ARIC Manuscript Proposal # 1545

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1.a. Full Title: HbA1c and Cancer Risk in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): HbA1c and Cancer

2. Writing Group:

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

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3. Timeline: The proposed manuscript is an analysis of existing data. We anticipate it will take 12 months from receipt of the data to submission of a manuscript to the ARIC Publications Committee.

4. Rationale:

We hypothesize that chronic hyperglycemia increases the risk of cancer and cancer death, in particular cancers for which obesity (1) and diabetes (2) are risk factors. Contemporary

epidemiologic evidence supports this hypothesis: Jee et al. (3) observed that cancer incidence was 22% higher in men and 15% higher in women who had elevated fasting glucose (≥140 mg/dL, an older definition), compared with those whose level was <90 mg/dL. Support also comes from ARIC: Ahmed et al. observed that participants with a fasting glucose of ≥100 mg/dL or who had diabetes (compared with non-diabetic participants with normal fasting glucose) had a 40% higher risk of colorectal cancer (4) and a possible 40% higher risk of breast cancer (5).

Unlike in ARIC (4, 5) and cohorts constructed from clinical health screenings (3), many of the major cancer cohorts with archived blood specimens collected untimed (non-fasting) samples precluding the measurement of fasting glucose. As an alternative, a small number of studies have evaluated glycosylated hemoglobin (HbA1c) with overall cancer risk or risk of cancers of specific sites. HbA1c, also known as glycated hemoglobin, is a time integrated measure of glycemia over the half-life of the red blood cell (~past two months) and is not affected by timing or quality of the last meal. HbA1c, long used as a tool to monitor glycemic control in diabetics, has been recently recommended as a diagnostic test for diabetes (6). Only four studies have investigated HbA1c and cancer overall: a cohort of New Zealanders (70% Maori) who underwent hepatitis B screening (7), a Japanese Atomic bomb survivors cohort (8), women who participated in the Women's Health Study trial of vitamin E and supplements (9), and participants in the National Health and Nutrition Examination Survey (10). In those studies, higher HbA1c was associated with a higher cancer risk (7) and high risk of cancer death (8-10). These studies (7-10) are not consistent in their findings on the association between HbA1c and cancer incidence or mortality separately in those with and without a history of diabetes; this question requires additional study.

A small number of studies have investigated HbA1c and risk of specific cancer sites. Dr. Platz's group previously measured HbA1c levels in case-control studies nested in the Nurses' Health Study (11) and CLUE II (12) and found that participants with higher percentage of HbA1c appeared to have a higher risk of colorectal cancer. Findings were similar in men in a Swedish cohort (13) and women in a large prospective cohort study in Europe (14). Other groups have reported positive associations of HbA1c with stomach (15), advanced stage breast cancer (16), and respiratory and endometrial cancers (7), and possibly with death from colorectal, lung, pancreas, breast, and leukemia (9).

Not all studies are in agreement, however. HbA1c was not positively associated with breast (17) or colorectal (18) cancer risk in the Women's Health Study. With longer time between when the blood sample used to measure HbA1c was obtained and diagnosis of colorectal cancer, the association previously observed in the Nurses' Health Study was no longer present (19). In addition, in diabetics, HbA1c does not appear to be associated with cancer risk (20, 21).

In contrast to other epithelial cancers, obesity (22) and diabetes (23) are inversely associated with risk of prostate cancer in the PSA era (the majority of cases are diagnosed at a localized stage), although obesity is positively associated with prostate cancer mortality and case fatality (22). Previously in ARIC, Tande with Drs. Folsom and Platz (24), as hypothesized observed inverse associations of diabetes, defined as a doctor's diagnosis or a fasting glucose ≥126 mg/dL, (RR=0.73, 95% CI 0.51-1.05) and the metabolic syndrome (RR=0.71, 95% CI 0.54-0.94) with prostate cancer risk. Consistent with the diabetes finding, there was a suggestion that men with a fasting glucose ≥110 mg/dL (vs lower) had a lower risk of prostate cancer (RR=0.85, 95% CI 0.66-1.08).

