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Major adverse cardiovascular events among Black and White Veterans receiving androgen deprivation therapy for prostate cancer: a retrospective cohort study

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Abstract

Background Androgen deprivation therapy (ADT) is the cornerstone treatment strategy for men diagnosed with high-risk prostate cancer (PC) but may increase risk for major adverse cardiovascular events (MACE). We examined whether men treated with ADT and radiation therapy (ADT + RT) developed MACE at a higher rate than men receiving RT alone. Secondly, we sought to determine if Black men receiving RT + ADT developed MACE at a higher rate than White men.

Methods This retrospective cohort study examined time to diagnosis of MACE among Veterans with PC. We used a 1:1 propensity score matching process to determine whether treatment type (ADT + RT vs. RT alone), race (Black vs. White men) or having a previous diagnosis of a cardiometabolic disease (CMD) were associated with differences in the rate at which men develop MACE.

Results Veterans with PC were White (68%) and Black (32%). At PC diagnosis, the mean age was 65.9 years. The majority had stage 2 disease (83.0%) classified as intermediate risk (43.1%). Treatment-matched models showed men receiving ADT + RT were less likely to develop MACE when they no pre-existing CMD. Men treated with ADT + RT or RT alone had significantly increased risks of MACE is they had pre-existing CMD. Black men had the same risk of MACE as non-Hispanic Whites.

Conclusions Preexisting CMD and multimorbidity are significant risks for MACE among men treated for PC within the VA healthcare system whether treated with ADT + RT or with RT alone, highlighting the importance pretreatment optimization of comorbidities.

Keywords Androgen deprivation therapy, Major adverse cardiovascular events, Cardiometabolic disease, Prostate cancer, Survivorship, Veterans

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Background

Prostate cancer (PC), the most common malignancy in American men [1], has excellent long-term survival in those with localized disease (> 99% at 5 years); [1] however, men with advanced, recurrent, or metastatic disease have poorer survival. The cornerstone treatment for high-risk disease includes androgen deprivation therapy (ADT), often combined with radiation therapy (RT). The National Comprehensive Cancer Network (NCCN) defines high-risk disease as a clinical stage of T3 or T4 or Gleason score over 7 or PSA over 20 ng/ml. ADT leads to significant adverse effects such as increased adipose tissue, loss of lean muscle and bone mineral density, insulin resistance, dyslipidemia, systemic inflammation, type 2 diabetes (T2D) [2, 3] and cardiovascular disease (CVD) [4–7]. Many men with PC also have multiple cardiovascular risk factors [8]. Moreover, disparities exist in PC-mortality rates between Black and non-Hispanic White (NHW) men, with Black men being more than twice as likely to die of PC [9].

Whether there are differences in the rate at which Black and White men (as reflecting social drivers of health) develop major adverse cardiovascular events (MACE) following treatment with ADT for high-risk PC and within the VA healthcare setting is unclear. In this study, we define MACE as a composite of CV death, myocardial infarction, or ischemic stroke. Cardiovascular and metabolic comorbidities often share causes, including poor diet and physical inactivity. For example, MACE,, type 2 diabetes, hypertension, circulatory and vascular diseases may be linked to obesity and aging-related changes in body composition. Specifically, increases in visceral and intramuscular fat alongside the loss of lean muscle may cause metabolic disruption [10], inflammation, and insulin resistance [11] all worsened by ADT [12].

The goals of this study were to: (1) examine and compare the rates at which Veterans treated with ADT and RT (ADT + RT) develop MACE compared to those treated with RT alone; (2) among those treated with ADT + RT, examine and compare differences in the rate at which Black and White men develop MACE; and (3) identify risk factors for MACE among Black and White US Veterans. The U.S. Veterans Affairs (VA) Healthcare System provides a unique opportunity to address these questions by allowing for the examination of a large cohort of men from across the country with similar access to healthcare services who can be matched by race and geographic location.

Methods

Data source

The analytic sample for this retrospective cohort study was created from U.S. VA Healthcare System data on men diagnosed with PC. The study was approved by the Central Virginia VA Healthcare system institutional review board with a waiver of the informed consent due to it being a retrospective cohort analysis. VA medical records, cancer registry data, and outpatient and pharmacy records were used to derive variables of interest. Figures 1 and 2 depict a study flow diagrams for inclusions and exclusions. The sample included men diagnosed and treated for PC at VA hospitals between 2000 and 2015. Primary exclusions were for non-PC index cancers ($n = 45{,}045$), additional cancer diagnoses within 1 year ($n = 3{,}853$), and missing birth or diagnosis date ($n = 201$). Men were also excluded if they received chemotherapy. We ensured a minimum of 5 years of post-diagnosis data, excluding 50,207 patients, leaving a final analytic cohort of 39,580 patients.

The primary outcome was time to MACE (cardiovascular death, myocardial infarction, or ischemic stroke) up to March 26, 2021. Patients were censored at death (non-CV) or study end. The main covariates were treatment type (ADT + RT vs. RT alone) and self-identified race (Black vs. White). Other covariates included age at diagnosis, Hispanic ethnicity (yes, no), marital status (married/partnered vs. single), BMI (underweight/normal, overweight, obese), rurality (rural, non-rural from 2010 Rural-Urban Commuting Area Codes (RUCA) [13]), National Comprehensive Cancer Network (NCCN) Risk (*low*: stage < T2a, Gleason score < 7 and prostate-specific antigen (PSA) < 10; *intermediate*: stage T2b-T2c or a Gleason score of 7 or PSA between 10 and 20; *high*: stage of T3 or T4 or Gleason score over 7 or PSA over 20 ng/mL; *unknown*), diagnosis year (2000–2005, 2005–2010, 2010–2015), American Joint Commission on Cancer (AJCC) stage (I-IVa), Elixhauser Score 1 year pre-diagnosis categorized (0, 1 or > 1) [14, 15], and preexisting cardiometabolic disease (CMD) ≤ 1 year prior to diagnosis. CMD was defined as having 1 or more (yes, no) of the following as determined by ICD9/ICD10 codes: abnormal glucose, metabolic diseases, circulatory system or ischemic heart disease, hypertensive disease, cerebral and peripheral vascular diseases within 1 year prior to treatment to be indicative of having preexisting CMD. Missing demographics were assumed to be missing at random (< 2% missing), so complete case analysis was used. Stage and risk were considered missing not at random and were kept in analysis with missing included as a separate category given patients with higher stage/risk are more likely to be missing than those with lower stage/risk.

