

Metformin for Reducing Racial/Ethnic Difference in Prostate Cancer Incidence for Men with Type II Diabetes

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Abstract

Racial/ethnic disparity in prostate cancer is under studied in men with diabetes who are at a higher risk of aggressive prostate cancer. This study assessed the race/ethnic disparity in prostate cancer incidence for men with type II diabetes (T2D) and whether the impact of metformin on prostate cancer incidence varied by race/ethnicity. We conducted a retrospective study in 76,733 male veterans with T2D during 2003 to 2012. Cox proportional hazards model adjusting for covariates and propensity scores of metformin use and race/ethnic group membership was utilized to compute the HR of prostate cancer incidence associated with race/ethnicity and compare HR associated with metformin use between race/ethnic groups. Mean follow-up was 6.4 ± 2.8 years; 7% were Hispanics; 17% were African Americans (AA); mean age was 67.8 ± 9.8 years; 5.2% developed prostate cancer; and 38.9% used metformin. Among these diabetic men without metformin use, prostate cancer

incidence was higher in Hispanics and AA than in non-Hispanic White (NHW). Use of metformin alone or metformin + statins was associated with a greater prostate cancer incidence reduction in Hispanics compared with NHW, but not between AA and NHW. Use of metformin + finasteride was associated with a greater prostate cancer incidence reduction in Hispanics and AA compared with NHW. Our results suggested that metformin treatment could be a potential strategy to reduce prostate cancer incidence in the minority populations who are at high risk for fatal prostate cancer. It will be important to further examine the pleiotropic effects of metformin in multi-race/ethnic prospective studies to better inform clinical management and potentially reduce racial/ethnic disparity in prostate cancer incidence among diabetic men. *Cancer Prev Res*; 9(10); 779–87. ©2016 AACR.

See related commentary by Wang et al., p. 777

Introduction

Racial/ethnic disparity in prostate cancer has been well established in the general U.S. population. Prostate cancer incidence is greater among African Americans (AA) yet lower among Hispanic men as compared with non-Hispanic white (NHW) men (1). Whether diabetes status has an impact on the racial/ethnic disparity pattern observed in the general population is an important issue that is under studied. Although U.S.

men with diabetes are at an overall lower risk for prostate cancer incidence than nondiabetic men, they are at a higher risk for aggressive prostate cancer (2, 3). Given the continually rising epidemic of diabetes, aggressive prostate cancer presents a significant public health concern, especially among minority populations (e.g., AA and Hispanics) who are at high risk for diabetes. One large population-based study in men with diabetes reported an increased prostate cancer incidence for both AA and Hispanics as compared with NHW, which is in contrast to reduced prostate cancer incidence observed for Hispanic men when diabetes status is not considered (4). Thus, racial/ethnic disparity in prostate cancer incidence for men with diabetes warrants further investigation.

Although a reduction in racial/ethnic disparity in prostate cancer screening knowledge and improvement in quality of life for cancer survivors has been achieved through nonpharmacologic interventions (such as informed decision making or behavioral modification; ref. 5), no pharmacologic intervention has yet been identified that would reduce racial/ethnic disparity in prostate cancer incidence or its mortality. Identifying prostate cancer prevention medications that can alter disparity in prostate cancer incidence and its related clinical outcomes is a research priority.

Metformin, the most commonly prescribed first-line glucose-lowering medication for patients with type II diabetes (T2D), has shown some promising yet variable results for prostate cancer prevention. The beneficial impact of metformin on

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prostate cancer reduction was found to vary by dose or concomitant use of statin or finasteride (6–9). It is also likely that the variation of metformin's prostate cancer prevention effect could be attributed to individual pharmacokinetic differences. Among the polymorphisms in genes that are associated with metformin transport or glucose-lowering effects (10–14), the allele frequency of one ethnic-specific MATE1 (multidrug and toxin compound extrusion-1), which is associated with reduced renal excretion of metformin (11–13, 15), is strikingly high at 5% in Hispanics. Notably, the expression of metformin organic cation transporter 1 (OCT1) is more pronounced in obese subjects (16, 17) who are at increased risk for metabolic syndrome and chronic inflammation. This implies that better metformin response could more likely be observed in populations with high prevalence of metabolic syndrome or chronic inflammation, such as Hispanics or AA (18, 19). In fact, Williams and colleagues observed a greater glycemic response to metformin in AA adults compared with NHW (20). These data collectively suggest that metformin use could potentially modify race/ethnic disparity in prostate cancer incidence. This hypothesis is yet to be tested in clinical studies.

The goal of this study is to assess (i) the race/ethnic disparity in prostate cancer incidence among men with T2D who are nonusers of metformin, and (ii) whether the impact of metformin on reducing prostate cancer incidence is greater in the race/ethnic groups with a higher prostate cancer incidence among men with T2D. To this end, we conducted a nationwide longitudinal cohort study (FY2003–FY2012) of insulin-naïve male veterans with T2D to examine racial/ethnic disparity in prostate cancer incidence and whether the impact of metformin on prostate cancer incidence differed by race/ethnicity. To strengthen the causal interpretation of our finding, two inverse propensity score weighting techniques (21, 22) were employed in our statistical analyses to minimize confounding due to baseline difference between metformin users and nonusers or difference in postbaseline clinical characteristics between race/ethnic groups.

