Research Article

Cancer Prevention Research

Hyperglycemia, Classified with Multiple Biomarkers Simultaneously in Men without Diabetes, and Risk of Fatal Prostate Cancer

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Abstract

The association between hyperglycemia and prostate cancer risk is inconsistent, and its association with prostate cancer mortality is understudied. Thus, we investigated the association between hyperglycemia and prostate cancer risk and mortality using multiple biomarkers simultaneously to classify hyper- and normoglycemia. We conducted a prospective analysis of 5,162 cancer-free men attending visit 2 (1990–1992) of the Atherosclerosis Risk in Communities (ARIC) study followed for total ($N = 671$) and lethal ($N = 69$) prostate cancer incidence and prostate cancer mortality ($N = 64$) through 2012. Men without diagnosed diabetes were classified as normo- or hyperglycemic using joint categories of fasting glucose, glycated hemoglobin, and glycated albumin (or fructosamine) defined by clinical or research cutpoints. We evaluated the multivariable-adjusted association of hyperglycemia with prostate cancer incidence and mortality using Cox proportional hazards regression; men with diagnosed diabetes were included as a separate exposure category. Among 4,753 men without diagnosed diabetes, 61.5% were classified as having hyperglycemia (high on $\geq$1 biomarker). HbA1c and glycated albumin together classified 61.9% of 1,736 men with normal fasting glucose as normoglycemic. Compared with men who were normal on all three biomarkers, men who were high on $\geq$1 biomarker had an increased risk of lethal [HR, 2.50; 95% confidence interval (CI), 1.12–5.58] and fatal (HR, 3.20; 95% CI, 1.26–8.48) disease, but not total prostate cancer incidence (HR, 0.98; 95% CI, 0.81–1.20); associations were similar including fructosamine instead of glycated albumin. Our findings indicate hyperglycemia is associated with an increased risk of lethal and fatal prostate cancer, but not total prostate cancer incidence.

Introduction

In contrast to several other types of cancer (1), diabetes is consistently inversely associated with prostate cancer incidence (1–3), and this association is stronger with a longer duration of diabetes (4, 5). A number of hypothesized mechanisms driving the inverse relationship include decreased circulating androgens associated with long-term diabetes (6, 7); pharmacologic effects of diabetes medications; and microvascular effects of diabetes on the prostate (8). There have been fewer studies of diabetes and prostate cancer mortality, and findings have been inconsistent. Some studies have reported a positive association between diabetes and prostate cancer mortality (9, 10), whereas others have reported a possible inverse association (11–13). As the U.S. diabetes prevalence has substantially increased in recent years (14), a better understanding of the relationship between the diabetes, underlying glycemia, and prostate cancer carcinogenesis is needed.

Glycemia biomarkers can be used to characterize states both early (e.g., prediabetes) and later (e.g., undiagnosed and diagnosed diabetes) in the natural history of diabetes. Two recent meta-analyses, both of which included Atherosclerosis Risk in Communities (ARIC) study findings with follow-up through 2006 (11, 15), reported an inverse association between fasting glucose and prostate cancer incidence (16), and no association between glycated hemoglobin (HbA1c) and prostate cancer incidence (17). Few studies have evaluated the association between biomarkers of hyperglycemia and prostate cancer

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mortality. In a prior study, a modest inverse association between glucose (fasting and non-fasting) and prostate cancer mortality was reported (18). In contrast, a suggestive positive association between fasting glucose and prostate cancer mortality was reported recently (19), and previously we reported a suggestive positive association between HbA1c and prostate cancer mortality in ARIC with follow-up through 2006 (11). Heterogeneity in the measurement of glycemia between biomarker types and the selection of the reference group (e.g., lowest quantile or clinically normal) could contribute to the inconsistency of these findings for incidence. More work is needed to determine the association between glycemia biomarkers and prostate carcinogenesis.

Thus, we conducted a prospective analysis to evaluate the association between hyperglycemia, assessed by multiple glycemia biomarkers—fasting glucose, HbA1c, glycated albumin, and fructosamine—individually, and jointly, and prostate cancer incidence and mortality in ARIC through 2012. We also estimated the association between diagnosed diabetes and these outcomes compared with men who had normal values for multiple biomarkers to increase the specificity of normoglycemia. We hypothesized that both hyperglycemia and diagnosed diabetes would have modest inverse associations with prostate cancer incidence, and positive associations with prostate cancer mortality; and that these associations would be stronger when multiple biomarkers were used to classify men according to their glycemia values as low, normal, or high. Consistent with our prior analysis (11), we also hypothesized that low glycemia would have an inverse association with prostate cancer incidence and positive association with prostate cancer mortality.

Materials and Methods

Study population

ARIC is a prospective cohort study that enrolled 15,792 participants ages 45 to 64 years from four field centers: Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN; and Washington County, MD, with the baseline visit occurring between 1987 and 1989. Twenty-seven percent of participants are African-American (20). Fasting glucose, HbA1c, glycated albumin, and fructosamine were measured at visit 2 (1990–1992). The analytic cohort for this analysis is 5,162 men without a cancer diagnosis by visit 2 who were fasting for at least 8 hours and had complete information on glycemia biomarkers. Participants gave written informed consent, and Institutional Review Boards at each study site approved the study protocol in accordance with the U.S. Common Rule.

