

# Impact of Androgen Deprivation Therapy on Racial/Ethnic Disparities in the Survival of Older Men Treated for Locoregional Prostate Cancer



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**Background:** Racial disparities persist in prostate cancer (CaP) treatment and survival, but disparities in androgen deprivation therapy (ADT) and the degree to which it affects racial differences in survival remains to be fully assessed.

**Methods:** Using the Surveillance, Epidemiology and End Results-Medicare linked data, we examined a large cohort of men ( $N = 64,475$ ) diagnosed with locoregional CaP during 1992 to 1999 and followed through 2003. The effects of ADT and race on survival were analyzed using a Cox proportional hazards model.

**Results:** The receipt of ADT was significantly lower in African Americans (24%) relative to Caucasians (27%), Asians (34%), and Hispanics (28.7%) ( $P < .05$ ). Compared with Caucasian race, African American race was associated with a statistically significant increased mortality ( $HR = 1.26$ , 95%  $CI = 1.21-1.32$ ), which remained significant after adjusting for ADT but was substantially decreased after controlling for primary therapies such as radical prostatectomy, radiation, and watchful waiting ( $HR = 1.06$ , 95%  $CI = 1.01-1.10$ ) and was no longer statistically significant after controlling for comorbidities ( $HR = 0.98$ , 95%  $CI = 0.94-1.03$ ).

**Conclusions:** There were marked racial variations in the receipt of ADT, primary therapies (namely surgery and surgery combined with radiation), and comorbidities. However, racial disparities in survival were not affected by racial variations in ADT but were explained by racial variations in primary therapies and by racial differences in comorbidities.

## Introduction

Substantial racial differences persist in the incidence and mortality of prostate cancer (CaP) in the United States; the incidence rate among African American men is reported to be the highest in the world.<sup>1-4</sup> While African Americans have a 60% increased risk of devel-

oping CaP, twice the risk of developing distant disease, and two-fold the mortality relative to Caucasians,<sup>5,7</sup> the incidence and mortality for Hispanics are lower than those for Caucasians.<sup>5</sup> The higher mortality among African Americans has been associated with less aggressive treatment compared with Caucasians,<sup>8</sup> advanced-stage CaP at presentation,<sup>9</sup> and biologically aggressive tumor in African Americans.<sup>10</sup> The younger age at presentation of CaP in African Americans compared with Caucasians is indicative of higher tumor stage and grade and more aggressive tumor, implying potential biologic variation in CaP presentation between these racial/ethnic groups.<sup>11-14</sup>

Radical prostatectomy (RP), external-beam radiation (XRT), or RP plus salvage XRT, also termed aggressive therapies, are considered the two major therapeutic options for treating clinically localized CaP.<sup>15,16</sup> Conservative management includes the use of orchiectomy and/or primary androgen deprivation therapy (ADT), mainly luteinizing hormone-releasing hormone (LHRH) agonist, or no therapy (watchful waiting) within 6 months of diagnosis.<sup>17</sup> Data on the variation in treatment received are conflicting in explaining racial disparities in CaP mortality and the survival disadvantage

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**Abbreviations used in this paper:** CaP = prostate cancer, RP = radical prostatectomy, XRT = external-beam radiation, ADT = androgen deprivation therapy, LHRH = luteinizing hormone-releasing hormone, SEER = Surveillance, Epidemiology and End Results, HMO = health maintenance organization.

of African Americans.<sup>15,18-20</sup> Several socioeconomic and behavioral differences are believed to explain at least part of the higher CaP incidence and mortality rates observed in African Americans. Some studies have attributed these disparities to differences in socioeconomic status,<sup>21-24</sup> advanced stage at diagnosis,<sup>7,5,9,25,26</sup> and treatment received.<sup>27</sup>

Disparities in primary therapies have been observed, with African Americans less likely to undergo RP. Most studies have focused on primary therapies in explaining racial differences in CaP mortality between African Americans and Caucasians. The goal of this study was to assess racial disparities in ADT and their impact on racial differences in survival using Surveillance, Epidemiology and End Result-Medicare linked validated data.<sup>28-31</sup> We conducted a population-based retrospective cohort study using time-independent covariates in a Cox proportional hazards model and presented the overall survival of African Americans compared with Caucasians, Asians, and Hispanics, as well as the covariates contributing to these variations other than ADT.

