ARIC Manuscript Proposal # 1792

PC Reviewed: 5/10/11   Status: **A**   Priority: **2**
SC Reviewed: _____   Status: _____   Priority: ____

1.a. Full Title: The influence of obesity, diabetes, and associated metabolic perturbations on cancer risk.

   b. Abbreviated Title (Length 26 characters): Obesity, diabetes and cancer

2. Writing Group:
     Writing group members: Corinne Joshu, Anna Prizment, Elizabeth Selvin, Jessica Yeh, Anna Kucharska-Newton, Josef Coresh, Fred Brancati, Elizabeth Platz others welcome

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
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3. Timeline: The proposed manuscript is an analysis of existing data. We anticipate it will take 3 years from receipt of the data to submission of a manuscript to the ARIC Publications Committee. The analysis will start in the near term, but some outcome information will not be available until part way through the U01.

4. Rationale:
     Diabetes has been associated with an increased risk of many cancers;[1-7] and a decreased risk of prostate cancer, including in ARIC.[8] A key unanswered question, as

articulated in a joint, consensus statement by the American Cancer Society and the American Diabetes Association, is whether the association between diabetes and cancer is due to shared risk factors, like obesity, or whether diabetes itself, and/or related metabolic perturbations, increase the risk of cancer.[8]

Obesity is a well established risk factor for diabetes, as well as many cancers.[9] Thus, the association between diabetes and cancer may be explained primarily by this shared risk factor. However, the metabolic perturbations that occur throughout the natural history of diabetes (e.g. hyperglycemia, hyperinsulinemia) have also been linked to cancer risk. For example, increased fasting blood glucose was associated with a statistically significant increased risk of cancer death in a large pooled analysis of 820,900 participants, which included ARIC participants.[10] Indeed, it is well documented that cancers require more glucose to generate energy than normal non-proliferative tissue, this is known as the Warburg effect.[11] Thus, hyperglycemia may be permissive for cancer cell growth. Hyperinsulinemia has also been associated with cancer risk.[4] The primary insulin action thought to influence cancer risk is its influence on the IGF axis. Insulin-like growth factor (IGF-I) has a role in cell proliferation; insulin-like growth factor binding proteins (IGFBP-1, IGFBP -2) bind IGF-I and inhibit its action. Insulin reduces the IGFBP-1 level, and thereby increases bioactive IGF-1, which could stimulate cancer cell growth.[12] Finally, in addition to changes in glucose and insulin levels, both obesity and diabetes lead to perturbations in the lipid profile, and changes in markers of inflammation, both of which may be relevant to cancer development and progression.

ARIC is an ideal cohort to pursue questions about these associations. Many other prospective cohorts that have addressed these questions have been limited by blood samples from one time point, and often use a nested-case control design, limiting analyses to the study of one cancer at a time. In ARIC, the relevant anthropometric and metabolic factors are repeatedly measured in all participants. In addition, repeated anthropometric factors are collected by trained staff, and not self-reported as in other studies. Thus, associations can be evaluated simultaneously across multiple common cancers; and the analyses can address metabolic changes over time.

5.   Main Hypothesis/Study Questions:

Specific Aim 1: To disentangle the influence of obesity, diabetes, and the associated metabolic perturbations on cancer risk (overall and by sub-site), we will jointly classify participants by weight status (i.e., normal, overweight, obese), glycemic level (i.e., hypo-, normal, hyper-), and insulin level (i.e., hypo-, normal, hyper-), and evaluate the association with cancer incidence, mortality, and case-fatality.

Specific Aim 2: To evaluate whether the associations identified in Aim 1 are independent of other changes associated with diabetes and obesity, we will further control the analyses for updated measures of the lipid profile (i.e., triglycerides, HDL, LDL) and markers of inflammation (i.e., white blood cell count, fibrinogen, C-reactive protein).

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 of all ARIC participants without cancer at Visit 1.

Independent Variables: BMI (Visits 1-4), waist circumference (Visits 1-4), Fasting glucose (Visits 1-4), HbA1c (Visit 2), Oral Glucose Tolerance Test (Visit 4), Fasting insulin (Visit 1 and Visit 4), triglycerides (Visits 1-4), HDL (Visits 1-4), LDL (Visits 1-4), white blood cell count (Visits 1 and Visit 2), fibrinogen (Visit 1), C-reactive protein (Visit 4)

Dependent Variable: Overall and site-specific cancer incidence, mortality, and case-fatality through 2006 (with expansion to 2011, if the U01 is funded).