The chronic hyperglycemia and cancer hypothesis is compelling. Thus, we will address this contemporary hypothesis of great importance given the rising prevalence of diabetes around the

world (25). We will focus on cancer overall excluding prostate cancer (given the hypothesis that HbA1c is inversely associated with risk of this cancer), and on the most common cancers diagnosed in Americans, including lung, prostate, breast, and colorectal cancers (26). Although the number of cases will likely be small, we will also attempt to assess associations for less common cancers for which obesity and/or diabetes are consistent risk factors, including pancreatic, endometrial, and kidney cancers (1). We will use HbA1c as the primary measure of hyperglycemia, rather than fasting glucose, because HbA1c better predicts the adverse effects chronic hyperglycemia such as retinopathy (6), better captures glucose levels over time (6), and from Dr. Selvin and colleagues' work in ARIC, HbA1c adds prediction beyond fasting glucose of the future development of diabetes (27). However, we will also evaluate the association of fasting glucose at baseline for this analysis (visit 2) or updated fasting glucose across the visits with cancer adjusted for HbA1c to assess whether fasting glucose has residual prediction.

This study will be conducted efficiently; HbA1c has already been measured for nondiabetic and diabetic participants in ARIC by Dr. Selvin et al. Unlike the vast majority of the published studies, we will address whether chronic hyperglycemia in the absence of a history of diabetes is a cancer risk factor separate from whether poor glycemic control in those with a history of diabetes is a cancer risk factor. We will classify participants as being diabetic based on a self-reported physician's diagnosis or glucose-lowering medication use. Finally, we will take into account measures of extent and distribution of adiposity and concentrations of circulating metabolic (e.g., fasting insulin and lipids) and inflammatory (e.g., white blood cell count and fibrinogen) sequelae of adiposity and diabetes, which are available in ARIC, to determine the independent association of chronic hyperglycemia with cancer risk and cancer mortality.

5. Main Hypothesis/Study Questions:

Our overall hypothesis is that chronic hyperglycemia and its sequelae, including subsequent development of diabetes increase the risk of cancer overall except prostate cancer, for which risk is decreased.

Question 1: Is HbA1c associated with an increased risk of cancer overall (excluding prostate cancer) independent of measures of obesity (body mass index and waist circumference) and other risk factors for cancer (e.g., age, race, cigarette smoking history, alcohol consumption, family history of cancer)?

1a: In people without a history of diabetes
1b: In people with a history of diabetes

Question 2: Is HbA1c associated with risk of the most common cancers – lung, prostate, breast, colorectum, cancers for which obesity and/or diabetes are risk factors – pancreas, endometrium, kidney, and any other cancer for which the sample size is adequate (e.g., at least 100 cases of specific sites independent of measures of obesity and other risk factors for cancer?

2a: In people without a history of diabetes
2b: In people with a history of diabetes

Ancillary to Questions 1 and 2: Is fasting glucose at baseline for this analysis (visit 2) or updated fasting glucose across the visits associated with risk of cancer overall (excluding prostate) or with the most common cancers after adjusting for HbA1c?

Question 3: Are the associations observed for Questions 1 and 2 independent other sequelae of obesity and diabetes

3a. Independent of fasting insulin, total, HDL and LDL cholesterol, triglycerides, white blood cell count, and fibrinogen

3b. Independent of subsequent diagnosis of diabetes

[Purpose: To determine whether chronic hyperglycemia *per se*, correlated sequelae of obesity and diabetes, or diabetes itself explanatory.]

Question 4: Where the sample size is adequate, do the associations observed for Question 1 and possibly 2 and 3 differ between:

4a: Men and women

4b: African-Americans and whites [hypothesize no difference]

4c: Younger and older individuals

4d: Normal weight and overweight or obese individuals

4e: Individuals with low, normal, and high fasting insulin (at visit 1) [to capture different points in the natural history of their insulin resistance/pre-diabetes]

Question 5: Where the sample size is adequate, is HbA1c associated with an increased risk of cancer death (including and excluding prostate cancer death) independent of measures of obesity and other risk factors for cancer death?

5a: In people without a history of diabetes

5b: In people with a history diabetes

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 in ARIC with Visit 2, when HbA1c was measured, as baseline

Inclusion/Exclusion into the analytic cohort:

- Exclude individuals diagnosed with cancer prior to Visit 2
- Exclude individuals for whom an HbA1c measurement is not available

Exposures:

- HbA1c from Visit 2

- Diabetes (physician diagnosis or diabetes medication use, at Visits 1 and 2 for baseline and at subsequent visits for Question 3.)