## Methods

### Data Source

After appropriate approval from the relevant institutional review boards, we conducted a retrospective cohort study using the merged Surveillance, Epidemiology and End Results (SEER)-Medicare database for men diagnosed with locoregional CaP at age 65 years or older between 1992 and 1999 in 11 SEER areas, which account for 14% of the US population. The SEER areas include Connecticut, Iowa, New Mexico, Utah, Hawaii, Los Angeles county, the San Jose-Monterey area, and the metropolitan areas of San Francisco/Oakland, Detroit, Atlanta, and Seattle.

### Study Population

The study population was composed of patients 65 years of age or older who were diagnosed with CaP from 1992 to 1999 in the 11 SEER regions and who had both Medicare part A and B and were not members of a health maintenance organization (HMO). Because SEER provides a combined category for CaP staging for regional and local tumor, tumor staging (I-IV) was used to control for residual confounding by the combined local/regional stages. All races were included in the study population: Caucasians (n = 53,764), African Americans (n = 6,321), Hispanics (n = 1,143), Asians (n = 1,830), and others (n = 1,417).

### Study Variables

**Outcome Variable:** All-cause mortality was defined as death from any cause reported as the underlying cause of death. The survival time in months was calculated from the month of diagnosis to the month of death or to the date of last follow-up.

**ADT:** Hormonal therapy or ADT was described as the receipt of LHRH agonist or orchiectomy. Patients were characterized as receiving ADT if any of the following Medicare procedure codes indicated so within 6 months of diagnosis: leuprolide (J1950 or J9217-J9219), goserelin (J9202), or orchiectomy (54520, 54521, 54530, or 54535). Orchiectomy was defined as surgical castration for the purpose of suppressing testicular testosterone.

**Chemotherapy, Surgery, and Radiation:** Chemotherapy was defined as having received chemotherapy if the Medicare procedure indicated so within 6 months of diagnosis. Chemotherapy was reported as either received or not received. The details of chemotherapy ascertainment have been described elsewhere.<sup>21,32-34</sup> The primary therapies in localized CaP include RP, radiotherapy, or observational management as watchful waiting, which has been reported elsewhere.<sup>21,34</sup>

**Comorbidity:** Comorbidity was ascertained from Medicare claims using diagnoses and procedures performed between 1 year prior to and 1 month after CaP diagnosis.<sup>21</sup> The detail on the comorbidity index has been previously described.<sup>35,36</sup> Comorbidity scores were categorized into four groups: 0, 1, 2, and 3 and higher.

**Demographics (Race, Age, and Marital Status):** Race was classified by using data from the SEER Program and categorized as Caucasians, African Americans, Hispanics, Asians, and others. The age at diagnosis was recoded and categorized into 65-69 years, 70-74 years, 75-79 years, and 80 years or older. Marital status was classified as married, unmarried, or unknown when information was unavailable.

**Socioeconomic Status Proxies:** Three variables from the 1990 census are available in the SEER-Medicare linked data, which were used to define socioeconomic status, namely education (percent adults aged  $\geq 25$  years of education at the Zip code level), poverty (percent of persons living below the poverty line at the census tract level), and income (median annual household income at the Zip code level). Poverty was used at the census tract level since these data are not available at the Zip code level. The three variables were categorized into quartiles, and when information was unavailable, we described this as an unknown category.<sup>21</sup> For education and income, the first quartile represents the highest education attainment and economic status, respectively.

**Clinical Features and Other Characteristics:** These data represent locoregional CaP. SEER defines localized disease as an invasive neoplasm confined entirely to the organ of origin, while regional disease refers to a neoplasm that has extended beyond the limits of the organ of origin directly into surrounding organs or tissues. CaP data from SEER are available as locoregional and distant or metastasis. Both grade and tumor stage (I, II, III, IV, or unknown) categories were

used in adjusting for confounding. The Gleason score ranges from 2 to 10, with 10 implying worst prognosis. A Gleason score of 2 to 4 represents slow-growing tumor, 5 to 7 represents moderately aggressive, and 8 to 10 represents high chance of tumor spread. The staging of CaP involves stage I–IV classification, with stage IV representing the worst prognosis. Stage I represents early cancer confined to a microscopic area, stage II refers to palpable tumor confined to the prostate gland, stage III represents tumor with possible spread to seminal vesicles, and stage IV refers to spread to lymph node, bones, lungs, or other areas. Geographic area is

available in the SEER and is represented the 11 SEER areas in the dataset used for this study.