Classification of diabetes and glycemia

Men who self-reported a doctor's diagnosis of diabetes and/or were taking diabetes medication at visit 2 were classified as having diagnosed diabetes, here after diabetes. Measurement of the glycemia biomarkers is described in Supplementary Materials. Men without diabetes were classified as low, normal, or high using established clinical- or research-based biomarker cutpoints: (1) fasting glucose (21): <3.1 mmol/L (low), 3.1–5.6 mmol/L (normal), >5.6 mmol/L (high); (2) HbA1c (11, 21–24): <5.0% (low), 5.0%–5.6% (normal), >5.6% (high); (3) glycated albumin (25): <11% (low), 11%–16% (normal), >16% (high); and (4) fructosamine (26): <200 μmol/L (low), 200–285 μmol/L (normal), >285 μmol/L (high). No men in the analytic cohort had low fasting glucose. Men were also jointly classified using three different combinations of multiple biomarkers: (1) fasting glucose and HbA1c; (2) fasting glucose, HbA1c, and glycated albumin; and (3) fasting glucose, HbA1c, and fructosamine. The joint categories were low on $\geq$1 biomarker, normal on all, and high on $\geq$1 biomarker. Men who were low on $\geq$1 biomarker were categorized as low, irrespective of other biomarker values. The cross-categorization of men by biomarker is shown in Table 3. Associations for high on 1, 2, or 3 biomarkers were similar; therefore, we report on only high on $\geq$1 biomarker. Because fructosamine includes all glycated serum proteins including albumin (27, 28), fructosamine and glycated albumin were not simultaneously considered.

Outcome ascertainment

First primary prostate cancers were ascertained from baseline through 2012 via linkage with the cancer registries in the four states where participants were recruited, abstraction of medical records collected following a cancer-specific telephone call, abstraction of archived hospital discharge summaries and medical records, and death certificates (29). Lethal prostate cancer was defined as a first primary prostate cancer case that either had distant metastasis to any organ at diagnosis (pathologic tumor–node–metastasis stage 4 or SEER summary stage 3, 4, or 7) or that led to death with prostate cancer as the underlying cause. Prostate cancer mortality was ascertained from death certificates and defined as death from prostate cancer as the underlying cause among men without a diagnosis of cancer at baseline.

Statistical analysis

Age- and race-adjusted mean and proportions of demographic characteristics at visit 2 were calculated by biomarker categories in men without diabetes, and in men with diabetes using regression modeling. We calculated the mean for each biomarker across the joint categories, and compared the agreement in biomarker classification of men without diabetes. For total and lethal incidence, men were followed from visit 2 until diagnosis of prostate cancer, diagnosis of another cancer, death from any cause, loss to follow-up, or December 31, 2012, whichever came first. A total of 30 men were lost to follow-up and were censored in the analysis of prostate cancer incidence. For

mortality, men were followed from visit 2 until death from prostate cancer, death from another cause, or December 31, 2012, whichever came first. The underlying cause of death was ascertained from vital statistics and the National Death Index, and no men were lost to follow-up in the mortality analysis. We used Cox proportional hazards regression to estimate the relative hazard (HR) and 95% confidence interval (CI) of prostate cancer incidence and mortality for each biomarker individually, and for each joint biomarker category; the reference group included men classified as normoglycemic. In each model, men with diagnosed diabetes were classified as such regardless of their biomarker value and included as a separate exposure category in the regression models. All models were adjusted for age (continuous, visit 2), joint categories for race and field center (White from Minnesota; White from Washington Co. or Forsyth Co.; Black from Jackson; Black from Washington Co. or Forsyth Co.), body mass index (BMI, kg/m^2, continuous, visit 2), waist circumference (cm, continuous, visit 2), education (<high school, high school with some college, and college graduate), and cigarette smoking status (current/former smoker who quit <10 years ago; former smoker who quit ≥10 years ago; and never smoker, visit 2). All models were also minimally adjusted including only terms for age (continuous) and race x field center to address potential overfitting of fully adjusted models. Because findings between minimally adjusted and fully adjusted models are comparable, we present only fully adjusted models in the main text, and minimally adjusted models in Supplementary Materials (Supplementary Tables S1 and S2). The proportional hazards assumption was tested in the multivariable-adjusted models with a global test and was met. Two approaches were used to assess collinearity in the covariates: (1) correlation of the estimate coefficients for the covariates included in the models, and (2) symmetric matrix inversion to assess perfect collinearity between covariates. Although the estimate regression coefficients for BMI and waist circumference appeared to be correlated (−0.90), correlation between the other covariates was minimal, and none of the covariates were perfectly collinear.