Materials and Methods

Study cohort

Our study cohort was derived from the electronic medical records (EMR) in the nationwide Veterans Administration Health Care System (VAHCS) databases. We began with 268,136 eligible beneficiaries who were 40 to 89 years of age in FY2003 and had a diagnosis of T2D (ICD-9 CM code: 250.00 or 250.02) but no cancer, cardiovascular diseases, or any glucose-lowering medication exposure during FY2001–FY2002. To obtain credible EMR for each patient, we limited the study cohort to patients with at least one visit to the general medicine, geriatric, or diabetes clinic each year. We further narrowed the study cohort to those who also met the following criteria during the study period: (i) having had prescription(s) of metformin as a glucose-lowering medication for ≥ 180 days or none; (ii) no prescription for insulin or any thiazolidinedione; (iii) no liver or renal diseases; and (iv) no missing covariates. We required criterion (ii) to eliminate potential effects associated with thiazolidinedione or insulin use on cancer incidence as reported in the literature (23, 24). In addition, to account for the potential interactions between metformin with statin and finasteride (6–9), we limited the cohort to 76,733 men who (i) have

had prescription(s) of statins for ≥ 180 days or none; and (ii) have had prescription(s) of finasteride for ≥ 180 days or none. All study procedures were approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio (San Antonio, TX) and the Research and Development Committee of the South Texas Veterans Health Care System at San Antonio.

Data sources

We used four linked VAHCS datasets (25) for this study. VAHCS Inpatient and Outpatient Medical SAS Datasets were used to identify the cohort of men with T2D and their associated characteristics, including demographic variables and comorbidities. Additional clinical variables were extracted from the VA Decision Support System [medication prescription records, HbA1c, low-density lipoprotein (LDL), and PSA laboratory results and dates of measurements] and VAHCS Corporate Data Warehouse (height and weight values).

Outcomes of interest

The outcome of interest in this study is the incidence (rate) of the initial prostate cancer diagnosis during the study period. The dependent variable used in our analyses is the time interval between the starting date and the initial prostate cancer diagnosis observed during the study period. The starting date was October 1, 2002 (the beginning of FY2003), for those without use of any glucose-lowering medication, the initiation of nonmetformin glucose-lowering medication for users of nonmetformin glucose-lowering medications, and the initiation of metformin for metformin users. A prostate cancer event was defined as having an ICD-9 diagnosis of 185 during the study period. The study termination date for each patient was either the date of the initial prostate cancer diagnosis, the date of death, or September 30, 2012 (the end of follow-up), whichever came first. Study subjects who did not have a prostate cancer diagnosis during the study period were treated as censored.

Predictors and measures

Medication exposure. In the primary analysis, metformin use was defined as a minimum of 180 days of prescription at any dose, an exposure cut-off point similar to that used in most clinical trials on metformin (26). Nonusers of metformin were patients who had no prescription for metformin during the study. Similarly, statin users consisted of patients who had any type of statin prescription at any dose for ≥ 180 days during the study, and nonusers were those who had no statin prescription during the study. Finasteride users were patients who had any finasteride prescription for ≥ 180 days during the study period, and nonusers were those who had no finasteride prescription during the study. These medication exposure variables are consistent with those in our prior study (6, 8).

In secondary analyses that assessed the impact of average daily dose of metformin use, patients with an average daily dose of $\geq 1,000$ mg were compared with those with $<1,000$ mg/day under ≥ 90 , ≥ 120 , or ≥ 180 days of prescription. That is, metformin users in the secondary analyses consisted of those in the primary analysis (all had prescription for ≥ 180 days) and the augmented users who had metformin prescription for 90 to 179 days.

Covariates. Covariates adjusted for in the analyses included age, race/ethnicity (Hispanic, AA, or NHW), and clinical

characteristics of the patient: age-adjusted Charlson comorbidity score (27), and the mean change of body mass index (BMI), LDL and hemoglobin A1c (HbA1c), and the maximum PSA level during the study period.

Statistical analyses

Racial/ethnic disparity in prostate cancer incidence among nonusers of metformin. The Cox proportional hazards model was used to assess whether the covariate-adjusted prostate cancer incidence differed by race/ethnicity under no metformin use. Predictors in this Cox model included indicators of race/ethnicity groups (AA and Hispanics), with NHW being the referent, indicators of statin (6, 7, 9) and finasteride use (28), age, change in LDL, HbA1c, and BMI, and the maximum PSA level during the study period. Under this Cox regression model, the impact of race/ethnicity was assessed by the HR associated with AA or Hispanic group relative to the NHW group. The coefficient was assessed by the Wald test with $P < 0.05$ being significant.