- Obesity- and diabetes-related correlates of HbA1c (Visit 2, unless otherwise noted)
  - ✓ Body mass index (all visits starting with Visit 2)
  - ✓ Waist circumference (all visits starting with Visit 2)
  - ✓ Fasting glucose (all visits starting with Visit 2)

- ✓ Fasting insulin (Visit 1 only, case-control subsample at Visit 2)
- ✓ Total, HDL, and LDL cholesterol, triglycerides
- ✓ Fibrinogen (Visit 1 only)
- ✓ White blood cell count

Outcomes:

- Cancer incidence
- Cancer mortality
- Cancer site
  - ✓ Lung and bronchus too)
  - ✓ Prostate
  - ✓ Breast (female)
  - ✓ Colon and rectum
  - ✓ Pancreas
  - ✓ Uterine
  - ✓ Kidney
  - ✓ Any other site with at least 100 cases
- Cancer groupings (obesity associated-post-menopausal breast, colon, pancreas, endometrial, kidney, gall bladder, liver; smoking associated-lung, head/neck, pancreas, kidney; female: breast, endometrial, ovary, cervical)

Other variables of interest:

At Visit 2, known and suspected risk factors for cancer incidence or mortality overall or specific common cancers (follow-up is relatively short, so we will not attempt to update any of the naturally time-dependent covariates in the models):

- Age
- Race
- Sex
- Education
- Income
- Family history of cancer overall and of specific sites (first degree: parent, sibling), Visit 3 phone interview
- Height
- Cigarette smoking history (pack-years and current/former/never smoker)
- Alcohol consumption (current intake of ethanol in grams and current/former/never drinker)
- Physical activity (frequency and intensity)
- 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

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)

Additional variables needed for censoring;

- Date of loss-to-follow up
- Death of death

Statistical Analyses:

- Table 1: We will calculate age/sex/race-standardized Visit 2 characteristics of the participants using clinically relevant cutpoints separately in participants without a history of diabetes (normal: <5.0, 5.0-<5.5, 5.5-<6.0; at risk for diabetes: 6.0-<6.5%; and undiagnosed diabetes: ≥6.5%) and in participants with a history of diabetes (<7.0%, 7.0-<8.0%, and ≥8.0%).
  - ✓ Median HbA1c
  - ✓ Mean age, female (%), African-American (%)
  - ✓ Mean BMI; normal (% BMI <25 kg/m^2), overweight (% BMI 25-<30 kg/m^2), obese (% BMI ≥30 kg/m^2)
  - ✓ Mean waist circumference; normal (% waist: males <40" [102 cm], females: <35" [88 cm]), abnormal (males: ≥40", females ≥35")
  - ✓ Mean height
  - ✓ Subsequent diagnosis of diabetes (%) [KM estimate of the cumulative incidence]
  - ✓ Family history of cancer (%)
  - ✓ Cigarette smoking history (% current, % former), mean pack-years in current and former cigarette smokers
  - ✓ Alcohol consumption (% current, % former), mean intake of ethanol in grams/day in current and /former drinkers
  - ✓ Mean MET-hours/day of physical activity
  - ✓ Use of a cholesterol-lowering drug (%), regular use of prescription and over-the counter aspirin (%), and regular use of prescription and over-the counter non-aspirin non-steroidal anti-inflammatory drugs (%)
  - ✓ Mean intake of energy (kcal/day), red and processed meats (servings/day), fruits (servings/day), vegetables (servings/day)
  - ✓ For women: history of use of oral contraceptives (% ever), use of post-menopausal hormones (% current, % former); mean parity, mean age at first birth
  - ✓ Mean fasting glucose, insulin, total, HDL and LDL cholesterol, triglycerides, white blood cell count and fibrinogen

Table 1: Age-, sex-, and race-standardized characteristics of participants without and with a history of diabetes by HbA1c category, ARIC (1990-92)