### Statistical Analyses

The Pearson chi-square statistic was used to examine the association between race and ADT and the distribution of other sociodemographic parameters (age, education, income, marital status, poverty) and clinicopathologic parameters (tumor stage, Gleason score, radiation, chemotherapy, comorbidity score, year of diagnosis, and geographic area). Time-to-event data were analyzed using log-rank tests, Kaplan-Meier method, and Cox pro-

**Table 1. — Study Size and Comparison of Demographics, Treatment, and Prognostic Factors Among Different Ethnic/Racial Groups in Older Men With Locoregional Prostate Cancer**

Variable	Race/Ethnicity (No. and %)					P Value*
	Caucasians	African Americans	Hispanics	Asians	Others	
<b>Overall</b> N = 64,475 (100%)	53,764 (83.4)	6,321 (9.8)	1,143 (1.8)	1,830 (2.8)	1,417 (2.2)	
<b>Age (yrs)</b>						< .001
65–69	15,416 (28.7)	2,131 (33.7)	411 (36.0)	447 (24.4)	354 (25.0)	
70–74	17,324 (32.2)	2,023 (32.0)	390 (34.1)	613 (33.5)	390 (27.5)	
75–79	12,271 (22.8)	1,314 (20.8)	221 (19.3)	449 (24.5)	319 (22.5)	
≥ 80	8,753 (16.3)	853 (13.5)	121 (10.6)	321 (17.5)	354 (25.0)	
<b>Comorbidity</b>						< .001
0	34,402 (64.0)	3,394 (53.7)	669 (58.5)	1,097 (59.9)	846 (59.7)	
1	12,565 (23.4)	1,611 (25.5)	290 (25.4)	465 (25.4)	328 (23.1)	
2	4,342 (8.1)	747 (11.8)	96 (8.4)	164 (9.0)	135 (9.5)	
≥ 3	2,455 (4.6)	569 (9.0)	88 (7.7)	104 (5.7)	108 (7.6)	
<b>Education</b>						< .001
1st	14,437 (26.8)	237 (3.7)	60 (5.2)	328 (17.9)	228 (16.1)	
2nd	14,059 (26.1)	472 (7.5)	122 (10.7)	300 (16.4)	262 (18.5)	
3rd	13,034 (24.2)	1,168 (18.5)	225 (19.7)	487 (26.6)	360 (25.4)	
4th	9,193 (17.1)	4,260 (67.4)	666 (58.3)	667 (36.4)	493 (34.8)	
Unknown	3,041 (5.7)	184 (2.9)	70 (6.1)	48 (2.6)	74 (5.2)	
<b>Gleason Score</b>						< .001
2–4	7,475 (13.9)	740 (11.7)	198 (17.3)	282 (15.4)	224 (15.8)	
5–7	33,218 (61.8)	3,789 (59.9)	650 (56.9)	998 (54.5)	733 (51.7)	
8–10	10,438 (19.4)	1,410 (22.3)	240 (21.0)	492 (26.9)	377 (26.6)	
Unknown	2,633 (4.9)	382 (6.0)	55 (4.8)	58 (3.2)	83 (5.9)	
<b>Marital Status</b>						< .001
Married	39,765 (74.0)	3,522 (55.7)	778 (68.1)	1,459 (79.7)	1,039 (73.2)	
Unmarried	9,963 (18.5)	2,267 (35.9)	295 (25.8)	255 (13.9)	276 (19.5)	
Unknown	4,036 (7.5)	532 (8.4)	70 (6.1)	116 (6.3)	102 (7.2)	
<b>ADT</b>						< .001
No	39,266 (73.0)	4,808 (76.0)	815 (71.3)	1,204 (65.8)	967 (68.2)	
Yes	14,498 (27.0)	1,513 (24.0)	328 (28.7)	626 (34.2)	450 (31.8)	
<b>Chemotherapy</b>						< .001
No	44,219 (82.2)	5,345 (84.6)	861 (75.3)	1,345 (73.5)	1,109 (78.3)	
Yes	9,545 (17.8)	976 (15.4)	282 (24.7)	485 (26.5)	308 (21.7)	
<b>Primary Therapy</b>						< .001
RP	12,907 (24.0)	1,070 (16.9)	328 (28.7)	411 (22.5)	273 (19.3)	
XRT	20,536 (38.2)	2,463 (39.0)	327 (28.6)	695 (38.0)	481 (33.9)	
RP plus XRT	1,205 (2.2)	89 (1.4)	26 (2.3)	57 (3.1)	31 (2.2)	
Neither RP nor XRT	19,116 (35.6)	2,699 (42.7)	462 (40.4)	667 (36.4)	632 (44.6)	
<b>Tumor Stage</b>						< .001
I	17,636 (32.8)	2,263 (35.8)	387 (33.9)	596 (32.6)	435 (30.7)	
II	6,701 (12.5)	866 (13.7)	147 (12.9)	247 (13.5)	180 (12.7)	
III	7,717 (14.3)	681 (10.8)	173 (15.1)	255 (14.0)	215 (15.2)	
IV	1,733 (3.2)	212 (3.3)	48 (4.2)	62 (3.4)	61 (4.3)	
Unknown	19,977 (37.2)	2,299 (36.4)	388 (34.0)	670 (36.6)	526 (37.1)	