To enhance the causal interpretability of the racial/ethnic difference in prostate cancer incidence, the inverse propensity scores (21, 22) of race/ethnicity group membership were incorporated as the weights in the Cox regression model to minimize confounding due to imbalance in baseline covariates between race/ethnic groups. The propensity scores were calculated using logistic regression analysis, in which the dependent variable was the indicator of being in a race/ethnic group, and the independent variables included baseline age, HbA1c, PSA, BMI, LDL, and Charlson comorbidity score. Each propensity score was the likelihood of belonging to a race/ethnic group conditioned on each subject's baseline characteristics.

Differential metformin impact on prostate cancer incidence between race/ethnic groups. To assess whether metformin could reduce the racial/ethnic difference in prostate cancer incidence, we first conducted Cox regression analyses of the entire study cohort to compare the HR associated with metformin use between race/ethnic groups. Predictors in this Cox model included indicators of AA, Hispanics, metformin use, statin and finasteride use, two-way interactions of medication indicators [based on prior studies (6–9)], interactions between race/ethnicity with variables involving metformin use (i.e., indicator of metformin use, the product of the metformin use indicator and statin use indicator, and the product of metformin use indicator and finasteride use indicator), age, change in LDL, HbA1c, and BMI, and the maximum PSA level during the study period. To enhance the causal interpretability of metformin's impacts, we also incorporated the propensity scores of metformin use as the inverse probability weights (IPW) in the Cox regression analyses (21). Each propensity score was the likelihood of being treated with metformin for a patient calculated by the logistic regression analysis, in which the dependent variable was the indicator of metformin use, and the independent variables included baseline HbA1c, age, and Charlson comorbidity score. Using these IPWs, individuals were weighted differently to achieve balance in baseline covariates between the metformin users and nonusers, and therefore, potential confounding due to imbalance in baseline characteristics was minimized (21, 22). The interactions between race/ethnicity with metformin use were used to compare the HR associated with metformin use (empirically)

between race/ethnic groups. Each model coefficient was assessed by the Wald test, with $P < 0.05$ being significant.

To gain further insight about the "potential biological" variation of metformin impact between race/ethnic groups, we further employed the generalizability weighting technique (22) to predict whether the impact of metformin would have differed between race/ethnic groups should the postbaseline clinical characteristics be equalized between groups. The generalizability analysis involved two steps. First, we conducted stratified Cox proportional hazards model to assess the HR of prostate cancer associated with metformin use for each race/ethnic group, with covariates and propensity scores of metformin use being adjusted for as described above. Second, we derived the impact of metformin on prostate cancer incidence for AA and Hispanics based on their respective likelihood functions such that the postbaseline clinical characteristics (HbA1c, BMI, LDL, and comorbidity) were calibrated between AA/Hispanics and NHW. The calibration was done by weighting the likelihood of the AA/Hispanics with the ratio of the proportion of the AA/Hispanic group in the cohort to the propensity score of being in the AA/Hispanic group conditioned on their clinical characteristics (22). The impact of metformin derived from this generalizability analysis could be interpreted as the projected impact of metformin for AA or Hispanics should the clinical characteristics during the study period be calibrated between race/ethnic groups and the baseline covariates be balanced between metformin users and nonusers.

The approach described above was modified for secondary analyses that examined the impact of the average metformin daily dose ($\geq 1,000$ mg vs. $< 1,000$ mg) among metformin users. The modifications in the secondary analyses were (i) the propensity scores of higher average metformin daily dose ($\geq 1,000$ mg/day) were incorporated as IPWs in the Cox regression analyses; (ii) the generalizability weights (to hypothetically equalize the postbaseline clinical characteristics between race/ethnic groups) were calculated only among metformin users; and (iii) three metformin exposure lengths, ≥ 90 , ≥ 120 , or ≥ 180 days of prescription, were analyzed separately.

All statistical analyses were conducted using SAS 9.1.

Results

In this study cohort of 76,733 men with T2D, the mean follow-up was 6.4 ± 2.8 years, 59,906 (78.1%) were NHW, 12,593 (16.4%) were AA, 4,234 (5.5%) were Hispanics, mean age was 67.8 ± 9.8 years, mean HbA1c was $6.5 \pm 1.0\%$, 3,983 (5.2%) had a prostate cancer diagnosis, 19,805 (25.8%) used metformin for ≥ 180 days, 59,952 (78.1%) used statins, and 10,282 (13.4%) used finasteride. Detailed study cohort characteristics are shown in Table 1.

From Table 1, we observed imbalance in subjects' characteristics at baseline between metformin users and nonusers as well as between race/ethnic groups, and some of these variables (age, BMI, HbA1c, PSA, and Charlson comorbidity score) were associated with prostate cancer outcome. Thus, to assess the impact of race/ethnicity or metformin use on prostate cancer incidence, it is necessary to balance potential confounders between the comparison groups, such as weighting subjects by the reciprocal (or inverse) of their propensity scores for race/ethnicity membership or metformin use.