NCCN risk was calculated from individual T/M stages, and metastatic cancer patients were excluded. Clinical data from cancer registries, pathology data, VA lab test servers, and pharmacy records were used to fill in missing values. Comorbidities were assessed using ICD9/ICD10 codes and Elixhauser scores [16] from the year prior to diagnosis.

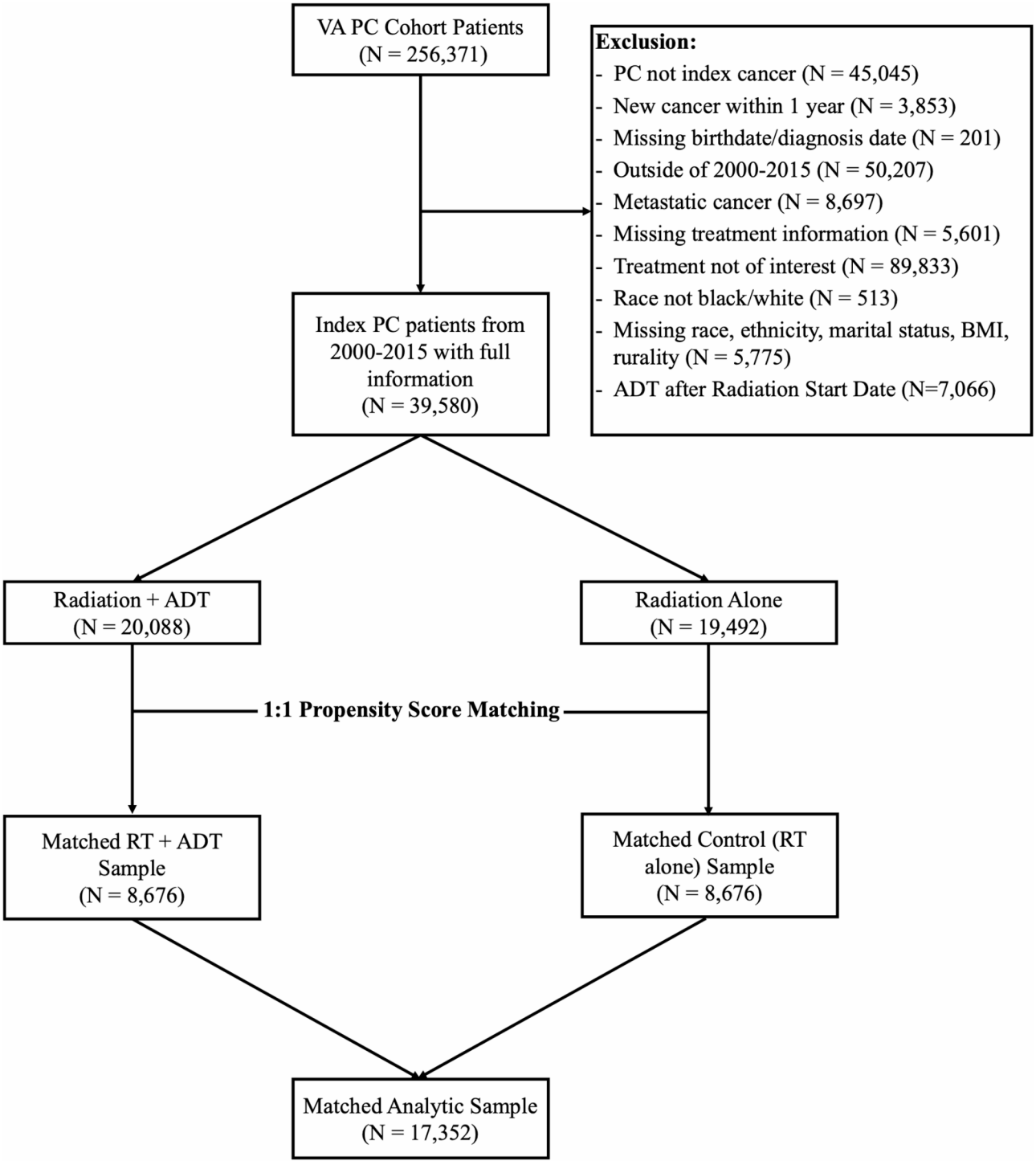


Fig. 1 Treatment matching

Men diagnosed with prostate cancer and treated within the U.S. Veterans Affairs Healthcare System between 2000 and 2015 were identified from patient records. Medical records were matched with cancer registry and pharmacy data to derive variables of interest. Following exclusions, men who received androgen deprivation therapy with radiation therapy and those who received radiation alone. A 1:1 propensity score matching process resulted in a total analytic sample of 17,352 men