	HbA1c%							
	No History of Diabetes					History of Diabetes		
	<5.0	5.0-<5.5	5.5-<6.0	6.0-<6.5	≥6.5*	<7.0	7.0-<8.0	≥8.0
Median HbA1c%								
Number of participants								
Mean age (years)								
Female (%)								
African-American (%)								
College education (%)								
Mean income ($/year)								
Mean BMI (kg/m^2)								
Overweight (%)								
Obese (%)								
Mean waist circumference (in)								
Abnormal (%)								
Mean height (in)								
Subsequent diagnosis of diabetes (%)								
Family history of cancer (%)								
Family history of diabetes (%)								
Cigarette smoking history								
Current (%)								
Mean (pack-years)								
Former (%)								
Mean (pack-years)								
Alcohol consumption								
Current (%)								
Mean (g/day)								
Former (%)								
Pack-years								
Mean physical activity (MET-hr/week)								
Cholesterol-lowering drug use (%)								
Regular aspirin use (%)								
Regular non-aspirin NSAIDs use (%)								
Mean daily intake								
Energy (kcal)								
Red and processed meat (servings)								
Fruit (servings)								
Vegetables (servings)								
Women								
Ever oral contraceptive use								
Post-menopausal hormone use								
Current (%)								
Former (%)								
Mean parity (number)								
Mean age at first birth (years)								
Mean fasting insulin (units)								
Mean fasting total cholesterol								
Mean fasting HDL cholesterol (mg/dL)								

Mean fasting LDL cholesterol (mg/dL)
Mean fasting triglycerides (units)
Mean white blood cell count
Mean fibrinogen (units)

*Undiagnosed diabetes
**Subset of participants

- Table 2: In people without a history of diabetes, we will use Cox proportional hazard regression (with time since Visit 2 as the time metric) to calculate the age (indicator variables for fine intervals or spline terms to allow for nonlinearity) / sex (F vs M) / race (African-American vs white)- and multivariable-(see below) adjusted relative risks and 95% confidence intervals of incident cancer overall (excluding prostate cancer), by site (report on colon separate from rectum in the text), and by cancer groupings (report in text only) in relation to HbA1c expressed based on:
  - ✓ Clinically relevant cutpoints in participants without a history of diabetes (normal: < 5.0, 5.0-<5.5, and 5.5-<6.0; at risk for diabetes: 6.0-<6.5, undiagnosed diabetes ≥6.5%) and in participants with diabetes (<7.0, 7.0-<8.0, ≥8.0%) [calculate p value from the test for trend across the categories using either a continuous variable or the medians of the quartiles]
  - ✓ Distributional cutpoints (e.g., quartiles in nondiabetics) [calculate p value from the test for trend across the quartiles using either a continuous variable or the medians of the quartiles]
  - ✓ At or above (≥6.0%) the normal range versus below (<6.0%)
  - ✓ Spline function of HbA1c

  Censor individuals at the date of their first invasive cancer diagnosis (except diagnosis of nonmelanoma skin cancer – they are still at risk for an invasive cancer endpoint), date of death, date of hysterectomy (for endometrial cancer only), loss-to-follow-up, or end of follow-up, whichever is the earliest.

Table 2: Association between HbA1c% and cancer risk overall and by site in participants without a history of diabetes, ARIC

	HbA1c%					p-trend	≥6.0 vs <6.0%
	<5.0	5.0-<5.5	5.5-<6.0	6.0-<6.5	≥6.5*		
All sites (except prostate)							
Cases / person-years							
Age/sex/race adjusted							
Multivariable adjusted*							
Multivariable adjusted**							
Multivariable adjusted***							
Lung							
Cases / person-years							
Age/sex/race adjusted							
Multivariable adjusted*							
Multivariable adjusted**							

Multivariable adjusted***
Prostate
Cases / person-years
Age/race adjusted
Multivariable adjusted*
Multivariable adjusted**
Multivariable adjusted***
Breast (female only)
Cases / person-years
Age/race adjusted
Multivariable adjusted§
Multivariable adjusted§§
Multivariable adjusted§§§
Colorectal
Cases / person-years
Age/sex/race adjusted
Multivariable adjusted*
Multivariable adjusted**
Multivariable adjusted***
Pancreas
Cases / person-years
Age/sex/race adjusted
Multivariable adjusted*
Multivariable adjusted**
Multivariable adjusted***
Endometrial
Cases / person-years
Age/race adjusted
Multivariable adjusted§
Multivariable adjusted§§
Multivariable adjusted§§§
Kidney
Cases / person-years
Age/sex/race adjusted
Multivariable adjusted*
Multivariable adjusted**
Multivariable adjusted***
Other common (100+ cases)
Cases / person-years
Age/sex/race adjusted
Multivariable adjusted*
Multivariable adjusted**
Multivariable adjusted***