Table 1. Cohort characteristics

	NHW	N = 36,776	AA	N = 7,774	Hispanic	N = 2,378
Nonusers of metformin	Mean	SD	Mean	SD	Mean	SD
Statin (%)	74		70		73	
Finasteride (%)	13		14		19	
PCa (%)	6		9		7	
Follow-up (days)	2,448.19	1,085.44	2,435.31	1,091.94	2,440.75	1,053.11
Age (years)	70.17	9.48	65.14	11.02	68.75	10.02
Charlson score	4.18	2.80	4.54	3.06	4.28	3.01
Baseline HbA1c (%)	6.28	0.89	6.42	1.09	6.25	0.91
HbA1c during study (%)	6.34	0.81	6.32	0.89	6.32	0.78
Baseline LDL (mg/dL)	105.91	27.04	112.60	30.53	107.23	27.32
LDL during study (mg/dL)	90.02	24.27	95.44	28.05	89.03	23.49
Baseline BMI (kg/m ²)	30.57	5.47	31.41	5.66	28.89	4.97
BMI during study (kg/m ²)	29.57	5.50	30.40	5.84	27.89	5.13
PSA during study (ng/mL)	2.65	4.02	4.61	5.96	2.49	3.99

	NHW	N = 23,130	AA	N = 4,819	Hispanic	N = 1,856
Metformin users	Mean	SD	Mean	SD	Mean	SD
Statin (%)	87		83		84	0.36
Finasteride (%)	13		12		17	0.37
PCa (%)	3		6		3	0.18
Follow-up (days)	2,167.48	868.22	2,151.08	858.43	2,102.30	829.90
Age (years)	64.42	9.31	59.02	9.50	63.08	9.25
Charlson score	3.49	2.39	3.42	2.48	3.25	2.36
Baseline HbA1c (%)	6.87	0.87	7.23	1.15	6.98	0.95
HbA1c during study (%)	6.94	0.84	7.16	1.06	7.04	0.92
Baseline LDL (mg/dL)	104.41	25.23	112.30	29.36	106.29	24.27
LDL during study (mg/dL)	84.87	22.89	92.64	32.55	86.87	22.59
Baseline BMI (kg/m ²)	31.82	5.50	31.45	5.70	30.11	4.83
BMI during study (kg/m ²)	30.69	5.62	30.53	5.83	29.03	5.01
PSA during study (ng/mL)	2.04	3.09	2.54	3.76	1.85	2.65

Abbreviations: AA, African American; NHW, non Hispanics white; PCa, prostate cancer.

Under no use of metformin, the covariate-adjusted Cox regression analysis without incorporating IPW (without balancing the covariates between race/ethnic groups) showed that HR associated with prostate cancer for Hispanics versus NHW was 1.79 [95% confidence interval (CI), 1.37–2.33; $P < 0.01$] and HR for AA versus NHW was 1.88 (95% CI, 1.60–2.11; $P < 0.01$). The increased prostate cancer incidence in Hispanics and AA remained significant in the analysis that incorporated IPW: HR associated with prostate cancer for Hispanics versus NHW was 2.11 (95% CI, 1.90–2.33; $P < 0.01$) and HR for AA versus NHW was 1.66 (95% CI, 1.50–1.83; $P < 0.01$). The reduction in the disparity between AA and NHW (from 1.88 to 1.66) associated with the IPW adjustment could be due to IPW calibration reducing the excessive PSA and LDL levels observed in AA relative to those in NHW. The increase in the disparity between Hispanics and NHW (from 1.79 to 2.11) associated with the IPW adjustment could be due to the IPW calibration putting more weight on individuals with older age and higher BMI in Hispanics to match those in NHW. The results above suggested that both AA and Hispanics were associated with an increased prostate cancer incidence even if the difference in covariates between groups would have been eliminated (see Table 2).

Table 2. Covariate-adjusted HR (95% CI) of prostate cancer incidence associated race/ethnicity among nonusers of metformin

	AA vs. NHW	Hispanic vs. NHW
Without IPW adjustment	1.88 (1.60–2.21)	1.79 (1.37–2.33)
With IPW adjustment	1.66 (1.50–1.83)	2.11 (1.90–2.33)

Abbreviations: AA, African American; NHW, non Hispanic white.

Impact of metformin

Table 3 contrasts the covariate-adjusted HR associated with metformin use (alone or in combination with statin or finasteride) among race/ethnic groups. We reported results under two scenarios: clinical variables (HbA1c, LDL, comorbidity, BMI) during the study period were (i) calibrated between race/ethnic groups using generalizability weights or (ii) without calibration.

Impact of metformin alone by race/ethnicity

In the analyses without adjusting for generalizability weights, metformin use alone was not associated with prostate cancer incidence among NHW (HR = 0.91; 95% CI, 0.81–1.02; $P = 0.11$) nor among AA (HR = 1.10; 95% CI, 0.94–1.27; $P = 0.23$), whereas it was associated with a significant reduction in prostate cancer incidence among Hispanics (HR = 0.62; CI, 0.49–0.80; $P < 0.01$). The testing of the interaction between metformin use alone and race/ethnicity indicators suggested that the impact of metformin alone on prostate cancer incidence differed significantly by race/ethnicity: the HR associated with metformin alone was 31% less in Hispanics compared with NHW ($P < 0.01$), and it was 21% greater in AA compared with NHW ($P < 0.01$).