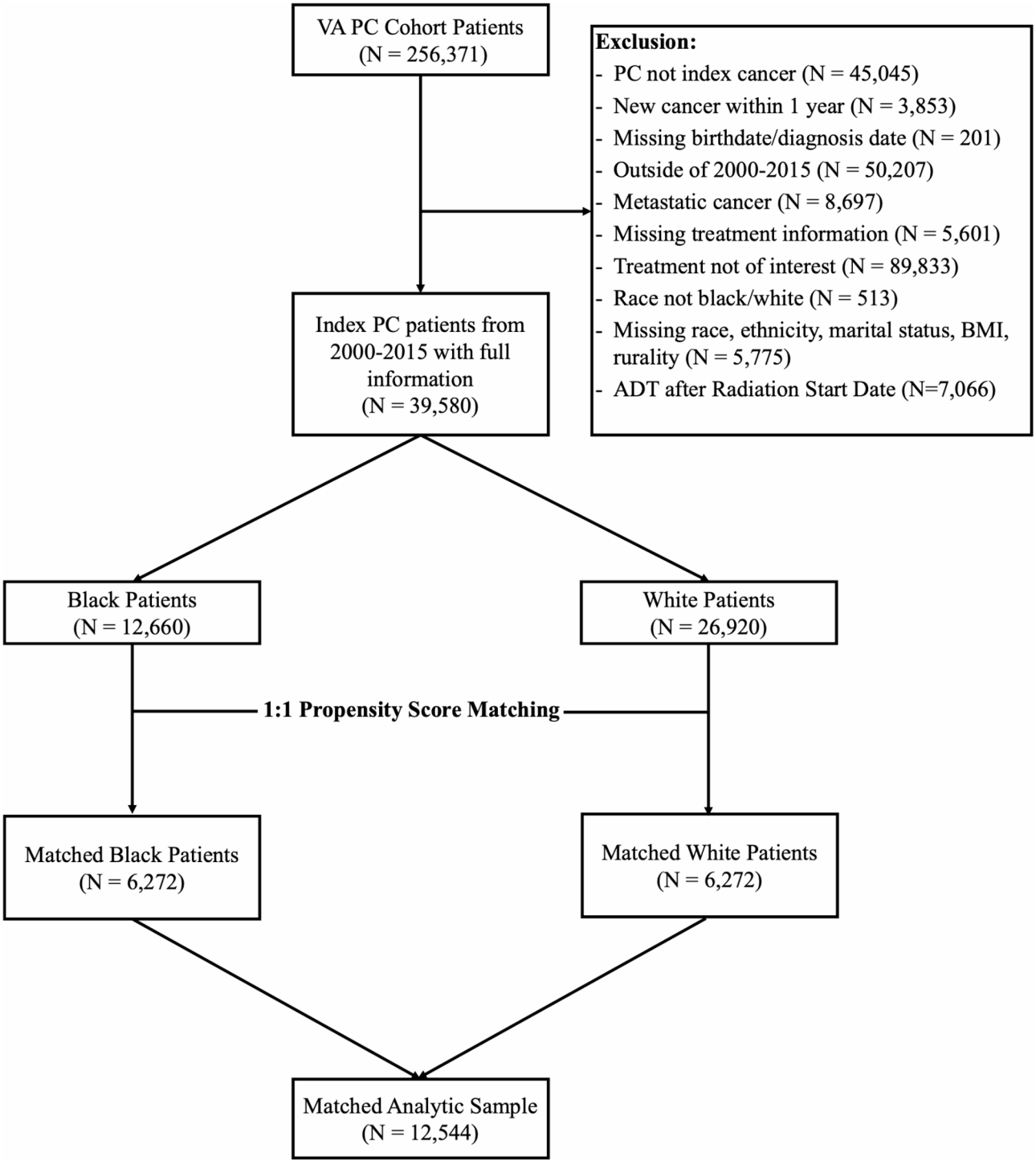


Fig. 2 Race-matching

Men diagnosed with prostate cancer and treated within the U.S. Veterans Affairs Healthcare System between 2000 and 2015 were identified from patient records. Medical records were matched with cancer registry and pharmacy data to derive variables of interest. Following exclusions, men who received androgen deprivation therapy with radiation therapy and those who received radiation alone. A 1:1 propensity score matching process resulted in a total analytic sample of 12,544 men

The primary goal of our study was to compare MACE rates in men treated with ADT + RT vs. RT alone and secondarily to assess whether there were disparities in MACE rates by race in an equal-access U.S. healthcare setting.

Statistical analysis

MACE prevalence was calculated as the percent of diagnosed patients. Covariates were summarized overall and by treatment group, with continuous variables reported as means (SD) and categorical variables as frequencies (%). ANOVA and Chi-Square tests were used to check for differences in covariates between treatment groups before matching. Flowcharts in Figs. 1 and 2 show sample retention through exclusions and matching.

The main covariates (treatment type and race) were used to create two matched datasets, one for treatment on MACE and one for race. Matching was done through 1-to-1 propensity score matching using the greedy matching method [17], where propensity scores were calculated using all the covariates listed other than the one being matched on. When matching on treatment, we also forced matches to have the exact same station, CMD diagnosis within the year leading up to PC diagnosis, age group (within 5 years), risk, race, and Hispanic origin. When matching on race, we also matched on these same variables except race. Different caliper values were tested until matches appeared close across all covariates. A plot of the standardized differences was used to check the quality of matching (Fig. 3).

For the primary analysis, multivariable Cox proportional hazard models were used to model the outcome (time to MACE). Separate models were compared using the full sample and the matched samples. The interaction between treatment and preexisting CMD tested whether ADT had a different association with MACE diagnoses depending on whether the patient had a recent cardiometabolic event. Using the matched data, stratified Cox proportional hazard models were fit for those with and without preexisting CMD diagnoses. The stratified models were used to adjust for the confounding effect of preexisting CMD diagnoses on the rest of the covariates in the model.