*Adjusted for sex, education, income, BMI (updated), waist circumference (updated), cigarette smoking history, alcohol consumption, family history of cancer, and family history of diabetes.
**Same as * and further adjusted for fasting insulin, HDL and LDL cholesterol, triglycerides, white blood cell count, and fibrinogen.

***Same as * and further adjusted for diabetes diagnosis after Visit 2 (updated)
§ Adjusted for sex, education, income, BMI (updated), waist circumference (updated), cigarette smoking history, alcohol consumption, family history of cancer, family history of diabetes, ever use of oral contraceptives, use of post-menopausal hormones, parity, and age at first birth.
§§ Same as § and further adjusted for fasting insulin, HDL and LDL cholesterol, triglycerides, white blood cell count, and fibrinogen.
§§§ Same as § and further adjusted for diabetes diagnosis after Visit 2 (updated).
[will adjust footnotes depending on which factors were ultimately included in the models]

We will include in all multivariable models the following covariates beyond age and race irrespective of whether they are confounders in ARIC:

- ✓ BMI (updated, indicator variables for 25-<30 and ≥30 vs <25 kg/m^2, also considering fitting a spline function to reduce likelihood of residual confounding by this correlate of both HbA1c and cancer)
- ✓ Waist circumference (updated, males: ≥40 vs <40", females ≥35 vs <35", also consider fitting a spline function to reduce the likelihood of residual confounding by this correlated of both HbA1c and cancer)
- ✓ Cigarette smoking history (continuous pack-years for current smokers, continuous pack-years for former smokers vs never smokers [for colorectal cancer we may need to introduce a lag of 20 years or switch to was a current smoker 20 years ago, was a former smoker 20 years ago, was a never smoker 20 years ago])
- ✓ Alcohol consumption (need to see the distribution in this cohort we might be able to use (vs never/rarely, <1 drink/day, 1 drink/day, ≥2 drinks per day)
- ✓ Family history of cancer
- ✓ Family history of diabetes

We will assess whether the following factors are confounders by additionally including them one at a time into the basic multivariable model and assessing whether a shift of ~10% or more in the RR for cancer overall or specific cancer sites occurs. If yes, then add to the multivariable models.

- ✓ Height (not as critical to get the shape right, a continuous term may suffice)
- ✓ Physical activity (indicator variables for quartiles of MET-hours/day)
- ✓ Cholesterol lowering drug use (yes vs no)
- ✓ Regular use of aspirin (yes vs no)
- ✓ Regular use of non-aspirin NSAIDs (yes vs no)
- ✓ Energy intake (indicator variables for quartiles)
- ✓ Intake of red and processed meats (indicator variables for quartiles)
- ✓ Fruit intake (indicator variables for quartiles)
- ✓ Vegetable intake (exclude French fries) (indicator variables for quartiles)

All multivariable models for women's cancers (breast, endometrial, of the grouping of women's cancers) will include the following covariates beyond the basic multivariable model irrespective of whether they are confounders in ARIC: history of use of oral contraceptives (% ever), use of post-menopausal hormones (% current, % former); parity (indicators for 1, 2, ≥3 vs 0), age at first birth (check distribution).

In the models for men and women combined, we will adjust for sex. If we decide that it is critical to take into account women-specific "exposures" in the analysis of total cancer and cancers that both sexes experience, then we will use joint effects terms (drop the term for sex), such as F*hormone replacement therapy + F*no hormone replacement therapy versus M. The alternative is to only report separately by sex. We will make these decisions based on total sample size, sex specific sample size, and presence of effect modification by sex.

To address Question 3: In a second multivariable model we will additionally adjust (check optimal expression for each) for

- ✓ Fasting insulin
- ✓ Total cholesterol
- ✓ HDL cholesterol
- ✓ LDL cholesterol
- ✓ Triglycerides
- ✓ White blood cell count
- ✓ Fibrinogen

To address Question 3: In a third multivariable model we will additionally adjusted for updated diagnosis of diabetes subsequent to Visit 2.