To explore the influence of how we classified diabetes, all models were also run with men categorized: (1) as having diagnosed diabetes or based on a clinical cutpoint for diabetes for fasting glucose (≥7.0 mmol/L) and/or HbA1c (≥6.5%; Supplementary Tables S3 and S4), and (2) by their biomarker values, irrespective of diabetes status, and adjusting for diagnosed diabetes (Supplementary Tables S5 and S6). Only results for men with diagnosed diabetes categorized separately are presented in the main text because inferences did not change. In sensitivity analyses (reported in Supplementary Materials), (1) only prostate cancer cases and deaths occurring ≥3 years after visit 2 were included to reduce the potential for undetected cancer to influence biomarker concentrations (Supplementary Tables S7 and S8), (2) first only men with health insurance, and then only men who reported visiting a doctor within 5 years were included to restrict the analyses to men with comparable access to care (Supplementary Tables S9–S14), (3) models were adjusted for visit 1 insulin concentration (Supplementary Tables S15 and S16), and (4) high on 1 or more biomarker was used as the reference category given the small number of deaths in the normal category (Supplementary Table S17). We also modeled continuous biomarker values among men without diagnosed diabetes (1) using restricted cubic splines with knots at the 10th, 50th, and 90th percentiles among men without diabetes (Supplementary Figs. S1–S3) and (2) as per 1-SD change in biomarker value. Because the restricted spline models revealed nonlinear associations, we restricted our analysis of per 1-SD change to portion of the biomarker distributions with linear associations with prostate cancer (e.g., men with biomarker values greater than normal). Statistical analyses were conducted using Stata 13.1 (StataCorp). All tests were two-sided with $P < 0.05$ indicating statistical significance.

Results

Among 5,162 men, 671 incident total prostate cancer cases were ascertained, 69 of these were classified as lethal disease, and 64 men died of prostate cancer. At the start of follow-up, 409 (8%) men had diagnosed diabetes. Compared with men who were classified as normal by each biomarker, men with diabetes appeared to have a higher mean BMI and waist circumference, and included a larger proportion of African Americans and men with less than a high school education (Table 1). Among men without diabetes, mean values of each biomarker appeared to increase with number of biomarkers classified as high (Table 2). Together, HbA1c and fasting glucose classified 23% of men as normal and 23% as high, whereas HbA1c and glycated albumin together classified 62% men with normal fasting glucose as normal, and 3% of men with high fasting glucose as high, and HbA1c and fructosamine classified 64% of men with normal fasting glucose as normal, and 2% of men with high fasting glucose as high (Table 3).

Total prostate cancer incidence

Compared with men without diabetes with normal fasting glucose, neither high fasting glucose nor diabetes was significantly associated with total prostate cancer incidence, though all HRs were <1.0 (Table 4). Similar inverse patterns of association were observed for HbA1c, glycated albumin, and fructosamine (Table 4). When biomarkers were modeled as continuous variables, high values were associated with a nonsignificant lower risk of total prostate cancer incidence (Supplementary Fig. S1). Low HbA1c, glycated albumin, and fructosamine were not associated

Table 1. Characteristics of men without diabetes by categories of age- and race-adjusted biomarkers of glycemia and men with diagnosed diabetes in the ARIC study, 1990–1992

	Fasting glucose (mmol/L)		HbA1c (%)			Glycated albumin (%)			Fructosamine (μmol/L)			
	Normal <5.6 (n = 1,736)	High ≥5.6 (n = 3,017)	Low <5.0 (n = 427)	Normal 5.0–5.6 (n = 2,846)	High ≥5.7 (n = 1,480)	Low <11 (n = 384)	Normal 11–16 (n = 4,255)	High ≥17 (n = 114)	Low <200 (n = 264)	Normal 200–285 (n = 4,409)	High >285 (n = 80)	Diagnosed diabetes (n = 409)
Mean age, y (SE)[a]	56.7 (0.14)	57.1 (0.10)	57.2 (0.09)	56.6 (0.10)	57.6 (0.14)	56.4 (0.26)	57.0 (0.08)	57.5 (0.28)	56.7 (0.31)	57.0 (0.08)	57.1 (0.33)	58.4 (0.28)
African American, % (SE)[b]	16.7 (0.009)	20.0 (0.007)	22.8 (0.006)	11.3 (0.007)	32.3 (0.009)	5.2 (0.02)	19.7 (0.006)	34.2 (0.02)	7.0 (0.02)	19.3 (0.006)	31.7 (0.02)	30.3 (0.02)
Mean BMI, kg/m^2 (SE)	26.6 (0.10)	28.2 (0.07)	27.9 (0.06)	27.0 (0.07)	28.6 (0.10)	28.2 (0.19)	27.6 (0.06)	26.9 (0.21)	28.2 (0.22)	27.6 (0.06)	27.0 (0.24)	29.8 (0.21)
Mean waist circumference, cm (SE)	97.2 (0.25)	101.4 (0.19)	100.7 (0.17)	98.6 (0.20)	102.2 (0.27)	102.3 (0.49)	99.8 (0.16)	97.0 (0.54)	102.3 (0.58)	99.8 (0.16)	97.0 (0.62)	105.4 (0.54)
Never smoker, % (SE)	32.9 (0.01)	27.9 (0.008)	29.0 (0.007)	32.7 (0.008)	24.1 (0.01)	23.6 (0.02)	30.0 (0.007)	36.5 (0.02)	23.2 (0.02)	30.0 (0.007)	36.7 (0.03)	27.6 (0.02)
Former/quit 10+ years ago % (SE)	27.6 (0.01)	33.3 (0.008)	30.0 (0.007)	32.4 (0.008)	29.4 (0.01)	32.8 (0.02)	31.2 (0.007)	28.9 (0.02)	28.0 (0.02)	31.4 (0.008)	33.7 (0.03)	33.3 (0.02)
Current/quit <10 years ago, % (SE)	39.5 (0.01)	38.8 (0.009)	41.0 (0.008)	34.9 (0.009)	46.5 (0.01)	43.6 (0.02)	38.8 (0.007)	34.6 (0.02)	48.8 (0.03)	38.6 (0.007)	29.7 (0.03)	39.1 (0.02)
Education												
Less than high school, % (SE)	18.1 (0.009)	21.3 (0.007)	19.2 (0.006)	16.6 (0.007)	27.3 (0.01)	18.1 (0.02)	20.3 (0.006)	24.0 (0.02)	19.9 (0.02)	20.1 (0.006)	23.2 (0.02)	28.9 (0.02)
High school/some college, % (SE)	37.1 (0.01)	36.8 (0.009)	37.6 (0.007)	38.2 (0.009)	34.2 (0.01)	40.7 (0.02)	37.7 (0.007)	31.8 (0.02)	38.9 (0.03)	36.9 (0.007)	33.2 (0.03)	37.7 (0.02)
College or above, % (SE)	44.8 (0.01)	41.9 (0.009)	43.2 (0.008)	45.2 (0.009)	38.5 (0.01)	41.2 (0.02)	43.0 (0.007)	44.2 (0.02)	41.2 (0.03)	43.0 (0.007)	43.5 (0.03)	33.5 (0.02)

