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The association of metformin use with prostate cancer aggressiveness among Black Americans and White Americans in a population-based study

Saira Khan, PhD, MPH¹, Jianwen Cai, PhD, MS², Matthew E. Nielsen, MD, MS^{3,4,5}, Melissa A. Troester, PhD, MPH, MS^{3,5}, James L. Mohler, MD^{4,5,6,7}, Elizabeth T. H. Fontham, DrPH, MPH⁸, Laura Farnan, PhD, MS⁵, Bettina F. Drake, PhD, MPH¹, Andrew F. Olshan, PhD, MS^{3,5}, and Jeannette T. Bensen, PhD, MS^{3,5}

¹Division of Public Health Sciences, Department of Surgery, Washington University in St. Louis School of Medicine, 660 S. Euclid Avenue, St. Louis, Missouri, 63110, USA

²Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina-Chapel Hill, 135 Dauer Drive, Chapel Hill, North Carolina, 27599 USA

³Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina-Chapel Hill, 135 Dauer Drive, Chapel Hill, North Carolina, 27599 USA

⁴Department of Urology, School of Medicine, University of North Carolina-Chapel Hill, 170 Manning Dr., Chapel Hill, North Carolina, 27599 USA

⁵Lineberger Comprehensive Cancer Center, School of Medicine, University of North Carolina-Chapel Hill, 450 West Drive, Chapel Hill, North Carolina, 27599 USA

⁶Department of Urology, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, New York, 14263, USA

⁷Department of Urology, University of Buffalo School of Medicine and Biotechnology, 100 High Street, Buffalo, New York, 14203, USA

⁸School of Public Health, Louisiana State University Health Science Center, 2020 Gravier Street, New Orleans, Louisiana 70112, USA

Abstract

Purpose: Metformin has been associated with a reduced incidence of prostate cancer and improved prostate cancer outcomes. However, whether race modifies the association between metformin use and prostate cancer aggressiveness remains uncertain. The association between metformin use and prostate cancer aggressiveness was examined separately in Black Americans (Blacks) and White Americans (Whites).

Correspondence: Saira Khan, PhD, MPH, Division of Public Health Sciences, Department of Surgery, Washington University in St. Louis School of Medicine, 660 S. Euclid Avenue, Campus Box 8100, St. Louis, MO 63110, khans@wustl.edu, Phone: 314-747-0964.

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent was obtained from all individual participants included in the study.

Methods: The study population consisted of 305 Black and 195 White research participants with incident prostate cancer and self-reported diabetes from the North Carolina-Louisiana Prostate Cancer Project (PCaP). High aggressive prostate cancer was defined using a composite measure of Gleason sum, prostate-specific antigen, and clinical stage. Multivariable logistic regression was used to assess the association between metformin use and high aggressive prostate cancer at diagnosis, separately among Whites and Blacks, with adjustment for age, screening history, site, education, insurance, and body mass index.

Results: Metformin use was associated positively with high aggressive prostate cancer in Blacks (OR: 2.01; 95% CI: 1.05, 3.83). By contrast, a weak inverse association between metformin use and high aggressive prostate cancer was found in Whites (OR: 0.80, 95% CI: 0.34, 1.85).

Conclusions: The association between metformin use and prostate cancer aggressiveness may be modified by race.

Keywords

prostate cancer; metformin; Black Americans; aggressiveness; PCaP

Introduction

Prostate cancer is the most common incident cancer among men in the United States [1]. Black Americans (Blacks) are almost twice as likely to be diagnosed with prostate cancer and have a prostate cancer death rate that is more than double that of White Americans (Whites) [1]. Meanwhile, diabetes is the 7th leading cause of death in the United States and Blacks are 1.5 times more likely to be diagnosed with, and 2 times more likely to die from, diabetes than non-Hispanic Whites [2, 3]. Few studies focus specifically on Blacks with prostate cancer *and* diabetes despite the high-risk profile of this population.

Metformin, a drug in the biguanide class used to treat diabetes, is hypothesized to slow prostate cancer growth through multiple mechanisms [4]. Metformin acts primarily by reducing hepatic glucose production. The decreased circulating glucose levels and the associated decrease in insulin-like growth factor-1 are hypothesized to protect against cancer cell growth [4]. Metformin also activates adenosine monophosphate-activated protein kinase (AMPK), reduces cyclin D1 levels, and contributes to cell cycle arrest in the G₀/G₁ phase, all of which, in turn, inhibit cellular growth and metabolism [4]. Finally, metformin has an anti-inflammatory effect. Metformin may target inflammation in neoplastic tissues to reduce the prostate cancer burden [4].