To assess whether fasting glucose has residual prediction beyond HbA1c, we will also evaluate the association of fasting glucose at baseline for this analysis (visit 2) or updated fasting glucose across the visits with cancer adjusted for HbA1c.

- Table 3: In participants with a history of diabetes, we will use Cox proportional hazard regression (with time since Visit 2 as the time metric) to calculate the age (indicator variables for fine intervals or spline terms to allow for nonlinearity) / race (African-American vs white)- and multivariable-(see below) adjusted relative risks and 95% confidence intervals of incident cancer overall (excluding prostate cancer), by site, and by cancer groupings (report in text only) in relation to HbA1c expressed based on

  - ✓ American Diabetes Associations cutpoints (<7.0, 7.0-<8.0 ≥8.0%)
  - ✓ A binary comparison of an extreme cutpoint (cutpoint could be based on percentiles or selected after reviewing a spline function of HbA1c or arbitrarily ≥7.0 vs <7.0)
  - ✓ Spline function of HbA1c

Table 3: Association between HbA1c% and cancer risk overall and by site in participants with a history of diabetes, ARIC

	HbA1c%			p-trend	≥7.0 vs <7.0
	<7.0	7.0-<8.0	≥8.0		
All sites except prostate					
Cases / person-years					
Age/sex/race adjusted					
Multivariable adjusted*					

Multivariable adjusted**
Lung
Cases / person-years
Age/sex/race adjusted
Multivariable adjusted*
Multivariable adjusted**
Prostate
Cases / person-years
Age/ race adjusted
Multivariable adjusted
Multivariable adjusted
Breast (female only)
Cases / person-years
Age/race adjusted
Multivariable adjusted§
Multivariable adjusted§§
Colorectal
Cases / person-years
Age/sex/race adjusted
Multivariable adjusted*
Multivariable adjusted**
Pancreas
Cases / person-years
Age/sex/race adjusted
Multivariable adjusted*
Multivariable adjusted**
Endometrial
Cases / person-years
Age/race adjusted
Multivariable adjusted§
Multivariable adjusted§§
Kidney
Cases / person-years
Age/sex/race adjusted
Multivariable adjusted*
Multivariable adjusted**
Other common
Cases / person-years
Age/sex/race adjusted
Multivariable adjusted*
Multivariable adjusted**

*Adjusted for sex, education, income, BMI (updated), waist circumference (updated), cigarette smoking history, alcohol consumption, family history of cancer, family history of diabetes, class of diabetes medication.
**Same as * and further adjusted for fasting insulin, HDL and LDL cholesterol, triglycerides, white blood cell count, fibrinogen.
§ Adjusted for sex, education, income, BMI (updated), waist circumference (updated), cigarette smoking

history, alcohol consumption, family history of cancer, family history of diabetes, class of diabetes medication, ever use of oral contraceptives, use of post-menopausal hormones, parity, and age at first birth.
§§ Same as § and further adjusted for fasting insulin, HDL and LDL cholesterol, triglycerides, white blood cell count, and fibrinogen.
[will adjust footnotes depending on which factors were ultimately included in the models]

Use the same approach as described for Table 2 to identify which of the factors should be included in the multivariable models.

- Table 4: We will repeat the analyses described for Tables 2 and 3 (most likely use the binary contrast of high to low HbA1c in participants without and with a history of diabetes (sample size may be too small, report in text only) stratifying by
  - ✓ Men and women (Table 4a)
  - ✓ African-Americans and whites (report in text only)
  - ✓ Younger and older individuals (median of the distribution at Visit 2) (report in text only)
  - ✓ Normal weight (<25 kg/m^2) and overweight or obese individuals (≥25 kg/m^2) [will try alternative cutpoints, including the median and ≥25 kg/m^2) (Table 4b)
  - ✓ Normal waist circumference (males: <40" [102 cm], females: <35" [88 cm]) and abnormal (males: ≥40", females ≥35") [will try alternative cutpoints, including the median and >75th percentile) (Table 4b)
  - ✓ Normal defined based on both BMI and waist circumference, intermediate, and overweight/obese [depends on the joint distributions in ARIC at Visit 2] (Table 4b)
  - ✓ Individuals with low, normal, and high fasting insulin (to capture different points in the natural history of their insulin resistance/pre-diabetes) [based on the distribution in ARIC at Visit 1] (Table 4b)