[a]Adjusted for race only.
[b]Adjusted for age only.

with prostate cancer incidence (Table 4; Supplementary Fig. S1). When men were classified using two or more biomarkers, neither high glycemia nor low glycemia was associated with total prostate cancer incidence; diabetes was not significantly associated with total prostate cancer incidence, though all HRs were <1.0 (Table 5). Inferences were similar in all sensitivity analyses (Supplementary Materials).

Lethal prostate cancer incidence

Compared with men without diabetes with normal fasting glucose, men with high fasting glucose had a significantly increased risk of lethal prostate cancer incidence (Table 4). Similar positive patterns of association were observed for HbA1c, glycated albumin, and fructosamine. When modeled as continuous variables, associations were not statistically significant and were in the same direction for high fasting glucose, HbA1c, and glycated albumin but not for high fructosamine (Supplementary Fig. S2). Men with diabetes had a nonstatistically significant increase in risk of lethal prostate cancer compared with men without diabetes who had normal fasting glucose, but not when compared with men without diabetes who had normal HbA1c (Table 4). When compared with men without diabetes with normal glycated albumin or fructosamine, men with diabetes had a nonstatistically significant decreased risk of lethal prostate cancer incidence. Men without diabetes with low HbA1c and low fructosamine had a nonstatistically significant increased risk of lethal prostate cancer, whereas men without diabetes with low glycated albumin had a nonstatistically significant decreased risk (Table 4).

When men without diabetes were classified using two or more biomarkers, high glycemia was associated with greater than a 2-fold increased risk of lethal prostate cancer for all biomarker combinations (Table 5). Men with diabetes had a nonstatistically significant increased risk of lethal prostate cancer (Table 5). Low glycemia was also associated with a 2-fold increased risk or greater in all biomarker combinations, but this was not statistically significant. Similar inferences were observed in all sensitivity analyses (Supplementary Materials).

Prostate cancer mortality

Compared with men without diabetes who had normal fasting glucose, men with high fasting glucose had a significantly increased risk of prostate cancer mortality (Table 4). Similar positive patterns of association were observed for HbA1c, glycated albumin, and fructosamine (Table 4). When modeled as continuous variables, associations were not statistically significant and were in the same direction for high fasting glucose and HbA1c, but not for high glycated albumin or fructosamine (Supplementary Fig. S3). Men with diabetes had a nonstatistically significant increased risk of prostate cancer mortality compared with men without diabetes who had normal

Table 2. Mean (SE) glycemia biomarker values for joint categories in men without diagnosed diabetes in the ARIC Study, 1990–1992

Joint categories		Fasting glucose (mmol/L)	HbA1c (%)	Glycated albumin (%)	Fructosamine (μmol/L)
FG & HbA1c	Low on HbA1c ($n = 427$)	5.58 (0.03)	4.75 (0.01)	12.2 (0.05)	225.1 (0.81)
	Normal on both ($n = 1,206$)	5.26 (0.007)	5.29 (0.005)	12.3 (0.03)	223.5 (0.52)
	High on 1 or both ($n = 3,120$)	6.25 (0.02)	5.70 (0.01)	12.9 (0.04)	232.4 (0.51)
FG; HbA1c; & GA	Low on any 1 marker ($n = 753$)	5.66 (0.02)	5.04 (0.02)	11.4 (0.05)	216.5 (0.72)
	Normal on all 3 markers ($n = 1,075$)	5.26 (0.008)	5.29 (0.005)	12.5 (0.03)	225.6 (0.51)
	High on 1 or more ($n = 2,925$)	6.26 (0.02)	5.72 (0.01)	13.1 (0.04)	234.3 (0.52)
FG; HbA1c; & fructosamine	Low on any 1 marker ($n = 666$)	5.61 (0.02)	5.00 (0.02)	11.8 (0.05)	212.7 (0.87)
	Normal on all 3 markers ($n = 1,110$)	5.27 (0.007)	5.29 (0.005)	12.4 (0.03)	225.9 (0.45)
	High on 1 or more ($n = 2,977$)	6.26 (0.02)	5.71 (0.01)	13.0 (0.04)	234.6 (0.51)

Abbreviations: FG, fasting glucose; GA, glycated albumin.

fasting glucose or HbA1c, but not when compared with men without diabetes who had normal glycated albumin and fructosamine. Men without diabetes with low HbA1c had a nonstatistically significant increased risk of prostate cancer mortality (Table 4), whereas men without diabetes with low glycated albumin or fructosamine had a nonstatistically significant lower risk of prostate cancer mortality. When biomarkers were modeled as continuous variables, associations were not statistically significant and were in the same direction (Supplementary Fig. S3).