The differential impact of metformin use alone between NHW and Hispanics persisted even with the postbaseline clinical characteristics being calibrated between race/ethnic groups using IPW (see Table 3): metformin use alone was associated with a significantly reduced prostate cancer incidence in Hispanics (HR = 0.50, $P < 0.01$) but not in NHW (HR = 0.91; 95% CI, 0.82–1.01) nor in AA (HR = 0.92; 95% CI, 0.82–1.04).

Table 3. HR (95% CI) of prostate cancer incidence associated with metformin use by race/ethnicity: comparison between unadjustment and adjustment of generalizability weights that calibrate between race/ethnic groups

	NHW	AA	Hispanics
Metformin	0.91 (0.82–1.01)	1.10 (0.94–1.27)	0.63 (0.49–0.80)
Metformin + Statin	0.58 (0.49–0.69)	0.92 ^a (0.82–1.04) 0.70 (0.58–0.86)	0.50 ^{a,b} (0.47–0.52) 0.40 (0.30–0.53)
Metformin + Finasteride	0.48 (0.37–0.63)	0.59 ^a (0.48–0.72) 0.61 (0.44–0.77) 0.25 ^{a,b} (0.16–0.39)	0.32 ^{a,b} (0.28–0.35) 0.58 (0.37–0.99) 0.25 ^{a,b} (0.20–0.30)

Abbreviations: AA, African American; NHW, non Hispanic white.

^aGeneralizability weights were used to calibrate posttreatment clinical characteristics between comparison groups.^bSignificantly different from NHW based on 95% CI of HR.

Metformin dose effect. Among metformin users who were not on statins or finasteride, for Hispanics, those who had an average daily dose of $\geq 1,000$ mg metformin (compared with $<1,000$ mg) were associated with less prostate cancer prevention benefit, while no differential dose effect was observed among AA. For AA, the IPW-adjusted HRs associated with an average daily dose of $\geq 1,000$ mg (vs. $<1,000$ mg) were 1.34 ($P = 0.15$), 0.91 ($P = 0.50$), and 1.06 ($P = 0.67$) under ≥ 180 , ≥ 120 , and ≥ 90 days of prescription. In contrast, for Hispanics, the IPW-adjusted HRs associated with an average daily dose of $\geq 1,000$ mg were 1.35 ($P = 0.10$), 1.75 (95% CI, 1.38–2.21; $P < 0.01$), and 1.98 (95% CI, 1.57–2.51; $P < 0.01$) under ≥ 180 , ≥ 120 , and ≥ 90 days of prescription. For NHW, although metformin did not appear to have an overall impact on prostate cancer incidence (see Table 3), there appeared to be some variation in dose effect among metformin users: the IPW adjusted HRs associated with an average daily dose of $\geq 1,000$ mg (vs. $<1,000$ mg) were 1.35 (95% CI, 1.13–1.61; $P < 0.01$), 1.52 (95% CI, 1.35–1.71; $P < 0.01$), and 1.48 (95% CI, 1.31–1.66; $P < 0.01$) under ≥ 180 , ≥ 120 , and ≥ 90 days of prescription.

In summary, metformin use alone could reduce the excess prostate cancer incidence in Hispanics (compared with NHW) but not the excess prostate cancer incidence in AA. However, this beneficial effect of reducing ethnic disparity in prostate cancer could vary by daily dose of metformin use.

Impact of combination use of metformin and statins by race/ethnicity

In the analyses without adjusting for generalizability weights, the HR associated with combination use of metformin and statins relative to no use of either drug was 0.58 (95% CI, 0.49–0.69; $P < 0.01$) for NHW, 0.70 (95% CI, 0.58–0.86; $P < 0.01$) for AA, and 0.40 (95% CI, 0.30–0.53; $P < 0.01$) for Hispanics. The beneficial impact of combination use of metformin and statin on reduced prostate cancer incidence was greater in Hispanics compared with that in NHW ($P < 0.01$), whereas it was less in AA compared with that in NHW ($P < 0.01$).

In the analyses adjusting for generalizability weights, the HR associated with combination use of metformin and statins relative to no use of either drug was 0.58 (95% CI, 0.49–0.69; $P < 0.01$) for NHW, 0.59 (95% CI, 0.48–0.72; $P < 0.01$) for AA, and 0.32 (95% CI, 0.28–0.35; $P < 0.01$) for Hispanics. That is, when (hypothetically) equalizing the clinical characteristics between the race/ethnic groups, the impact of combination use of metformin and statins differed significantly between NHW and Hispanics but not between NHW and AA.