Few existing studies have examined the association between metformin use and prostate cancer aggressiveness specifically in *diabetic men with prostate cancer*. In a SEER-Medicare study, metformin use was associated with a reduced odds of aggressive prostate cancer [5]. However, this study was restricted to the elderly and consisted primarily of White participants [5]. Here, the association of metformin use and a composite measure of prostate cancer aggressiveness was examined in a population-based sample of Blacks and Whites who participated in the North Carolina-Louisiana Prostate Cancer Project (PCaP). PCaP enrolled a racially diverse population of men diagnosed with incident prostate cancer in the

Southern United States, and over-sampled for Blacks to achieve racial balance. PCaP obtained detailed demographic, clinical, pathologic, and interview data that provides an opportunity to study racial-differences in the metformin-prostate cancer aggressiveness association. This study builds on our previous research on diabetes and prostate cancer in PCaP [6, 7] and is one of the first studies to examine metformin use and prostate cancer aggressiveness in Blacks with diabetes and prostate cancer.

Methods

Study Population

PCaP has been described in detail [8]. PCaP is a population-based, case-only, cross-sectional study of men with incident prostate cancer. Participants enrolled in PCaP were diagnosed with adenocarcinoma of the prostate between July 2004 and August 2009, and were identified using state tumor registries. Eligibility criteria for PCaP research participants included: resident of North Carolina or Louisiana study areas, first diagnosis of histologically confirmed adenocarcinoma of the prostate, 40–79 years old at diagnosis, could complete the study interview in English, did not live in an institution (i.e. nursing home), not cognitively impaired or in a severely debilitated physical state, and not under the influence of alcohol, severely medicated, or apparently psychotic at the time of the interview. Eligible men had to self-identify as African American/Black or Caucasian/White in response to the open-ended question, “What is your race?” Black and White men were enrolled in PCaP at an equal rate using a randomized recruitment method [9]. Participation rates were 62% in North Carolina, 73% in pre-hurricane Katrina Louisiana, and 63% in post-hurricane Katrina Louisiana.

Research participants were visited in-home by a Registered Nurse, on average, 5 months after diagnosis. The nurse administered the study questionnaire, took biologic samples, made anthropometric measures, and recorded medications taken. The structured study questionnaire included questions on comorbidities (including diabetes), socioeconomic status (education level, insurance status), and prostate cancer screening history. Medical records of all consenting individuals were requested from physicians (up to 3). Medical records were abstracted for information regarding prostate cancer diagnosis and treatment and included physical and laboratory assays at or near the time of the prostate cancer diagnosis, clinical stage, Gleason sum, prostate-specific antigen (PSA), and initial prostate cancer treatment. Informed consent was obtained by the nurse at the time of the in-home visit. Men with diabetes were identified based on self-report. Research participants were asked, “Has a doctor or other health professional ever told you that you had diabetes or sugar diabetes?”

Among PCaP participants (n=2258), 500 self-reported diabetes (305 Blacks, 195 Whites). Research participants were excluded for missing outcome status (prostate cancer aggressiveness), missing covariates (screening history, body mass index (BMI), education, and insurance status), or if underweight. Underweight research participants were excluded due to small number of underweight men in our study population (n=10). Our final analytic sample consisted of 441 research participants with self-reported diabetes (264 Black men

and 177 White men). Blacks were slightly more likely to be excluded (13.4%) than Whites (9.2%).

Exposure, Covariates, and Outcome

The primary exposure of interest was metformin use (yes/no). Research participants collected all prescription and non-prescription medications used in the 2-week period prior to the in-home visit and presented them to the research nurse at the time of the interview. The research nurse documented all medications that were currently used by the participant.