The association of race with the rate of MACE was also tested with a Cox proportional hazard model using race-matched data. This matched model was compared to a model with the full sample. The interaction between race and treatment type tested whether treatment type had a differing association with the outcome depending on race. Stratified Cox proportional hazard models were created for Black and White patients to examine race specific factors that lead to increased risk of MACE.

The overall effect of rurality on rate of MACE events was tested in the full sample, treatment-, and race-matched models. In the stratified models, we also examined the effect of rurality within levels of pre-existing cardiometabolic conditions and race. All analyses were performed using SAS 9.4 where an alpha level of 0.05 was used for all significance tests.

Results

Sample characteristics

Table 1 summarizes the cohort demographics and clinical characteristics. The median follow-up time was 3,495 days for the overall sample, 3,503 days for the treatment matched sample, and 3,364 days for the race matched sample. Supplemental Table 1 provides a breakdown of demographics and clinical characteristics by race. At diagnosis, men in our cohort averaged 65.9 years (median = 66.0), 32.0% were Black and 3.9% were of Hispanic origin. A similar number of men were married/partnered (49.6%) as single (50.4%), while the majority

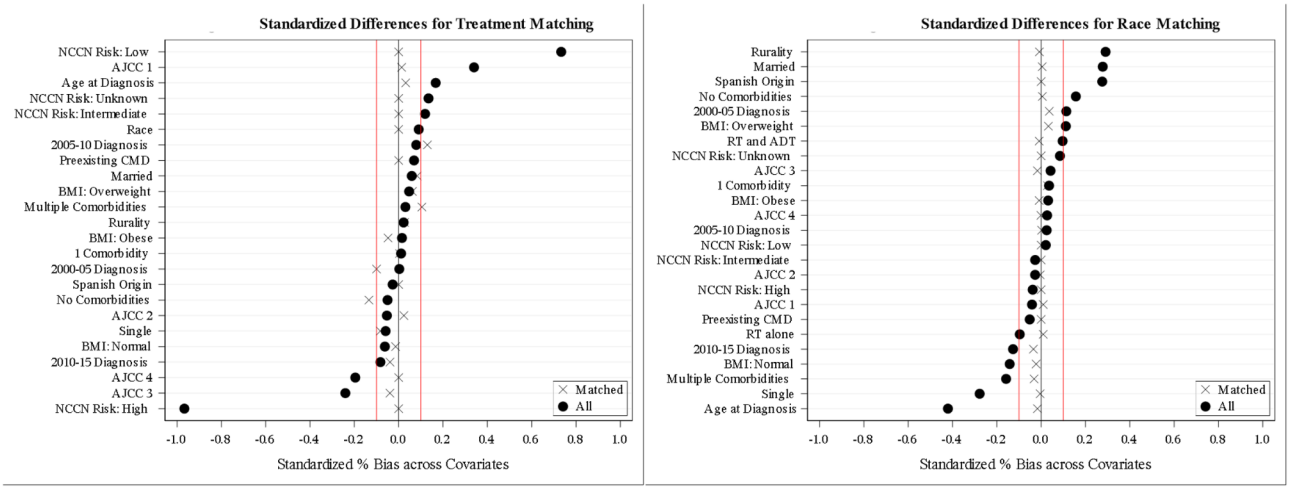


Fig. 3 Standardized difference plots for treatment and race matching

Table 1 Sample characteristics

	Treatment Type			
	RT + ADT (N = 20,088)	**RT alone (N = 19,492)**	**Total (N = 39,580)**	***P*-value**
Age				
Age: Mean (SD)	66.5 (7.46)	65.2 (6.97)	65.9 (7.25)	< .0001[1]
Age: Median (Range)	66.0 (40.0, 92.0)	65.0 (39.0, 92.0)	66.0 (39.0, 92.0)	< .0001[3]
Race, n (%)				< .0001[2]
Black	6,841 (34.1%)	5,819 (29.9%)	12,660 (32.0%)	
White	13,247 (65.9%)	13,673 (70.1%)	26,920 (68.0%)	
Hispanic Origin, n (%)				0.0065[2]
Hispanic	846 (4.2%)	717 (3.7%)	1,563 (3.9%)	
Non-Hispanic	19,242 (95.8%)	18,775 (96.3%)	38,017 (96.1%)	
Marital Status, n (%)				0.0004[2]
Married	9,680 (48.2%)	9,967 (51.1%)	19,647 (49.6%)	
Single	10,408 (51.8%)	9,525 (48.9%)	19,933 (50.4%)	
BMI, n (%)				< .0001[2]
Normal/Underweight	6,803 (33.9%)	6,032 (30.9%)	12,835 (32.4%)	
Overweight	6,603 (32.9%)	6,840 (35.1%)	13,443 (34.0%)	
Obese	6,682 (33.3%)	6,620 (34.0%)	13,302 (33.6%)	
Rural, n (%)				0.0274[2]
Yes	1,965 (9.8%)	2,037 (10.5%)	4,002 (10.1%)	
No	18,123 (90.2%)	17,455 (89.5%)	35,578 (89.9%)	
Stage (AJCC), n (%)				< .0001[2]
I	564 (2.8%)	2,226 (11.4%)	2,790 (7.0%)	
II	16,870 (84.0%)	15,979 (82.0%)	32,849 (83.0%)	
III	1,036 (5.2%)	199 (1.0%)	1,235 (3.1%)	
IV	524 (2.6%)	55 (0.3%)	579 (1.5%)	
Unknown	1,094 (5.4%)	1,033 (5.3%)	2,127 (5.4%)	
NCCN Risk, n (%)				< .0001[2]
Low	1,704 (8.5%)	7,297 (37.4%)	9,001 (22.7%)	
Intermediate	8,071 (40.2%)	8,978 (46.1%)	17,049 (43.1%)	
High	9,156 (45.6%)	1,404 (7.2%)	10,560 (26.7%)	
Unknown	1,157 (5.8%)	1,813 (9.3%)	2,970 (7.5%)	
Diagnosis year, n (%)				< .0001[2]
00–05	5,256 (26.2%)	5,123 (26.3%)	10,379 (26.2%)	
05–10	7,234 (36.0%)	7,767 (39.8%)	15,001 (37.9%)	
10–15	7,598 (37.8%)	6,602 (33.9%)	14,200 (35.9%)	
Elixhauser score, n (%)				< .0001[2]
0	4,187 (20.8%)	3,671 (18.8%)	7,858 (19.9%)	
1	7,677 (38.2%)	7,551 (38.7%)	15,228 (38.5%)	
> 1	8,224 (40.9%)	8,270 (42.4%)	16,494 (41.7%)	
Preexisting CMD, n (%)				0.6154[2]
Yes	4,104 (20.4%)	4,022 (20.6%)	8,126 (20.5%)	
No	15,984 (79.6%)	15,470 (79.4%)	31,454 (79.5%)	
Abnormal Glucose	1759 (8.8%)	1565 (8.0%)	3324 (8.4%)	0.0091[2]
Circulatory System/ Ischemic Heart Disease	184 (0.9%)	169 (0.9%)	353 (0.9%)	0.6046[2]
Hypertensive Disease	3387 (16.9%)	3411 (17.5%)	6798 (17.2%)	0.0921[2]
Cerebral and Peripheral Vascular Diseases	144 (0.7%)	141 (0.7%)	285 (0.7%)	0.9388[2]