Other variables of interest: Age; Race; Sex; Education; Income; Family history of cancer overall and of specific sites (first degree: parent, sibling); Height; Smoking Status; Alcohol consumption; Physical activity; Use of cholesterol-lowering drugs, aspirin, non-aspirin non-steroidal anti-inflammatory drugs; Intake of energy, red and processed meats, fruits, vegetables; Study site; Family history of diabetes;Diabetes diagnosis (Visits 1-4), Use of medications to treat diabetes

For women: History of use of oral contraceptives; Use of post-menopausal hormones (current/former/never use); Parity; Age at first birth; History of hysterectomy (at all visits)

Data Analysis Plan:

To address **Aim 1**: We will use Cox proportional hazards regression (with time since Visit 1 as the time metric) to estimate the multivariate adjusted risk of overall and site-specific cancer incidence, mortality, and case-fatality in relation to participants:

   1. Jointly classified by weight status (i.e., normal, overweight, obese), glycemic level (i.e., hypo-, normal, hyper-), and insulin level (i.e., hypo-, normal, hyper-) at visit 1.

   2. With updated classifications across all 4 visits. For variables unmeasured at all visits (e.g. insulin), we will explore the best modeling strategy (e.g. modeling the most recent visit value; modeling the slope of the change between visits).

To address **Aim 2**: We will further control the analyses for updated measures of the lipid profile (e.g., triglycerides, HDL, LDL) and markers of inflammation (e.g., white blood cell count, fibrinogen).

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

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?

         ____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)?

1766: Xuesong Han, Patrick Bradshaw, Kimberly Truesdale, June Stevens. Weight change and cancer risk: The Atherosclerosis Risk in Communities Study.

1545: Elizabeth Platz, Corinne Joshu, Aaron Folsom, Frederick Brancati, Jessica Yeh, Josef Coresh, Elizabeth Selvin. HbA1c and Cancer Risk in the Atherosclerosis Risk in Communities (ARIC) Study.

1227: Aaron Folsom, James Peacock, Sue Bielinski, James Pankow, Gerardo Heiss. TCF7L2 variants and cancer risk.

568: Kucharska-Newton AM, Rosamond WD, Mink PJ, Alberg AJ, Shahar E, Folsom AR. HDL-cholesterol and incidence of breast cancer in the ARIC cohort study. Ann Epidemiol. 2008 Sep;18(9):671-7.

569: Mink PJ, Shahar E, Rosamond WD, Alberg AJ, Folsom AR. Serum insulin and glucose levels, and breast cancer incidence: the Atherosclerosis Risk in Communities (ARIC) study. Am J Epidemiol 2002;156:349-52.

570: Mertens AJ, Sweeney C, Shahar E, Rosamond WD, Folsom AR. Physical activity and breast cancer incidence in middle-aged women: a prospective cohort study. Breast Cancer Res Treat. 2006 May;97(2):209-14.

957: Ahmed RL, Schmitz KH, Anderson KE, Rosamond WD, Folsom AR. The metabolic syndrome and risk of incident colorectal cancer. Cancer 2006;107:28-36.

1075: Kucharska-Newton AM, Rosamond WD, Schroeder JC, McNeill AM, Coresh J, Folsom AR. HDL-cholesterol and the incidence of lung cancer in the Atherosclerosis Risk in Communities (ARIC) study. Lung Cancer. 2008. PMID: 18342390

1078: Tande AJ, Platz EA, Folsom AR. The Metabolic Syndrome Is Associated with Reduced Risk of Prostate Cancer. Am J Epidemiol. 2006. 164(11):1094-1102.

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
        ___   **A. primarily the result of an ancillary study (list number* #2003.05 (Selvin), #2006.15 (Selvin) and #1995.04 (Folsom))**
        ___   **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.

1.   Larsson SC, Wolk A. Diabetes mellitus and incidence of kidney cancer: a meta-analysis of cohort studies. *Diabetologia* 2011.
2.   Mitri J, Castillo J, Pittas AG. Diabetes and risk of Non-Hodgkin's lymphoma: a meta-analysis of observational studies. *Diabetes Care* 2008;31(12):2391-7.
3.   Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. *Diabetologia* 2007;50(7):1365-74.
4.   Giovannucci E, Michaud D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. *Gastroenterology* 2007;132(6):2208-25.
5.   Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. *Int J Cancer* 2007;121(4):856-62.
6.   El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. *Clin Gastroenterol Hepatol* 2006;4(3):369-80.
7.   Larsson SC, Orsini N, Brismar K, Wolk A. Diabetes mellitus and risk of bladder cancer: a meta-analysis. *Diabetologia* 2006;49(12):2819-23.
8.   Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *Diabetes Care* 2010;33(7):1674-85.
9.   Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008;371(9612):569-78.
10.   Seshasai SR, Kaptoge S, Thompson A, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011;364(9):829-41.
11.   Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* 2009;324(5930):1029-33.

12.   Pollack MN. Insulin, insulin-like growth factors, insulin resistance, and neoplasia. *Am J Clin Nutr* 2007;86(3):s820-2.