Covariates were selected based on known confounders in the literature and to maintain consistency with prior PCaP studies and included race, age, screening history, BMI, education, insurance status, and study site. Race, socioeconomic factors (education and insurance status), and screening history were based on self-report. Education was categorized as less than high school, high school graduate or some college, or college graduate and above. Research participants were categorized as having insurance if they had any insurance prior to prostate cancer diagnosis. A positive screening history was defined as reporting at least one PSA or digital rectal exam (DRE) prior to prostate cancer diagnosis. Study site was categorized as North Carolina or Louisiana, and BMI was calculated using standardized anthropometric measurements of height and weight obtained during the in-home visit. Research participants' BMIs were categorized, using World Health Organization classifications, as normal (BMI 18.5 to <25), overweight (BMI 25 to <30), or obese (BMI 30). In a sensitivity analysis, we additionally adjusted for insulin use. Insulin is generally prescribed late in the disease course, when diabetes has progressed, and disease is advanced [10]. Moreover, given that insulin and insulin-like growth factor are known promoters of prostate cancer cell growth, insulin is more likely to be a potential confounder of the metformin-prostate cancer aggressiveness association than other anti-diabetic drugs [11]. Therefore, we adjusted for insulin use as a proxy for diabetes severity.

The primary outcome measure was a measure of prostate cancer aggressiveness at diagnosis based on a composite of Gleason, clinical stage, and PSA [8]. High aggressive prostate cancer was defined as Gleason sum ≥ 8 , or PSA >20 ng/ml, or Gleason sum ≥ 7 and clinical stage T3–T4. Low aggressive prostate cancer was defined as Gleason sum <7 and clinical stage T1–T2 and PSA <10 ng/ml. All other prostate cancer was defined as intermediate aggressive. Low and intermediate aggressive prostate cancer were combined into a single category in our analyses.

Statistical Analyses

Logistic regression was used to assess the association between metformin use and a binary measure of high aggressive prostate cancer (high aggressive vs. low/intermediate). Multivariable models were adjusted for race, age at diagnosis, screening history, socioeconomic status (education and insurance status), and study site. In a sensitivity analysis, we additionally adjusted for insulin use as a proxy for diabetes severity. Potential differences in the metformin-high aggressive prostate cancer association between Blacks and Whites were examined using stratification by race. Given we had an *a priori* objective to

examine effect modification across strata of race (a non-modifiable risk factor) and not the joint effects race and metformin use, a formal test for interaction was not performed [12].

All analyses were conducted using SAS 9.4 (Cary, NC).

Results

Characteristics of the PCaP Research Participants (Table I)

The study cohort consisted of 441 men with self-reported diabetes. Forty percent of the study cohort consisted of White participants. Among White participants, the mean age of diagnosis (66 years of age) was similar in both non-metformin and metformin users. The majority of White men, independent of metformin use, had a history of prostate cancer screening in the year prior to diagnosis. Both White metformin and White non-metformin users were somewhat more likely to be from Louisiana than North Carolina. Over half of White participants were high school graduates or had some college education and the majority were obese or overweight, independent of metformin status. More than 90% of White participants had some insurance prior to diagnosis. The prevalence of high aggressive tumors was similar in both White non-metformin users and White metformin users. Although the difference was not significant, insulin use was somewhat more prevalent among non-metformin users (15.2%) than metformin users (6.9%).

Sixty percent of the cohort consisted of Black participants. Among Black participants, the mean age at diagnosis was similar in both non-metformin (64 years) and metformin users (63 years). The majority of Black participants had a history of prostate cancer screening, although non-metformin users (83.3%) were less likely to have had prostate cancer screening than metformin users (92.1%). Independent of metformin status, Black men were somewhat more likely to be from Louisiana than North Carolina. Just over half of Black men, regardless of metformin use, were high school graduates or had some college education. The majority of Black men were either overweight or obese and had insurance prior to prostate cancer diagnosis. The prevalence of high aggressive tumors was lower, though not statistically different, among Black non-metformin users (18.7%) as compared to Black metformin users (25.4%). Black non-metformin users were more likely to use insulin (30.0%) than Black metformin users (19.3%).

Metformin and High Aggressive Prostate Cancer (Table II)

Our results suggest that metformin use may be associated with high aggressive prostate cancer in the overall cohort (Odds Ratio (OR): 1.42; 95% Confidence Interval (CI): 0.87, 2.34) after adjustment for age at diagnosis, race, screening history, study site, education, insurance, and BMI. However, there was evidence of heterogeneity in the metformin-high aggressive prostate cancer association by race. In Whites our results were suggestive of a weak inverse association between metformin use and high aggressive prostate cancer although the confidence interval was wide (OR: 0.80; 95% CI: 0.34, 1.85). In contrast, metformin use in Blacks was associated with a two-fold increased odds of high aggressive prostate cancer (OR: 2.01, 95% CI: 1.05, 3.83).