Metformin dose effect. The prostate cancer prevention effect associated with the combination use of metformin and statins in NHW or AA did not differ by the average daily dose of metformin. For NHW who were on the combination of metformin and statins, the IPW-adjusted HRs associated with an average daily dose of $\geq 1,000$ mg (vs. $<1,000$ mg) were 0.93 ($P = 0.86$), 1.03 ($P = 0.52$), and 1.05 ($P = 0.65$) under ≥ 180 , ≥ 120 , and ≥ 90 days of prescription of metformin; similarly, the corresponding IPW adjusted HRs for AA were 1.02 ($P = 0.95$), 0.75 ($P = 0.23$), and 0.79 ($P = 0.36$), respectively. In contrast, the prostate cancer prevention effect associated with the combination use of metformin and statins for Hispanics was significantly reduced under a higher average daily dose of metformin use. The IPW-adjusted HRs associated with an average daily dose of $\geq 1,000$ mg among Hispanics were 1.92 (95% CI, 1.00–3.66; $P = 0.05$), 2.14 (95% CI, 1.33–3.42; $P < 0.01$), 2.22 (95% CI, 1.36–3.63; $P < 0.01$) under ≥ 180 , ≥ 120 , and ≥ 90 days of prescription.

In summary, the combination use of metformin and statins could reduce the disparity in prostate cancer incidence between Hispanics and NHW. However, this ethnic disparity reduction effect could be attenuated by higher daily dose of metformin use.

Impact of combination use of metformin and finasteride by race/ethnicity

In the analyses without adjusting for generalizability weights, the HR associated with concurrent use of metformin and finasteride (compared with no use) was 0.48 (95% CI, 0.37–0.63; $P < 0.01$) for NHW, 0.58 (95% CI, 0.44–0.77; $P < 0.01$) for Hispanics, and 0.61 (95% CI, 0.37–0.99; $P = 0.02$) for AA. The impact of combination use of metformin and finasteride (compared with no use) on reduced prostate cancer incidence did not differ significantly between NHW and Hispanics ($P = 0.27$), while this impact was greater in NHW compared with that in AA ($P < 0.01$).

In the analyses adjusting for generalizability weights, HR associated with the combination use of metformin and finasteride (compared with no use) was 0.48 (95% CI, 0.37–0.63; $P < 0.01$) for NHW, 0.25 (95% CI, 0.16–0.39; $P < 0.01$) for AA, and 0.25 (95% CI, 0.20–0.30; $P < 0.01$) for Hispanics.

Metformin dose effect. The prostate cancer prevention effect associated with the combination use of metformin and finasteride did not vary by metformin daily dose in NHW nor Hispanics regardless of the length of metformin prescription. For NHW under the combination use of metformin and finasteride, the IPW-adjusted HRs of prostate cancer incidence

associated with an average daily dose of $\geq 1,000$ mg metformin (vs. $<1,000$ mg) were 1.11 ($P = 0.65$), 1.43 ($P = 0.05$), and 1.20 ($P = 0.32$) under ≥ 180 , ≥ 120 , and ≥ 90 days of prescription, and the corresponding HRs for Hispanics were 1.78 ($P = 0.19$), 1.07 ($P = 0.83$), and 1.21 ($P = 0.60$), respectively. In contrast, the effect of combination use of metformin and finasteride among AA varied by the average daily dose of metformin use under ≥ 90 or ≥ 120 days of metformin prescription, but not under longer period (≥ 180 days). The IPW-adjusted HRs associated with an average daily dose of $\geq 1,000$ mg (vs. $<1,000$ mg) of metformin among AA were 1.77 (95% CI, 0.82–3.80; $P = 0.14$), 2.27 (95% CI, 1.28–4.00; $P < 0.01$), and 2.61 (95% CI, 1.45–4.70; $P < 0.01$) under ≥ 180 , ≥ 120 , and ≥ 90 days of prescription.

In summary, the combination use of metformin and finasteride could reduce the excess prostate cancer incidence in both Hispanics and AA. This beneficial effect of reducing ethnic disparity in prostate cancer did not vary by daily metformin dose. However, the racial disparity reduction effect could be attenuated by higher daily dose of metformin use.

Impact of metformin on prostate cancer grade

We conducted further Cox regression analyses to examine the impact of metformin on high- versus low-grade prostate cancer among prostate cancer patients. In this study of men with T2D, those with prostate cancer and age similar to those in the Prostate Cancer Prevention Trial (PCPT), 50.4% had high-grade cancer, whereas the PCPT, consisting of 8% diabetics, found 40% high-grade cancer cases. The high grade prostate cancer prevalence in our study is also consistent with Abdollah and colleagues' study (2), in which the prevalence of high-grade prostate cancer was 49% in patients with diabetes. Similar metformin effects were found in the high- and low-grade cases.

Covariates associated with prostate cancer incidence by race/ethnicity

Covariates adjusted for in the Cox regression analyses and their associations with prostate cancer incidence for each race/ethnic group are shown in Table 4. Older age was associated with increased prostate cancer incidence, and the magnitude was similar between race/ethnic groups. Increased levels of PSA, BMI, and LDL over time were also associated with increased prostate cancer incidence for all race/ethnic groups. However, the magnitudes of these associations were stronger in Hispanics than those in non-Hispanics. Higher comorbidity score and decreased HbA1c level during the study period were associated with increased prostate cancer incidence in NHW but not non-NHW.