When men without diabetes were classified using two or more biomarkers, high glycemia was associated with a greater than 3-fold increased risk of prostate cancer mortality for all biomarker combinations (Table 5). Men with diabetes had an increased risk of prostate cancer mortality, though the associations were not statistically significant. Low glycemia was also associated with an increased risk of prostate cancer mortality, though this association was only statistically significant for the combination of fasting glucose and HbA1c. Inferences were similar for all sensitivity analyses (Supplementary Materials).

Discussion

In this prospective investigation of the association between hyperglycemia and prostate cancer, we used multiple glycemia biomarkers individually and jointly to evaluate the association between hyperglycemia and total and lethal prostate cancer incidence and prostate cancer mortality. In men without diagnosed diabetes, elevated glycemia was not associated with total prostate cancer incidence. In contrast, among men without diagnosed diabetes, men who were high on one or more biomarkers had more than 2 times the risk of lethal prostate cancer and more than 3 times the risk of dying from prostate cancer compared with men with normal values on multiple biomarkers. The association between diagnosed diabetes and total prostate cancer incidence was inverse, though not statistically significant. In contrast, the association between diagnosed diabetes and lethal prostate cancer and prostate cancer mortality was positive, though also not statistically significant.

To our knowledge, this is the first investigation to use this combination of biomarkers to classify glycemia in relation to prostate cancer. Each biomarker is susceptible to different sources of measurement error (27, 28, 30, 31), and agreement in the classification of normo- or hyperglycemia across markers is not perfect. Improved classification of glycemia should be achieved by using multiple glycemia biomarkers jointly. In our analysis of prostate cancer mortality, associations for hyperglycemia for each biomarker individually were attenuated compared with the associations for the joint biomarker categories, suggesting nondifferential misclassification. In particular, better classification of the reference group (normoglycemia) appeared to strengthen the observed association between high glycemia and prostate cancer mortality when using multiple glycemia biomarkers jointly.

In our study, hyperglycemia, measured by individual biomarkers or joint combinations of biomarkers, was not significantly associated with total prostate cancer incidence, though the HRs for glycated albumin and fructosamine were less than one. Prior meta-analyses of fasting glucose (16) and HbA1c (17), both of which included ARIC data through 2006 (11, 15), reported modest inverse associations between hyperglycemia and total prostate cancer incidence, though findings were not statistically significant for HbA1c. Further, in the meta-analyses of fasting glucose (16), the association between hyperglycemia and total prostate cancer incidence was attenuated and no longer statistically significant when restricted to studies that adjusted for BMI, like our study. In a prior study that incorporated repeated measures of glucose and fructosamine, fructosamine, but not glucose, was inversely associated with prostate cancer incidence; further, there was no significant association when men in the highest tertile of both biomarkers were compared with men in the lowest tertile of both biomarkers (32). Our findings for individual glycemia biomarkers and joint categories of these biomarkers are consistent with prior literature suggesting either no association, or a possibly modest inverse association between hyperglycemia and total prostate cancer incidence. We also found that diagnosed diabetes was not significantly associated with total prostate cancer incidence, though the HR for diabetes was consistently less

Table 3. Cross-tabulation of number of men (%) by category of each glycemia biomarker in men without diagnosed diabetes in the ARIC study, 1990–1992

		Fasting glucose		
		Low (≤3.0 mmol/L)	Normal (3.1–5.6 mmol/L)	High (≥5.6 mmol/L)
HbA1c	Low (<5.0%)	NA	230 (4.5)	197 (3.8)
	Normal (5.0%–5.6%)	NA	1,206 (23.4)	1,640 (31.8)
	High (≥5.7%)	NA	300 (5.8)	1,180 (22.9)

		Normal fasting glucose (3.1–5.6 mmol/L)			High fasting glucose (≥5.6 mmol/L)			
		HbA1c			HbA1c			
		Low (<5.0%)	Normal (5.0%–5.6%)	High (≥5.7%)		Low (<5.0%)	Normal (5.0%–5.6%)	High (≥5.7%)
Glycated albumin	Low (<11%)	30 (1.7)	127 (7.3)	18 (1.0)	Low (<11%)	28 (0.9)	122 (4.0)	59 (2.0)
	Normal (11%–16%)	200 (11.5)	1,075[a] (61.9)	280 (16.1)	Normal (11%–16%)	169 (5.6)	1,510 (50.0)	1,021 (33.8)
	High (≥16%)	0 (0.0)	4 (0.2)	2 (0.1)	High (≥16%)	0 (0.0)	8 (0.3)	100[b] (3.3)

		Normal fasting glucose (3.1–5.6 mmol/L)			High fasting glucose (≥5.6 mmol/L)			
		HbA1c			HbA1c			
		Low (<5.0%)	Normal (5.0%–5.6%)	High (≥5.7%)		Low (<5.0%)	Normal (5.0%–5.6%)	High (≥5.7%)
Fructosamine	Low (<200 μmol/L)	14 (0.8)	92 (5.3)	26 (1.5)	Low (<200 μmol/L)	11 (0.4)	88 (2.9)	33 (1.1)
	Normal (200–285 μmol/L)	215 (12.4)	1,110[a] (64.0)	274 (15.8)	Normal (200–285 μmol/L)	187 (6.2)	1,547 (51.1)	1,084 (35.8)
	High (>285 μmol/L)	1 (0.06)	4 (0.23)	0 (0.0)	High (>285 μmol/L)	0 (0.0)	7 (0.2)	68[b] (2.3)

NOTE: Numbers and percentages outlined in bold represent agreement in classification of glycemia across biomarkers being compared.