Our results were consistent with additional adjustment for insulin. In Whites, our results were suggestive of a weak inverse association (OR: 0.77; 95% CI: 0.33, 1.81). By contrast, in Blacks metformin was associated with an increased risk of high aggressive prostate cancer even with adjustment for insulin use (OR: 2.19; 95% CI: 1.13, 4.25).

Discussion

Metformin was associated with an increased odds of aggressive prostate cancer, at diagnosis, among Blacks in this population-based study of diabetic Whites and Blacks with incident prostate cancer. In contrast, metformin use in Whites was suggestive of a reduced odds of high aggressive prostate cancer. To our knowledge, this is one of the first studies to examine the association of metformin use and prostate cancer aggressiveness at diagnosis in a cohort with a significant number of Black participants.

Few studies have examined the association between metformin use and aggressiveness at diagnosis among men with a prostate cancer diagnosis. In a SEER-Medicare study of elderly men with incident prostate cancer, Raval et al. reported that metformin use was associated with reduced odds of advanced prostate cancer (OR: 0.68, 95% CI: 0.48, 0.97) [5]. A larger number of studies have reported an inverse association between metformin use and risk of incident prostate cancer. Although findings have been inconsistent [13–17], a meta-analysis showed a reduced incidence of prostate cancer among metformin users [14]. The current analysis is consistent with an inverse relationship between metformin use and prostate cancer aggressiveness in White men, although the effect estimate was imprecise (OR: 0.80, 95% CI: 0.34, 1.85). In contrast, in both the overall cohort and Black participants, our findings are inconsistent with other studies, and suggest that metformin use may be associated with increased odds of high aggressive prostate cancer. Differences between these findings and previous studies may be explained by demographic differences between our study population and those from previous studies. Previous studies have been predominantly White, whereas our population was 59% Black and 41% White. In Raval et al. 72% of the population consisted of Whites, while only 12% of the population was Black [5].

Although this demographic variability is most likely the contributing factor in the difference in findings from our study, it is important to consider other factors. In our study both non-metformin users and metformin users were more likely to be on insulin than in Raval et al. (Insulin use among non-metformin users: 23.9% our study vs. 2.3% Raval et al.; Insulin use among metformin users: 14.5% our study vs. 6.5% Raval et al.) [5]. Thus if we accept that insulin use is a marker of diabetes severity, then it is possible, as a whole, the men in our cohort had more severe diabetes. Moreover, in our study non-metformin users were more likely to be on insulin than metformin users while the opposite was true in Raval et al. (i.e. metformin users more likely to be on insulin). It is possible that these potential differences in diabetes severity across treatment groups could have contributed to the differences in our findings with those of Raval et al. However, it is important to note our results were consistent with or without adjustment for insulin. Future research should identify specific exposures that vary by race that may help explain the differences between Black and White participants in the PCaP cohort.

Even fewer studies exist that have examined the association between metformin use and prostate cancer in Blacks. While direct comparisons cannot be made between a case-control study and a case-only study like ours, it is of note that a population-based case-control study of men from Washington state has also reported effect modification by race of the metformin-prostate cancer risk association [18]. In this study, Wright et al. reported that metformin use was associated with a *reduced* odds of prostate cancer in Whites (OR: 0.61; 95% CI: 0.37, 1.02), but with an *increased* odds of prostate cancer in Blacks (OR: 1.62; 95% CI: 0.53, 5.02), although both estimates were imprecise [18].

Some previous work has suggested there may be biological mechanisms underlying the differential response to metformin across race groups [19]. Previous research suggests that 34% of the glycemic response to metformin is heritable [20] and Blacks may exhibit a better glycemic response to metformin than Whites. [21]. In a large single health system study in southeast Michigan (n=19,672) Williams et al. found that metformin use was associated with greater reduction in hemoglobin A1c (HbA1c) levels in Blacks as compared to Whites even after controlling for baseline HbA1c, duration of metformin treatment, and other diabetic medications [21]. However, it is difficult to directly relate these observations to observed or expected results for cancer aggressiveness.