Note: [1]ANOVA F-test *p*-value; [2]Chi-Square *p*-value; [3] Kruskal-Wallis *p*-value

RT: Radiation Therapy; ADT: Androgen Deprivation Therapy; RT: Radiation therapy; BMI: Body Mass Index; RUCA: Rural-Urban Commuting Area; NCCN: National Comprehensive Cancer Network; CMD: Cardiometabolic Disease; AJCC: American Joint Commission on Cancer

were overweight (34.0%) or obese (33.6%). The most common diagnosis year group was 2005–2010 (37.9%). Most patients lived in non-rural zip codes (89.9%). The most common NCCN risk group was intermediate (43.1%) followed by high (26.7%), low (22.7%), and unknown (7.5%). The most common AJCC stage was II (83.0%) followed by stage I (7.0%), unknown (5.4%), stage III (3.1%), then stage IV (1.5%). Most patients had 1 (38.5%) or more (41.7.6%) comorbidities, and 20.5% had a CMD diagnosis in the year before diagnosis. Overall, 233 men (0.6%) were diagnosed with a MACE at some point following PC diagnosis.

Matching on treatment and race

There were 8 676 patients in each treatment-matched group and 17 352 in the treatment-matched analytic sample (Fig. 1). Each race-matched group had 6 272 patients and 12 544 in final analytic sample (Fig. 2). Before matching, the ADT + RT group had a higher proportion of patients who were older, with higher risk and stage, and less preexisting CMD. Propensity score matching balanced these covariates between so that patient data used for analysis were similar across treatment groups. The biggest differences between Black and White patients prior to matching were rurality, Hispanic origin, marriage, comorbidities, and age. Figure 3 shows the standardized difference plots for each of the matching procedures and the closeness of the matched samples across the other covariates.

Examining MACE by treatment

Table 2 shows hazard ratios from Cox proportional hazard models (non-matched and matched samples) examining the effect of treatment on MACE events while accounting for covariates. The survival curves for treatment-matched models shows the interaction between having a pre-existing CMD diagnosis and treatment type, which was significant in both the non-matched sample and the matched sample (Fig. 4). Men having treatment with ADT + RT were less likely to have a MACE event when they had no pre-existing CMD. Of note, among the other covariates, having a pre-existing CMD was associated with a large hazard ratio in both the non-matched (RT alone: 2.7, ADT + RT: 4.4) and matched (RT alone: 2.5, ADT + RT: 4.2) models. Rurality was not significantly associated with time to MACE in either model ($p > .05$).

Supplemental Table 2 shows hazard ratios from the multivariable Cox proportional hazard models stratified on pre-existing CMD. In the model with no preexisting CMD, those with ADT + RT experienced MACE at a lower rate than those on RT alone (HR: 0.46, CI: 0.27, 0.78). Patients diagnosed with PC in the years 2005–2010 and 2010–2015 were less likely to have a MACE event than those diagnosed in 2000–2005 if they had no preexisting CMD (HR: 0.37, CI: 0.21, 0.68) and (HR: 0.16, CI: 0.07, 0.35), respectively, but there was no association if they had preexisting CMD. Rurality was not significant in either of the stratified models ($p > .05$).

Examining MACE by race

Race-matched data was used to examine the association of race with time to MACE events during the study follow-up period (Fig. 4). Black (solid lines) and White men (dotted lines) experienced similar time to MACE whether receiving RT + ADT (blue) or RT alone (red). Table 3 shows hazard ratios for the race-matched multivariable Cox proportional hazards (non-matched and race-matched) models. The race by treatment interaction was not significant in either model. There were no significant associations found between race and MACE events. The other covariates being adjusted for had similar hazard ratios to those from the treatment-matched model. Rurality did not have a significant association with MACE. We used the race-stratified models, shown in supplemental Tables 3, to examine race-specific risk factors for MACE events during follow-up. Treatment type was not significant in either of the models. Black men were more likely to develop a MACE when they had pre-existing CMD (HR: 4.21while White men with preexisting CMD were not. Conversely, White men with intermediate (HR: 4.05, CI: 1.21, 13.50) or with unknown (HR: 5.42, CI: 1.15, 25.55) NCCN risk were more likely to have a MACE event than White patients with low NCCN risk; however, these differences were not found in Black men. White men had slightly more ischemic heart disease than Black men, therefore it is possible these men had intermediate risk PC and thus received more aggressive treatment placing them at further risk of MACE, albeit relatively small compared to non-Veterans as shown in other recent studies. Both Black (HR: 0.23, 95% CI: 0.07, 0.77) and White (HR: 0.23, 95% CI: 0.08, 0.71) patients diagnosed in 2010–2015 had a lower rate of MACE events than those diagnosed in 2000–2005.