Discussion

In this cohort of 76,733 male veterans with T2D who were free from cancer and cardiovascular disease at baseline and remained insulin and thiazolidinedione naïve during FY2003–FY2012, we found that under no use of metformin, both AA and Hispanics were associated with a higher prostate cancer incidence than NHW men after adjusting for covariates (Table 2). Our finding of the higher prostate cancer incidence in AA was consistent with the data in the general population, yet our observation of higher prostate cancer incidence among Hispanic men contradicts the reported lower risk for Hispanic men in the general population (1). However, our results are consistent with those reported by Waters and colleagues (4). The reason for the higher prostate cancer risk in Hispanic men who are diabetic is not completely known. On the basis of prior studies in patients with T2D, one potential explanation for the impact of diabetes on prostate cancer disparity between race/ethnic groups could be due to worse metabolic outcomes (e.g., higher HbA1c or cholesterol levels) among Hispanics or AA (compared with NHW; refs. 18, 19), which subsequently led to chronic inflammation, hyperinsulinemia and dyslipidemia and then increased the risk of prostate cancer. In contrast, in our cohort, among nonusers of metformin, glycemic control seemed similar between race/ethnic groups, and LDL was slightly higher in AA and Hispanics (see Table 1). As no direct measures of chronic inflammation or hyperinsulinemia were available in our study, our IPW-adjusted analyses implied that the racial/ethnic disparity could partly be due to chronic inflammation or hyperinsulinemia that was not mediated via glycemic control. The possibility of screening bias due to ethnic differences in PSA levels is not supported by our data as they were similar between NHW and Hispanic men.

Results from this study showing that a reduction in prostate cancer incidence due to metformin use alone or in combination with statins was greater in Hispanics compared with NHW support the hypothesis that metformin alone or in combination with statins could potentially reduce ethnic disparity in prostate cancer incidence. As the impact of statins did not differ by race/ethnicity, the superior impact of the combination use of metformin and statins in Hispanics could be driven by the superior impact of metformin use in Hispanics. In addition, the greater reduction in prostate cancer incidence due to combination use of metformin and finasteride in Hispanics or AA (relative to NHW) suggests that metformin in combination with finasteride could reduce racial/ethnic disparity in prostate cancer incidence. Like prior studies (6–9), there appeared to be an add-on beneficial effect of finasteride or statins to metformin on reduced prostate cancer incidence in this study (Fig. 1)

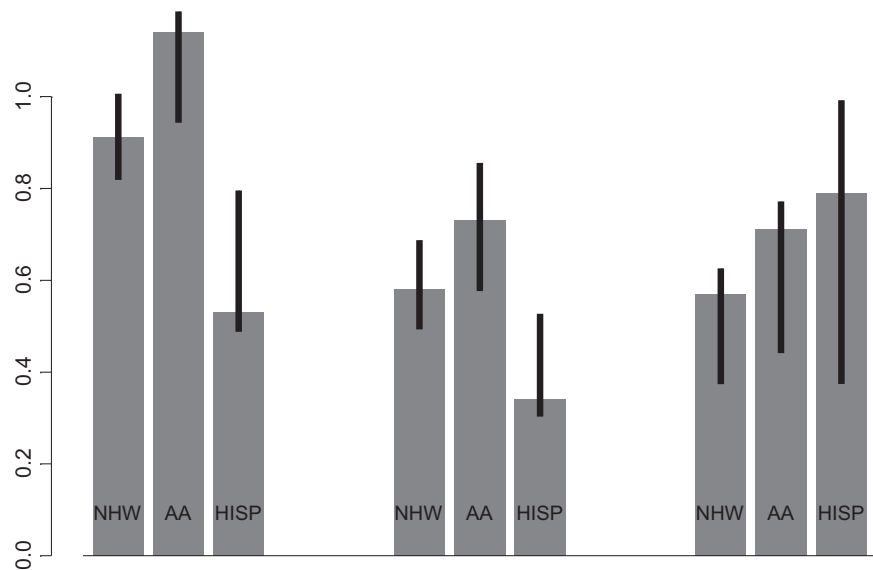
Table 4. HR of PCa incidence associated with covariates by race/ethnicity

	NHW HR	P	AA HR	P	Hispanics HR	P
Age	1.026	<0.0001	1.026	<0.0001	1.021	0.0031
Charlson comorbidity	1.044	<0.0001	0.999	0.9564	0.995	0.8429
Δ A1C	0.942	0.0153	1.004	0.9115	0.957	0.6213
Δ LDL	1.003	<0.0001	1.002	0.0045	1.011	0.0006
Δ BMI	1.009	<0.0001	1.015	<0.0001	1.135	0.0009
PSA	1.002	<0.0001	1.003	<0.0001	1.048	<0.0001

Abbreviations: AA, African American; NHW, non Hispanic white.