Table 4a: Association between HbA1c% and cancer risk overall and by site in participants without a history diabetes separately in men and women, ARIC

	HbA1c%					p-trend	≥6.0 vs <6.0%	p-interaction
	<5.0	5.0-<5.5	5.5-<6.0	6.0-<6.5	≥6.5			
All sites								
Men (except prostate)								
Cases / person-years								
Age/race adjusted								
Multivariable adjusted*								
Multivariable adjusted**								
Multivariable adjusted***								
Women								
Cases / person-years								
Age/race adjusted								
Multivariable adjusted§								
Multivariable adjusted§§								
Multivariable adjusted§§§								
Lung								

Men (except prostate)								
Cases / person-years								
Age/race adjusted								
Multivariable adjusted*								
Multivariable adjusted**								
Multivariable adjusted***								
Women								
Cases / person-years								
Age/race adjusted								
Multivariable adjusted§								
Multivariable adjusted§§								
Multivariable adjusted§§								
Colorectal								
Men (except prostate)								
Cases / person-years								
Age/race adjusted								
Multivariable adjusted*								
Multivariable adjusted**								
Multivariable adjusted***								
Women								
Cases / person-years								
Age/race adjusted								
Multivariable adjusted§								
Multivariable adjusted§§								
Multivariable adjusted§§§								

*Adjusted for education, income, BMI (updated), waist circumference (updated), cigarette smoking history, alcohol consumption, family history of cancer, and family history of diabetes.
**Same as * and further adjusted for fasting insulin, HDL and LDL cholesterol, triglycerides, white blood cell count, and fibrinogen.
***Same as * and further adjusted for diabetes diagnosis after Visit 2 (updated)
§ Adjusted for education, income, BMI (updated), waist circumference (updated), cigarette smoking history, alcohol consumption, family history of cancer, family history of diabetes, ever use of oral contraceptives, use of post-menopausal hormones, parity, and age at first birth.
§§ Same as § and further adjusted for fasting insulin, HDL and LDL cholesterol, triglycerides, white blood cell count, and fibrinogen.
§§§ Same as § and further adjusted for diabetes diagnosis after Visit 2 (updated).
[will adjust footnotes depending on which factors were ultimately included in the models]

Table 4b: Association between HbA1c% and cancer risk overall (excluding prostate) in participants without a history of diabetes by extent and distribution of adiposity, ARIC

	HbA1c%					p-trend	≥6.0 vs <6.0%	p-interaction
	<5.0	5.0-<5.5	5.5-<6.0	6.0-<6.5	≥6.5			
Body mass index								
Normal								
Cases / person-years								

Age/sex/race adjusted
Multivariable adjusted*
Multivariable adjusted**
Multivariable adjusted***
Overweight/Obese
Cases / person-years
Age/sex/race adjusted
Multivariable adjusted§
Multivariable adjusted§§
Multivariable adjusted§§§

Waist circumference
Normal range
Cases / person-years
Age/sex/race adjusted
Multivariable adjusted*
Multivariable adjusted**
Multivariable adjusted***
"Abnormal"
Cases / person-years
Age/sex/race adjusted
Multivariable adjusted§
Multivariable adjusted§§
Multivariable adjusted§§§

Joint categories of BMI and waist circumference
Normal
Cases / person-years
Age/sex/race adjusted
Multivariable adjusted*
Multivariable adjusted**
Multivariable adjusted***
Intermediate
Cases / person-years
Age/sex/race adjusted
Multivariable adjusted§
Multivariable adjusted§§
Multivariable adjusted§§§
Overweight/Obese
Cases / person-years
Age/sex/race adjusted
Multivariable adjusted§
Multivariable adjusted§§
Multivariable adjusted§§§

