ARIC Manuscript Proposal # 1791

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

1.a. Full Title:
The natural history of diabetes in relation to the natural history of cancer.

b. Abbreviated Title (Length 26 characters):

2. Writing Group:
Writing group members: Corinne Joshu, Elizabeth Selvin, Anna Prizment, Jessica Yeh, 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.\(^6\) However, the mechanism(s) underlying these associations is unknown. This question is further complicated by changes in the metabolic profile that occur throughout the natural history of diabetes. For example, an early or pre-diabetic person may be hyperinsulinemic, yet have relatively normal glucose levels.\(^9\) Alternatively, late in the natural history, a diabetic person may have relatively low insulin levels, and but have high circulating glucose levels. In addition, diabetes can also lead to perturbations in the lipid profile, and changes in markers of inflammation. The timing in the natural history of diabetes that is most relevant to the risk of cancer is unknown.

   There is some evidence that the risk of cancer differs by the duration of diabetes. For example, in an analysis of a large prospective cohort study, the risk of colorectal cancer increased with duration of diabetes in men, but not women; and colorectal cancer risk in men also increased by duration of insulin use.\(^10\) Additional evidence suggests that different diabetes therapies may also impact cancer risk differently. For example, some observational studies have found metformin, which reduces levels of circulating glucose and insulin, to be inversely associated with cancer risk; whereas insulin use has been positively associated with cancer risk.\(^11\) Indeed, both the American Cancer Society and the American Diabetes Association, in a joint, consensus statement, highlighted the need for more research to address the whether cancer risk is influenced by duration of diabetes, a “critical and complex issue” that may be complicated by multidrug therapy that is commonly used to treat diabetes.\(^11\)

   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:**

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).

**Specific Aim 1:** To identify the timing in the natural history of diabetes that is most relevant to the risk of cancer overall and by sub-site, we will use updated measures of fasting glucose, insulin, self-reported diabetes diagnosis, and use of diabetic medications, to classify participants by their point in the natural history of diabetes (i.e. non-diabetic, pre-diabetic, un-diagnosed diabetic, early diagnosed diabetic, and late diagnosed diabetic) and evaluate the association with risk of cancer incidence, mortality, and case-fatality.
Specific Aim 2: To evaluate whether the associations identified in Aim 1 are modified by sex and/or diabetes treatment type (e.g. metformin, thiazolidinediones, insulin secretagogues, insulin and insulin analogs) and duration of their use.

Specific Aim 3: To evaluate whether the associations identified in Aim 1 are independent of other changes associated with diabetes and obesity (overall and central), we will further control the analyses for updated trajectories of metabolic factors (during Visits 1-4), including obesity (i.e. body mass index, waist circumference), 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: Diabetes diagnosis (Visits 1-4), BMI (Visits 1-4), Waist circumference (Visit 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; 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. Stage in the natural history of diabetes (i.e. non-diabetic, pre-diabetic, undiagnosed diabetic, early diagnosed diabetic, and late diagnosed diabetic) at visit 1. Because participants may receive a diagnosis at different points in the natural history of diabetes, we will define “early” and “late” diagnosed diabetics using both the metabolic profile, as well as time since diagnosis (e.g. <6 years, ≥6 years).
2. Updated classifications of the stage in the natural history of diabetes across all of the 4 ARIC visits. After visit 4 participants will remain at the last known stage of diabetes. Sensitivity analyses will censor follow-up 3 years after visit 4 as well as examine update diabetes stage using the CARMRI data. 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 stratify the analyses by sex. We will explore the best modeling strategy for diabetes medication use (e.g. modeling the duration of each drug/class of drug used; stratifying diabetics using on class of drugs used).

To address **Aim 3**: We will further control the analyses for updated measures of obesity (e.g., BMI, waist circumference), the lipid profile (e.g., triglycerides, HDL, LDL) and markers of inflammation (e.g., white blood cell count, fibrinogen).

Limitations: We recognize that age of onset of diabetes prior to visit 1 is of limited precision and accuracy. Only a limited number of ARIC participants will have longstanding diabetes at visit 1 limited power for this subgroup in Aim 1. Similarly staging diabetes using ARIC data has limited precision. However, overall the ARIC data is more detailed than nearly all cancer studies and will advance the literature despite its limitations.

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

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

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.cscce.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.


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.