Figure 1.

HRs (Y-axis) associated with use of metformin alone, combination of metformin with statins, and combination of metformin with finasteride (relative to no use of metformin, statins, nor finasteride) by race/ethnicity (X-axis) adjusting for covariates, propensity score of metformin use but without generalizability weights. Abbreviations: AA, African American; HISP, Hispanics; NHW, non Hispanic white.



However, the heterogeneous impacts of metformin (dose and duration) seen in this study remain to be confirmed by prospective studies.

Our finding of a greater impact of metformin on prostate cancer prevention in Hispanics or AA compared with NHW could be a reflection of the emerging evidence that approximately 30% of metformin response is heritable (29, 30). Although drug response in these studies was measured in terms of metabolic measures, such as HbA1c, preclinical studies have shown significant physiologic alterations in metformin transport that can affect its bioavailability in general, and these genetic variants significantly differ in allele frequency by ethnic group (10). Therefore, pharmacogenomics of metformin response in terms of prostate cancer prevention warrants further investigation as a plausible explanation for the differences observed.

Our study found older age, increased PSA, BMI, and LDL to be associated with increased prostate cancer incidence across all race/ethnic groups (see Table 4), suggesting that the management of PSA, BMI, and LDL could be crucial for prostate cancer prevention in men with T2D. As metformin could be associated with PSA, BMI, or LDL in some of the race/ethnic groups (Supplementary Table S1), whether the greater prostate cancer prevention benefit by metformin seen in AA and Hispanics with T2D was mediated through PSA, BMI, or LDL remains to be seen. Increased HbA1c was associated with decreased prostate cancer incidence only among NHW, which is consistent with the lower prostate cancer prevalence in diabetics reported in the literature (31). However, it is not clear about the null association between HbA1c and prostate cancer among non-NHW men with T2D. Comorbidity was associated with increased prostate cancer incidence only among NHW but not non-NHW, which could be due to the larger sample size in NHW or the lower likelihood of aggressive tumors among NHW that intrinsically rendered comorbidities more prognostically important (32).

The more favorable metformin impact in Hispanics versus non-Hispanics found in this study is unlikely to be subject to prostate cancer detection bias as we found no association between metformin use with PSA level or benign prostatic hyperplasia (BPH) diagnosis in any race/ethnic group. The null

association between metformin use and PSA level was also reported in Randazzo and colleagues' recent study (33), and the null association between metformin use and BPH diagnosis was seen in Murff and colleagues' large retrospective VA study (34).

There are limitations to this historical observational study. The duration of T2D and the starting dates of nonpharmacologic treatments for T2D among patients who were nonusers of glucose-lowering medications, two key variables for our analyses, were not available to us. However, all race/ethnic groups in our study cohort appeared to have similar T2D history to the extent that all patients were free from cancer and cardiovascular disease at baseline, insulin naïve, and with well glycemic control (with a slightly greater HbA1c level among the metformin users). Thus, the interpretability of the impacts associated with race/ethnicity and metformin use derived from this study might depend on the similarity of the diabetes duration between the comparison groups and the accuracy of the starting date used in the analyses. In addition, due to the limited cancer grade data available in the VA cancer registry, our finding of metformin's impact on prostate cancer grade should be further validated. Finally, to strengthen the causal interpretability of the result as in this nonrandomized study, we employed inverse propensity score weighting methods to balance covariates between comparison groups. Although these adjusted results could shed light on the biological explanation of variation in metformin response, further sensitivity analyses are necessary to assess the impact of unmeasured confounding on estimation bias (35).

In conclusion, our study is the first to show that in men with T2D, metformin use could potentially reduce racial/ethnic disparity in prostate cancer incidence. Given that metformin is currently a first-line choice to treat T2D, these results may appear inconsequential to clinical management. However, as with all antidiabetic drugs, the use of metformin may gradually fade, especially as other glycemia-lowering drugs, such as those in the incretin pathway, come into favor. It will be important to thoroughly examine the potential pleiotropic effects of metformin to maximize the benefits given its well-defined safety profile and generic availability. It will also be important to confirm these results in clinical trials designed to examine

ethnic-specific effects especially given the historical underrepresentation of the growing Hispanic population and the potential effect of ethnic-specific genetic variation on drug and/or therapeutic response. Likewise, investigating other new T2D treatments with respect to reducing race/ethnic disparity in prostate cancer incidence will be beneficial for clinical management for diabetic and possibly prediabetic men.

Disclosure of Potential Conflicts of Interest

D. Mahalingam is a consultant/advisory board member for Baxalta, Denreon, Genspera, and Sanofi. No potential conflicts of interest were disclosed by the other authors.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.-P. Wang

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.-P. Wang, D.M. Lehman, J.G. Kuhn, D. Mahalingam, S. Weitman, C. Lorenzo, E.A. Stuart, I.M. Thompson

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.-P. Wang

Study supervision: C.-P. Wang, A.G. Ramirez

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