Several unmeasured factors may modify relationships between metformin and cancer aggressiveness including medication adherence, drug choice, and location. First, anti-diabetic medication adherence in Blacks is lower than Whites even when access to medications is equal [22–24]. The lower adherence to anti-diabetic medications is observed in diverse patient populations including patients in a managed care setting and Medicaid enrollees [22, 23]. However, this alone does not explain our finding for Black men. If medication adherence is poor among Black men, then we might expect that *all* diabetic Black men should be at increased odds of high aggressive prostate cancer, not just metformin users. Yet in a previous analysis among PCaP participants, we found that diabetes was not associated with high aggressive prostate cancer in Black men [6]. It is possible that metformin users were most likely to be non-adherent. Indeed in a study of Medicaid enrollees with Type-2 diabetes, Black metformin users had a lower medication adherence rate than Black patients on other anti-diabetic drugs [23].

Second, physicians often consider multiple factors other than established guidelines in choosing an anti-diabetic medication, which include the patient's overall health, adherence behavior, and motivation to improve [25]. While previous research has indicated that *overall* diabetic treatment regimens do not differ between Blacks and Whites [26, 27], Blacks with a high HbA1C levels are more likely to receive non-recommended therapies [27]. Third, both adherence and treatment patterns may vary geographically. Adherence to anti-diabetic medications in the Southern United States is worse than in other parts of the country [28, 29], even though the prevalence of diabetes is highest in the Southern United States [30].

Finally, and related to adherence and treatment, the severity of diabetes, glycemic control, duration of metformin use, prior metformin use, and dosage was not assessed in PCaP. However, we did attempt to control for diabetes severity by adjusting for insulin use in a sensitivity analysis. Insulin use was used as proxy for diabetes severity as insulin is often a

marker of diabetes progression and severity, and is traditionally prescribed late in the disease course. [10]. In addition, metformin usage was based on a single measurement around the time of prostate cancer diagnosis. However, national estimates suggest that 45%–49% of diabetic patients use metformin [31, 32]. In the PCaP study population, 42% of diabetic men were metformin users, suggesting that the prevalence of metformin use in PCaP is consistent with national estimates.

It is likely that metformin users in our study consisted of both short-term users and long-term users. Thus it is possible that, on average, White men, had a longer duration of metformin use than Black men. This potential longer duration of use, could explain why our results suggested that metformin use may be inversely associated with high aggressive prostate cancer only among White men. Moreover, because our measure of metformin use was ascertained at a single point in time, approximately 5 months after diagnosis with prostate cancer, it is possible that non-metformin users in our study had previously used metformin. This would likely bias our results towards the null as men classified as non-metformin users were actually past metformin users. Conversely, it is possible that some metformin users initiated use sometime after diagnosis, but before the in-home interview. Such men would have a very short, post-diagnostic use of metformin. Again it is likely that this would bias our results toward the null as some metformin users would have had minimal metformin exposure. However, despite these factors that could have diluted our findings, we still observed a significant positive association between metformin use and high aggressive prostate cancer among Black men. Lastly, our study population of diabetes cases were identified by self-report, and it is possible that men inaccurately report their diabetes status. A previous validation study has indicated that the specificity of prevalent self-reported can range from 95.6% to 96.8% and the sensitivity can range from diabetes can range from 58.5% to 70.8%, depending on the reference definition employed [33]. However, it is important to note the diabetes prevalence in PCaP is in line with national estimates. According to the Centers for Disease Control and Prevention (CDC), 20.8% of individuals greater than 65 years have diagnosed diabetes and 25.2% of individuals greater than 65 have either diagnosed or undiagnosed diabetes [30]. Consistent with these estimates, among all PCaP participants, 22% of participants reporting having diabetes.

Despite these limitations, there are several strengths to our study. PCaP is a *population-based* study of both White and Black participants diagnosed with prostate cancer. The detailed clinical and epidemiological data allowed adjustment for important confounders, which include socioeconomic status (insurance status and education) and PSA screening history. To our knowledge, we are one of the first studies to examine the association between metformin use and high aggressive prostate cancer specifically in Blacks. Examining this association in Blacks is critical since Blacks are a clinically important, high-risk population that are more likely to be diagnosed with prostate cancer, more likely to experience adverse prostate cancer outcomes, and more likely to be diagnosed with diabetes [1, 2, 34]. Previous studies on metformin and prostate cancer have largely consisted of White participants, and this study provides evidence that the association between metformin use and high aggressive prostate cancer may not be consistent across races.