Discussion

In this study, we found that the majority of Veterans treated with ADT + RT had intermediate or high-risk disease while those receiving RT alone had low to intermediate risk disease. Approximately 70% of men were overweight or obese and 20% had been diagnosed with a cardiometabolic condition prior to their PC diagnosis. In this study, men who had a pre-existing CMD and who were treated with ADT + RT developed MACE at ~4 times the rate than men without a CMD. Men treated with ADT + RT and who had more than 1 comorbidity also experienced MACE at twice the rate than men with no comorbidities. Further, Black men who had a pre-existing CMD also developed MACE at 4.2 times the

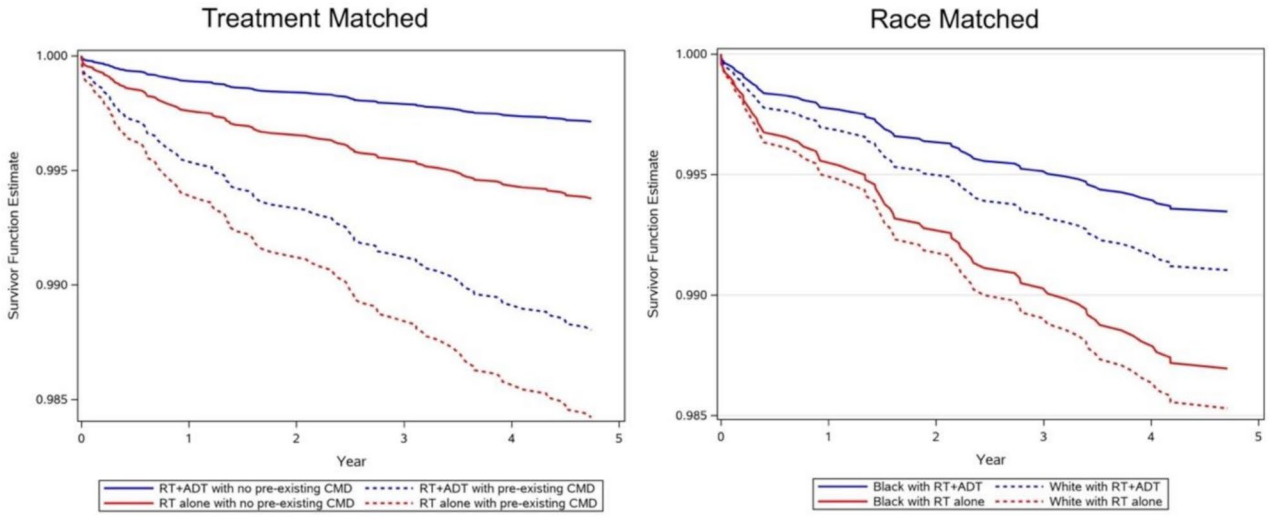
Table 2 Hazard ratios of multivariable Cox proportional hazard models (treatment matched)

Covariate	Hazard Ratio Estimates					
	Non-Matched			Matched		
	Point Estimate	95% Confidence Limits			Point Estimate	95% Confidence Limits
Age at diagnosis	**1.028**	**1.009**	**1.048**	1.014	0.983	1.046
Race						
Black vs. White	1.194	0.897	1.589	1.137	0.729	1.772
Hispanic Origin						
Hispanic vs. non-Hispanic	1.500	0.879	2.559	1.553	0.665	3.625
Marital Status						
Married/partnered vs. Single	1.000	0.769	1.299	0.884	0.593	1.316
BMI						
Obese vs. Normal/Underweight	0.884	0.642	1.217	0.979	0.608	1.577
Overweight vs. Normal/Underweight	0.794	0.578	1.090	0.781	0.477	1.278
Rural - Urban (RUCA)						
Rural vs. Urban	0.931	0.596	1.453	1.137	0.602	2.146
Stage (AJCC)						
II vs. I	1.016	0.472	2.188	0.776	0.207	2.913
III vs. I	0.8161	0.279	2.736	0.484	0.043	5.390
IV vs. I	1.725	0.490	6.073	0.000	0.000	Inf
Unknown vs. I	0.523	0.179	1.527	0.410	0.071	2.359
NCCN Risk						
High vs. Low	**1.608**	**1.009**	**2.562**	1.094	0.485	2.471
Intermediate vs. Low	**1.573**	**1.071**	**2.310**	1.333	0.733	2.424
Risk: Unknown vs. Low	1.189	0.664	2.128	0.684	0.265	1.767
Diagnosis Year						
05–10 vs. 00–05	**0.489**	**0.352**	**0.679**	**0.428**	**0.264**	**0.694**
10–15 vs. 00–05	**0.312**	**0.211**	**0.461**	**0.239**	**0.133**	**0.429**
Elixhauser Score						
1 vs. 0	1.179	0.755	1.840	2.022	0.979	4.176
> 1 vs. 0	**1.897**	**1.240**	**2.903**	**2.221**	**1.075**	**4.588**
RT + ADT vs. RT alone						
(No pre-existing CMD)	**0.532**	**0.365**	**0.774**	**0.461**	**0.271**	**0.783**
(With pre-existing CMD)	0.886	0.584	1.343	0.757	0.392	1.462
Preexisting CMD Yes vs. No						
(RT alone)	**2.655**	**1.828**	**3.856**	**2.543**	**1.448**	**4.467**
(ADT + RT)	**4.423**	**2.959**	**6.611**	**4.178**	**2.146**	**8.135**