Abbreviation: NA, not applicable; no participants in analytic cohort had low fasting glucose.

[a]Number of men without a diagnosis of diabetes classified as within the normal glycemia range on three biomarkers.

[b]Number of men without a diagnosis of diabetes classified as within the high glycemia range on three biomarkers.

Table 4. Association between biomarkers of glycemia and prostate cancer in the ARIC study, 1990–2012

	Prostate cancer incidence			Lethal prostate cancer incidence			Prostate cancer mortality		
	Number of cases/ person-years	HR[a] (95% CI)		Number of cases/ person-years	HR[a] (95% CI)		Number of cases/ person-years	HR[a] (95% CI)	
Fasting glucose									
Normal	229/28,842	1 (Ref.)		16/28,904	1 (Ref.)		14/32,500	1 (Ref.)	
High	397/49,448	0.97 (0.82–1.15)		48/49,528	1.82 (1.02–3.24)		45/55,921	1.85 (1.01–3.41)	
Diabetes	45/5,765	0.84 (0.61–1.17)		5/5,766	1.29 (0.46–3.61)		5/6,435	1.67 (0.59–4.77)	
Per 1-SD increase[b]		0.90 (0.82–1.00)			1.10 (0.92–1.32)			1.13 (0.93–1.38)	
Wald *P* value[c]			0.73			0.04			0.05
Wald *P* value[d]			0.73			0.04			0.05
HbA1c									
Low	52/7,314	0.91 (0.68–1.22)		6/7,326	1.42 (0.59–3.42)		6/8,199	1.54 (0.63–3.73)	
Normal	365/48,227	1 (Ref.)		30/48,228	1 (Ref.)		28/54,187	1 (Ref.)	
High	209/22,844	0.97 (0.81–1.16)		28/22,878	1.36 (0.78–2.36)		25/26,034	1.31 (0.73–2.33)	
Diabetes	45/5,765	0.84 (0.61–1.16)		5/5,766	0.99 (0.37–2.35)		5/6,435	1.24 (0.46–3.32)	
Per 1-SD increase[b]		0.87 (0.73–1.03)			1.24 (0.96–1.59)			1.35 (1.03–1.77)	
P trend[e]			0.95			0.56			0.77
P trend[f]			0.92			0.61			0.82
Glycated albumin									
Low	43/6,332	0.99 (0.72–1.36)		2/6,339	0.52 (0.13–2.16)		2/6,977	0.55 (0.13–2.28)	
Normal	570/70,193	1 (Ref.)		58/70,328	1 (Ref.)		54/79,451	1 (Ref.)	
High	13/1,765	0.72 (0.41–1.25)		4/1,765	2.09 (0.74–5.89)		3/1,993	1.84 (0.56–6.01)	
Diabetes	45/5,765	0.85 (0.62–1.16)		5/5,766	0.84 (0.33–2.14)		5/6,435	1.06 (0.41–2.69)	
Per 1-SD increase[b]		0.95 (0.90–1.01)			1.01 (0.88–1.16)			1.00 (0.84–1.18)	
P trend[e]			0.32			0.09			0.18
P trend[f]			0.53			0.10			0.18
Fructosamine									
Low	30/4,082	1.04 (0.72–1.51)		3/4,084	1.12 (0.35–3.62)		2/4,642	0.80 (0.19–3.31)	
Normal	588/72,958	1 (Ref.)		59/73,087	1 (Ref.)		55/82,379	1 (Ref.)	
High	8/1,250	0.62 (0.31–1.26)		2/1,261	1.49 (0.36–6.20)		2/1,400	1.81 (0.43–7.60)	
Diabetes	45/5,765	0.85 (0.63–1.16)		5/5,766	0.85 (0.33–2.14)		5/6,435	1.07 (0.42–2.71)	
Per 1-SD increase[b]		1.00 (0.99–1.00)			1.00 (0.99–1.01)			1.00 (0.99–1.01)	
P trend[e]			0.21			0.70			0.38
P trend[f]			0.34			0.86			0.46

NOTE: HbA1c: Low < 5.0%, Normal, 5.0% to 5.6%, High > 5.6%; Fasting glucose: Normal ≥ 5.6 mmol/L, High > 5.6 mmol/L; Glycated albumin: Low < 11%, Normal 11% to 16%, High > 16%.

[a]Model adjusted for age (years), race (African American from Jackson, MS; African American from Forsyth Co., NC, and Washington Co., MD; White from Forsyth Co., NC, and Washington Co., MD), education (less than high school, high school/some college, college or above), BMI (kg/m^2), waist circumference (cm), and smoking status (never; former/quit 10+ years ago; current/quit <10 years ago).