Conclusion

Our study suggests that metformin use may be inversely associated with high aggressive prostate cancer in Whites, but positively associated with high aggressive prostate cancer in Blacks. Future studies with large numbers of White and Black participants with incident prostate cancer and diabetes for whom detailed information on medication duration, medication adherence, and measures of glycemic control are available are needed to refine our understanding of racial differences in metformin-associated prostate cancer aggressiveness.

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Table I

Characteristics of PCaP research participants with diabetes (n=441), by metformin and race

	White Americans (n=177)			Black Americans (n=264)		
	Non-metformin Users (n= 105)	Metformin Users (n=72)	<i>p-value</i> ^d	Non-metformin Users (n=150)	Metformin Users (n=114)	<i>p-value</i> ^d
Age years (Mean, SD)	66.4 (7.1)	65.9 (6.6)	0.64	63.7 (7.1)	62.8 (6.6)	0.29
Screening History (n, %) ^a			0.06			0.04
Yes	97 (92.4)	71 (98.6)		125 (83.3)	105 (92.1)	
No	8 (7.6)	1 (1.4)		25 (16.7)	9 (7.9)	
Study Site			0.40			0.31
North Carolina	49 (46.7)	29 (40.3)		70 (46.7)	46 (40.4)	
Louisiana	56 (53.3)	43 (59.7)		80 (53.3)	68 (56.7)	
Education (n, %)			0.61			0.66
Less than high school	12 (11.4)	8 (11.1)		50 (33.3)	32 (28.1)	
High school graduate or some college	61 (58.1)	37 (51.4)		78 (52.0)	64 (56.1)	
College graduate or above	32 (30.5)	27 (37.5)		22 (14.7)	18 (15.8)	
BMI (n, %) ^b			0.70			0.71
Normal	7 (6.7)	7 (9.7)		17 (11.3)	15 (13.2)	
Overweight	36 (34.3)	26 (36.1)		53 (35.3)	44 (38.6)	
Obese	62 (59.1)	39 (54.2)		80 (53.3)	55 (48.2)	
Insurance Status before prostate cancer diagnosis			0.20			0.66
Had insurance	102 (97.1)	67 (93.1)		133 (88.7)	103 (90.4)	
Did not have insurance	3 (2.9)	5 (6.9)		17 (11.3)	11 (9.7)	
Prostate Cancer Aggressiveness ^c			0.42			0.19
Low/Intermediate	84 (80.0)	61 (84.7)		122 (81.3)	85 (74.6)	
High	21 (20.0)	11 (15.3)		28 (18.7)	29 (25.4)	
Insulin Use						
Yes	16 (15.2)	5 (6.9)	0.09	45 (30.0)	22 (19.3)	0.05
No	89 (84.8)	67 (93.1)		105 (70.0)	92 (80.7)	

^aScreening history was based on self-report and defined as having at least one PSA or DRE prior to prostate cancer diagnosis.^bResearch subjects were categorized as normal (BMI 18.5 to <25), overweight (BMI 25 to <30), or obese (BMI ≥ 30).^cHigh aggressive prostate cancer was defined as Gleason sum ≥ 8, or PSA >20 ng/ml, or Gleason sum =7 and clinical stage cT3-cT4.

Low aggressive prostate cancer was defined as Gleason sum <7 and clinical stage cT1-cT2 and PSA <10 ng/ml. All other cases were defined as intermediate aggressive prostate cancer.

^dThe p-value was determined using chi-square tests for all categorical variables. For age, the p-value was calculated using a t-test.

Table II.

Prevalence odds ratios (ORs) and 95% confidence intervals (CI) for high aggressive prostate cancer among diabetic men in PCaP

	All Research Participants (n=441)				White Americans (n=177)				# of men
	# of men	# with outcome	Unadjusted OR (95% CI)	Adjusted OR ^a (95% CI)	# of men	# with outcome	Unadjusted OR (95% CI)	Adjusted OR ^b (95% CI)	
Metformin Use									
No	255	49	Ref	Ref	105	21	Ref	Ref	150
Yes	186	40	1.15 (0.72, 1.84)	1.42 (0.87, 2.34)	72	11	0.72 (0.32, 1.61)	0.80 (0.34, 1.85)	114

^aModel included metformin use, age in years, race, screening history, study site, education, insurance, and BMI.

^bModel included metformin use, age in years, screening history, study site, education, insurance, and BMI.