MS #2708 led by Susan Lakoski "Physical Activity, Autonomic Function, and Incident Breast Cancer: ARIC"

MS #1797 led by Laura Rasmussen-Torvik "The Association of AHA Ideal Cardiovascular Health with Cancer Incidence: The ARIC study"

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, 2011.07)
___ 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 this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using 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 ___X_ No.

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