[b]Restricted to men without diagnosed diabetes with biomarker values ≥ normal.

[c]Wald *P* value comparing median biomarker value between categories among men without diagnosed diabetes.

[d]Wald *P* value comparing change in biomarker category among men without diagnosed diabetes.

[e]Trend for change in median value of biomarker category among men without diagnosed diabetes.

[f]Trend for change in biomarker category among men without diagnosed diabetes.

than one for all models. Our findings are consistent with the results of our prior ARIC analyses (11, 15), and a meta-analysis of 56 studies reporting a statistically significant summary relative risk of 0.88 (2). Collectively, our findings and prior studies are supportive of a modest, inverse association of diabetes and prostate cancer.

In our study, hyperglycemia measured by fasting glucose was associated with a significantly increased risk of lethal prostate cancer incidence and prostate cancer mortality, and hyperglycemia was positively, though nonsignificantly associated with lethal and fatal prostate cancer for all other individual biomarkers. When men were categorized by joint combinations of biomarkers, hyperglycemia was consistently and positively associated with increased lethal and fatal prostate cancer. Compared with total prostate cancer incidence, lethal disease is more clinically relevant, and it is less prone to both detection bias and overdiagnosis of less aggressive or indolent prostate cancer owing to PSA-based prostate cancer screening. The similar patterns of association for high glycemia and diabetes for lethal prostate cancer incidence and prostate cancer mortality are further supported by the fact that prostate cancer etiology appears to be heterogeneous, and most risk factors are associated with only lethal or fatal disease (33). Although prior studies have not evaluated the association between hyperglycemia and lethal prostate cancer, findings from the few prior studies to evaluate hyperglycemia and prostate cancer mortality are mixed. Our findings are consistent with a recent, large cohort study of hyperglycemia in men without diabetes in which men in the highest quintile of fasting glucose had a significantly increased risk of prostate cancer mortality compared with men in the lowest quintile; this association was positive, but no longer statistically significant, after adjustment for confounders including weight (19). In contrast, a pooled analysis of fasting and nonfasting men irrespective of diabetes status reported a nonsignificant, modest inverse association between the highest quintile of glucose and prostate cancer

Table 5. Association between joint categories of glycemia biomarkers and prostate cancer in the ARIC study, 1990–2012

	Prostate cancer incidence		Lethal prostate cancer incidence		Prostate cancer mortality	
	Number of cases/ person-years	HR[a] (95% CI)	Number of cases/ person-years	HR[a] (95% CI)	Number of cases/ person-years	HR[a] (95% CI)
Joint classification: fasting glucose and HbA1c						
Low on HbA1c	52/7,314	0.90 (0.65–1.23)	6/7,326	2.79 (0.93–8.34)	6/8,199	3.88 (1.18–12.78)
Normal on both markers	159/20,243	1 (Ref.)	7/20,305	1 (Ref.)	5/22,899	1 (Ref.)
High on 1 or both markers	415/50,733	0.96 (0.79–1.16)	51/50,801	2.74 (1.23–6.10)	48/57,375	3.53 (1.40–8.95)
Diagnosed diabetes	45/5,765	0.83 (0.59–1.16)	5/5,766	1.98 (0.61–6.41)	5/6,435	3.11 (0.88–11.06)
Joint classification: fasting glucose, HbA1c, and glycated albumin						
Low on any 1 marker	88/12,661	0.93 (0.71–1.21)	8/12,680	2.02 (0.73–5.61)	8/14,118	2.75 (0.89–8.48)
Normal on all 3 markers	141/18,059	1 (Ref.)	7/18,121	1 (Ref.)	5/20,409	1 (Ref.)
High on 1 or more marker	397/47,570	0.98 (0.81–1.20)	49/47,631	2.50 (1.12–5.58)	46/53,893	3.20 (1.26–8.14)
Diagnosed diabetes	45/5,765	0.84 (0.60–1.19)	5/5,766	1.80 (0.56–5.83)	5/6,435	2.90 (0.80–10.32)
Joint classification: fasting glucose, HbA1c, and fructosamine						
Low on any 1 marker	77/10,977	0.91 (0.69–1.20)	7/10,991	2.00 (0.70–5.74)	6/12,378	2.38 (0.72–7.84)
Normal on all 3 markers	147/18,721	1 (Ref.)	7/18,781	1 (Ref.)	5/21,181	1 (Ref.)
High on 1 or more marker	402/48,592	0.97 (0.80–1.18)	50/48,660	2.58 (1.16–5.75)	48/54,914	3.40 (1.34–8.63)
Diagnosed diabetes	45/5,765	0.83 (0.59–1.17)	5/5,766	1.85 (0.57–5.98)	5/6,435	3.00 (0.84–10.67)

[a]Model adjusted for age (years), race (African American from Jackson, MS; African American from Forsyth Co., NC, and Washington Co., MD; White from Forsyth Co., NC, and Washington Co., MD), education (less than high school; high school/some college; college or above), BMI (kg/m^2), waist circumference (cm), and smoking status (never; former/quit 10+ years ago; current/quit <10 years ago).

mortality as compared with the lowest quintile (18). More work is needed in this area to conclusively determine the association between hyperglycemia and prostate cancer mortality.