*Adjusted for sex, education, income, residual variation in BMI (updated), residual variation in waist circumference (updated), cigarette smoking history, alcohol consumption, family history of cancer, and

family history of diabetes.
**Same as * and further adjusted for fasting insulin, HDL and LDL cholesterol, triglycerides, white blood cell count, and fibrinogen.
***Same as * and further adjusted for diabetes diagnosis after Visit 2 (updated)
§ Adjusted for sex, education, income, residual variation in BMI (updated), residual variation in waist circumference (updated), cigarette smoking history, alcohol consumption, family history of cancer, family history of diabetes, ever use of oral contraceptives, use of post-menopausal hormones, parity, and age at first birth.
§§ Same as § and further adjusted for fasting insulin, HDL and LDL cholesterol, triglycerides, white blood cell count, and fibrinogen.
§§§ Same as § and further adjusted for diabetes diagnosis after Visit 2 (updated).
[will adjust footnotes depending on which factors were ultimately included in the models]

We will test for stratum-specific differences in the associations by two models, the first being a multivariable model containing HbA1c (binary) and the possible effect modifier (binary or 3 categories), the second being the same as the first model with an additional term that is the product of HbA1c (binary) and the possible effect modifiers (binary or 3 categories). We will use the likelihood ratio test to test for statistical interaction. We recognize that a very large number of tests will be done in the evaluation of effect modification. Our strategy will be to look for inferential differences in the stratum specific estimates and be conservative in reporting on them.

- Table 5: Repeat analyses described for Tables 2, 3, 4 (sex only) using the same analytic cohort, but changing the endpoint to death from cancer (probably too few to run cancer sites or groups). Censor at date of cancer death, date of death from other causes, date of hysterectomy (for endometrial cancer only), loss-to-follow-up, or end of follow-up, whichever is the earliest.

Table 5: Association between HbA1c% and cancer mortality in participants without and with a history of diabetes, ARIC

	HbA1c%					p-trend	Extreme contrast
	<5.0	5.0-<5.5	5.5-<6.0	6.0-<6.5	≥6.5		≥6.0 vs <6.0%
Individuals without diabetes							
Men and women							
Cases / person-years							
Age/sex/race adjusted							
Multivariable adjusted*							
Multivariable adjusted**							
Men (excluding prostate)							
Cases / person-years							
Age/sex/race adjusted							
Multivariable adjusted*							
Multivariable adjusted**							
Women							
Cases / person-years							

Age/sex/race adjusted				
Multivariable adjusted*				
Multivariable adjusted**				
Individuals with diabetes	<7.0	7.0-<8.0	≥8.0	≥7.0 vs <7.0
Men and women				
Cases / person-years				
Age/sex/race adjusted				
Multivariable adjusted*				
Multivariable adjusted**				
Men (excluding prostate)				
Cases / person-years				
Age/sex/race adjusted				
Multivariable adjusted*				
Multivariable adjusted**				
Women				
Cases / person-years				
Age/sex/race adjusted				
Multivariable adjusted*				
Multivariable adjusted**				

*Adjusted for sex, education, income, BMI, waist circumference, cigarette smoking history, alcohol consumption, family history of cancer, and family history of diabetes.
**Same as * and further adjusted for fasting insulin, HDL and LDL cholesterol, triglycerides, white blood cell count, and fibrinogen.
***Same as * and further adjusted for diabetes diagnosis after Visit 2 (updated)
[will adjust footnotes depending on which factors were ultimately included in the models]

Project Specific Limitations:

- Small number of cases for cancer site-specific analysis and analyses of effect modification.
- May not have information on stage at diagnosis and other pathologic characteristics
- Have only one measure of HbA1c; the etiologically relevant time for these cancers is unknown
- In the analyses among diabetics only: We have not considered competing causes of death (other than to censor at time of death from causes other than cancer)
- May be difficult to determine whether an association between HbA1c and cancer incidence, mortality, or case fatality is due to hyperglycemia per se or some other metabolic, growth factor, hormonal, of inflammatory factor/pathway that is perturbed in obese and diabetic people.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes X No
(diabetes-related work)

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? ____ 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.) **Not applicable**

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
Not applicable

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
Not applicable

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)?

From: http://www.cscc.unc.edu/aric/published_public.php

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 Mar 12; [Epub ahead of print] PMID: 18342390

1078: Tande AJ, Platz EA, Folsom AR. The Metabolic Syndrome Is Associated with Reduced Risk of Prostate Cancer. Am J Epidemiol. 2006 Sep 12;

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* __#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.
EAP

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