Note: RT: Radiation Therapy; ADT: Androgen Deprivation Therapy; RT: Radiation therapy; BMI: Body Mass Index; RUCA: Rural-Urban Commuting Area; NCCN: National Comprehensive Cancer Network; CMD: Cardiometabolic Disease; AJCC: American Joint Commission on Cancer, **Bold** typeface = Statistically significant

rate at which Black men without CMD highlighting the importance of CVD screening and management for all men diagnosed with PC. This may be particularly important given a separate analysis found that only 68% of Veterans with PC received comprehensive CV screening and of those men, over half had uncontrolled risk factors [18]. A lower rate of MACE in men diagnosed with PC more recently, while controlling for age suggests improved management of CMD risk factors. In race-matched models, Black men developed MACE at a similar rate as White men. For all men, across both treatment- and race-matched models, having pre-existing CMD was associated with a higher rate of developing MACE.

Overall, the rate of MACE in this study (0.6%) was low while other recent analyses have reported rates between 3.9 and 5.2% [19]. This large non-Veteran dataset, was also able to examine MACE rates between patients seen in oncology vs. urology settings and may reflect differences for patients who are not seen in a more accessible healthcare setting like the VA healthcare system. In the PRONOUNCE Trial, men with known CVD were randomly assigned to receive either a GnRH agonist (leuprolide) or antagonist (degralix). Over 12 months it was found that a low proportion of men receiving the agonist (4.1%) or the antagonist (5.5%) experienced MACE, however the men in this trial were optimally managed for cardiometabolic and cardiovascular risk. ADT has been



Note: Survival functions were estimated with multivariable Cox proportional hazard models. Survival was estimated at the mean age, 1 Elixhauser comorbidity, 2005-2010 diagnosis year, intermediate risk, AJCC stage 2, married, and non-Hispanic ethnicity. The treatment matched model included the interaction between treatment and pre-existing CMD with white race. The race matched model included the interaction between race and treatment with pre-existing CMD.

Fig. 4 Adjusted survival curves for treatment matched and race matched samples

found in previous studies to be associated with increased risk of cardiovascular events [20, 21] and diabetes [22]. One recent study found that ADT + RT led to higher rates of stroke, transient ischemic attack and deep vein thrombosis in Veterans [7]. However, we did not observe an association when comparing receipt of ADT + RT versus RT alone unless men had multiple comorbidities, and CMD morbidity specifically. For example, in the Tsai et al. study, Veterans had a higher risk for developing T2D if they received GnRH agonists compared to no treatment. In this study, men diagnosed more recently (2010–2015) had lower risk of MACE, perhaps reflecting improved attention to CV risk following PC treatment. Yet, recently published data from the RADICAL-PC trial reported a high prevalence of CVD risk factors among men with PC [8]. A separate study among Veterans with PC found a large proportion had underassessed CV risk factors and undertreatment based on current guidelines for managing these risk factors [18]. Sun and colleagues' analysis examined data from men diagnosed between 2010 and 2017, while we examined men diagnosed with PC between 2000 and 2015, which may reflect the improved but not sufficiently improved medical management of CV risk. Overall, this data suggests that ADT exacerbates underlying conditions rather than causing CV disease/MACE, highlighting the need for multidisciplinary/comprehensive management when treating PC.

In our study, regardless of treatment, Black Veterans developed MACE at a similar rate to White Veterans. However, in race-stratified models (to examine race-specific risk factors) we found that White men with intermediate or unknown risk developed MACE at 4 and 5.4 times the rate of White men with low-risk disease, respectively, yet this was not the case for Black men. The reasons for this finding are not clear, though White men with intermediate NCCN risk at diagnosis may be treated more aggressively. We did not examine the use of GnRH agonists or antagonists in this analysis, which may be associated with greater risk of MACE in certain patients. Race-stratified models showed Black men with preexisting CMD developed MACE at 4.2 times the rate of Black men without CMD but there were no differences in the rate for White men with or without CMD. The previously mentioned [21] under-assessment and under treatment of CV risk factors in men diagnosed with PC within the VA and the fact that Black men had more glucose abnormalities and hypertension may further explain increased risk of MACE among Black men with CMD. Closer monitoring and intervention for Black Veterans with PC who also have these conditions may help in reducing the risk of MACE. This may include greater communication and education of patients regarding their risk for MACE following PC diagnosis and treatment. Importantly, in both Black and White Veterans, having a more recent diagnosis (2010–2015) was associated with a significantly lower rate of MACE than those diagnosed in 2000–2005 perhaps reflecting an improved recognition and surveillance of CVD-related risk. Hoffman and colleagues [23], examined PC treatment patterns for Veterans, particularly older patients and those with localized disease between

Table 3 Hazard ratios of multivariable Cox proportional hazard models (race-matched)