In all of our models, diagnosed diabetes had a nonsignificant, positive association with *lethal prostate cancer and* prostate cancer mortality compared with men without diabetes with normal glycemia values based on one or more biomarker. Our findings for prostate cancer mortality are consistent with a pooled analysis of Asian cohorts that reported a significant, positive association between self-reported diabetes (versus no) and prostate cancer mortality (9). In contrast, in the Cancer Prevention Study-II, self-reported diabetes (versus no) was associated with a lower risk of prostate cancer mortality (13). In both studies, the reference group potentially included men with prediabetes, undiagnosed diabetes, and low glycemia, unlike in our study. In a large pooled analysis, which included ARIC, men with diabetes ascertained by self-report, medication use, or fasting glucose $\geq$ 7.0 mmol/L (vs. fasting glucose < 7.0 mmol/L) had a modest but significantly lower risk of prostate cancer mortality (12). Unlike the prior two studies described (9, 13), this pooled study (12) excluded men with fasting glucose $\geq$ 7.0 mmol/L (indicative of undiagnosed diabetes) from the reference group, but did not exclude men with fasting glucose between >5.6 and < 7.0 mmol/L from the reference group. When we categorized men with diagnosed diabetes and men with fasting glucose > 7.0 mmol/L together, and separately categorized men with fasting glucose >5.6 and <7.0 mmol/L from men with normal values (Supplementary Table S1), we found that compared with men with normal values, men with diabetes or fasting glucose > 7.0 mmol/L, and men with fasting glucose > 5.6 and < 7.0 mmol/L both had a higher risk of prostate cancer mortality. This finding indicates that including men with high fasting glucose in the reference group can attenuate the positive association between diabetes and prostate cancer mortality. Thus, these differences in how the reference group is defined across studies could account for apparent differences in findings. More work is needed to understand the role of diabetes in prostate cancer death.

The addition of a low glycemia category likely improved the classification of the normal glycemia reference group in our study. Previous research has suggested HbA1c < 5.0% in individuals without diabetes may be indicative of ill health (34), with several studies showing increased risks of all-cause mortality and cancer death in this group (11, 21–24, 34, 35). We observed an increased risk of prostate cancer mortality in men without diagnosed diabetes who had glycemia values below the normal range compared with men who were classified as normal based on multiple biomarkers, providing additional evidence that low glycemia should be categorized separately when evaluating the association between glycemia and prostate cancer.

Our observation that hyperglycemia was inversely associated with total incidence and positively associated with lethal incidence and mortality is similar to the pattern reported for obesity and prostate carcinogenesis (36), suggesting that glycemia has different effects throughout the natural history of prostate carcinogenesis. The inverse association between diagnosed diabetes and prostate cancer incidence has been hypothesized to be due to a decline in circulating sex hormones that occurs with longer duration of elevated glycemia and diabetes (6). The positive association with lethal incidence and mortality could be explained by the Warburg effect, where proliferating cancer cells develop a dependency on extracellular glucose for energy metabolism through aerobic glycolysis (37). Oncogenic activation in metabolic pathways, including the PI3K/Akt/mTOR pathway, which is associated with

increased glycolysis, may also help explain this phenomenon (37, 38).

Several aspects of our prospective study merit discussion. First, we were able to well-classify men based on glycemia values. All men fasted for at least 8 hours and had four biomarkers of glycemia at one time point. Joint categories were used to reduce misclassification by any one biomarker. In addition, diabetes was based on self-report and medication use, further reducing potential misclassification (39). Second, we separately classified men with low glycemia from men with normal glycemia. Prior work has indicated that low glycemia is associated with an increased risk of all-cause, and potentially prostate cancer–specific mortality; thus, it is preferable to separately categorize these men in studies of glycemia and prostate carcinogenesis. Third, our analyses were adjusted for clinically measured, as opposed to self-reported, BMI, and waist circumference. Fourth, although we had 77,198 person-years of follow-up for the lethal disease analysis and 86,855 person-years of follow-up for the prostate cancer mortality analysis, we only had 69 cases of lethal disease and 64 prostate cancer deaths, which is a study limitation. We conducted several sensitivity analyses, including categorizing men with diagnosed diabetes and men with a biomarker value indicative of diabetes, but no reported diagnosis of diabetes, together, thereby doubling the number of cases in this group (Supplementary Table S2), and using high on any one marker as the reference group (Supplementary Table S15), which yielded similar inferences as our main analysis. Nonetheless, additional studies are needed before definitive conclusions can be made about the association between hyperglycemia, diabetes, and prostate cancer mortality. Finally, we used biomarkers measured at a single study visit; thus, we did not account for change in glycemia over time. In subanalyses, we restricted to cases that occurred more than 3 years after baseline (Supplementary Tables S5 and S6) to reduce the chance of undetected prostate cancer influencing glycemia values. However, we do not know that our glycemia categorization, however well-captured, at this one point in mid to late life is the point most etiologically relevant to prostate carcinogenesis.

In this prospective study, we used multiple biomarkers of glycemia to improve normo- and hyperglycemia classification for etiologic research. Although hyperglycemia and diabetes were not significantly associated with total prostate cancer incidence, glycemia values outside of the normal range were associated with increased risk of lethal prostate cancer and prostate cancer mortality. These findings add to our understanding of the association of hyperglycemia and diabetes with prostate carcinogenesis, and further emphasize the importance of diabetes prevention.

Disclosure of Potential Conflicts of Interest

E.A. Platz is Senior Editor at the AACR. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The content of this work is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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