Covariate	Hazard Ratio Estimates					
	Non-Matched			Matched		
	Point Estimate	95% Wald Confidence Limits		Point Estimate	95% Wald Confidence Limits	
Age at diagnosis	1.020	0.967	1.077	0.989	0.951	1.029
Race						
Black vs. White (RT only)	1.441	0.999	2.078	0.887	0.476	1.651
Black vs. White (ADT + RT)	0.938	0.611	1.441	0.728	0.323	1.641
Hispanic						
Hispanic vs. non-Hispanic	1.494	0.876	2.547	1.411	0.192	10.364
Marital Status						
Married/partnered vs. Single	0.999	0.769	1.298	1.204	0.734	1.976
BMI						
Obese vs. Normal/Underweight	0.884	0.642	1.217	0.804	0.433	1.494
Overweight vs. Normal/Underweight	0.791	0.576	1.087	0.832	0.458	1.511
Rural - Urban (RUCA)						
Rural vs. Urban	0.933	0.598	1.456	0.545	0.075	3.951
Stage (AJCC)						
II vs. I	1.034	0.480	2.230	0.497	0.144	1.719
III vs. I	0.862	0.275	2.704	0.000	0.000	Inf
IV vs. I	1.737	0.493	6.119	0.000	0.000	Inf
Unknown vs. I	0.535	0.183	1.562	0.258	0.040	1.671
NCCN Risk						
High vs. Low	**1.633**	**1.024**	**2.603**	2.407	0.985	5.885
Intermediate vs. Low	**1.578**	**1.074**	**2.320**	1.612	0.773	3.362
Risk: Unknown vs. Low	1.236	0.690	2.215	**3.058**	**1.158**	**8.075**
Diagnosis Year						
05–10 vs. 00–05	**0.490**	**0.353**	**0.681**	0.576	0.309	1.074
10–15 vs. 00–05	**0.312**	**0.211**	**0.462**	**0.218**	**0.096**	**0.496**
Elixhauser Score						
1 vs. 0	1.181	0.756	1.845	0.790	0.348	1.796
> 1 vs. 0	**1.897**	**1.239**	**2.904**	1.606	0.761	3.392
Preexisting CMD						
Yes vs. No	**3.345**	**2.523**	**4.435**	**2.803**	**1.579**	**4.977**

Note: RT: Radiation Therapy; ADT: Androgen Deprivation Therapy; RT: Radiation therapy; BMI: Body Mass Index; RUCA: Rural-Urban Commuting Area; NCCN: National Comprehensive Cancer Network; CMD: Cardiometabolic Disease; AJCC: American Joint Commission on Cancer, **Bold** typeface = Statistically significant

2003 and 2008. They reported that treatment patterns in the VA followed evidence-based guidelines to not treat older and sicker patients with surgery and radiotherapy. Over time a greater proportion of men also received no treatment and fewer received primary ADT. Monitoring comorbidity status and implementing timely strategies to manage CV risk is critical for reducing the risk of MACE among all Veterans.

This study had several significant strengths. We examined a large and diverse cohort (~32% Black) of well characterized men diagnosed with PC and who have similar access to health care, unusual in the US setting. We also employed a rigorous analytic method to examine the association between treatment with ADT and incidence of MACE, including the use of a propensity score matching procedure to control for confounding.

A limitation of retrospective data is that we may have found a greater influence of ADT on MACE had we followed men for a longer period after diagnosis. While there are many strengths of data collected on men treated within the VA Healthcare system, there is also the chance that some men may have MACE diagnosed and treated outside the VA. Additionally, all men with high-risk disease should receive ADT + RT per guidelines, thus if they do not receive ADT it may be because of underlying CV risk factors. We also limited the study to men who initiated ADT prior to receiving radiation and did not include men who had either surgery or radiation prior to ADT. While our analysis used RUCA codes to assess place-based risk for cardiovascular events and poor access to healthcare facilities, there may be a more precise use of zipcode data in conjunction with other social drivers of health to create a Social Deprivation

Index [24] and to determine whether living in a specific area or circumstance increases risk for CMD or MACE in Veterans with PC. In future studies, MACE should be examined frequently following diagnosis in a longitudinal mixed-model (LMM) to consider covariates associated with increased risk of MACE over time (e.g., over 10 or more years). We did not compare outcomes in men who received GnRH agonists vs. antagonists. Recently, the HERO trial reported higher rates of CV events in men who received GnRH agonists compared with the antagonist *relugolix*, particularly those with pre-existing MACE [25]. Therefore the results reported here may not be reflective of all ADT treatments, especially considering newer agents have only been available in recent years.

Conclusions

Within the VA healthcare system, men treated with ADT + RT for PC do not appear to be at greater risk for MACE than those receiving RT alone. Black men have similar risk of MACE as White men, whether receiving RT alone or in combination with ADT. However, for Black men, having a pre-existing CMD increases their risk for MACE by 4.2 times compared to Black men without CMD. Importantly, for men with CMD at PC diagnosis and for those who have other comorbidities, there is significant risk of a MACE, highlighting the need for CV risk screening when treating PC.

Abbreviations

ADT	Androgen Deprivation Therapy
CMD	Cardiometabolic disease
CVD	Cardiovascular disease
MACE	Major adverse cardiovascular events
PC	Prostate Cancer

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions

Data collection and processing: DB, BD. Data analysis and figure design: DB, BD, ARL. Conception and study design: ARL, DB, BD, WGH. Article draft writing: ARL, DB, WGH, AKP, SH, VBS, BBP, RLB, MGC. Article editing and final approval: All authors.

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Data availability

The United States Department of Veterans Affairs (VA) places legal restrictions on access to veteran's health care data, which includes both identifying data and sensitive patient information. The analytic data sets used for this study are not permitted to leave the VA firewall without a Data Use Agreement. This limitation is consistent with other studies based on VA data. However, VA data are made freely available to researchers behind the VA firewall with an approved VA study protocol. For more information, please visithttps://www.virec.research.va.gov.

Declarations

Competing interests

AKP has received honorarium for serving on the scientific consultancy panels of SANOFI - Genzyme, Bayer, and Tempus & Cardinal Health. The remaining authors declare they have competing interests.

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