P value for chi-square on racial/ethnic difference in the distribution of study characteristics. RP = radical prostatectomy, XRT = external-beam radiation, ADT = androgen deprivation therapy.

portional hazards regression model. The overall survival was estimated using Kaplan-Meier product limit by race/ethnicity. Univariable log-rank test were used to test the association between various clinicopathologic characteristics and CaP survival. The proportionality assumption was satisfied when the log-log Kaplan-Meier curves for survival functions by ADT and race were parallel and did not intersect.<sup>32</sup> Multivariable analyses based on Cox proportional hazards regression model were used to examine the effect of the various covariates on the risk of dying according to race. This model generates the hazard rate as a function of the baseline hazard (ho) at time (t) and the effect of one or more independent variables ( $x_1, x_2, x_3, \dots, x_n$ ). Interactions between ADT and race, as well as ADT and primary therapies, were tested using the product terms of these covariates for inclusion in the model building. The interaction terms were allowed in the model if the significance level was  $< .10$ . Further, analyses were adjusted for sociodemographics, tumor characteristics, ADT, chemotherapy, primary therapies received, and comorbidities. Finally, we tested the model with and without interaction using a likelihood ratio test for model fitness, and we presented the results of the model without interaction. Statistical tests were two-sided at .05 significance level. All analyses were performed using STATA Statistical package, version 10.0 (STATA Corporation, College Station, Texas).

## Results

This analysis includes 64,475 cases, with 17,415 (27%) receiving ADT. Table 1 presents the comparison of sociodemographics, tumor characteristics, and prognostic factors among different racial/ethnic groups in older men diagnosed with locoregional CaP from 1992 through 1999 and followed till December 2003. Com-

pared with Caucasians, African Americans were more likely to be diagnosed with locoregional disease at a younger age (28.7% vs 33.3%,  $\chi^2_{(12)} = 241.6, P < .001$ ), less likely to be married at the time of diagnosis (55.7% vs 74.0%,  $\chi^2_{(8)} = 1200, P < .001$ ), and disproportionately represented in the lowest quartile of the education level (26.8% vs 3.7%,  $P < .001$ ). Table 1 also presents the comorbidity index, Gleason score, tumor stage, and ADT by race. Relative to Caucasians, African Americans were more likely to present with a higher comorbidity index (9.0% vs 4.6%,  $P < .001$ ), slightly less likely to be diagnosed with low Gleason score (11.7% vs 13.9%,  $P < .001$ ), and slightly less likely to receive chemotherapy alone (15.4% vs 17.8%,  $P < .001$ ). In addition, compared with Caucasians, African Americans were less likely to receive ADT alone (27% vs 24%), whereas Hispanics (27% vs 28.2%) and Asians (27% vs 34.2%) were more likely to receive ADT alone ( $P < .001$ ).

Table 2 presents the comparison of treatments received among different ethnic/racial groups. The receipt of primary therapies and chemotherapy was statistically significantly different by race ( $P < .001$ ). Compared with Caucasians, African Americans were less likely to receive RP (87% vs 85.8%), more likely to receive RP plus ADT (13% vs 14.2%), less likely to receive radiation plus ADT (28.5% vs 21.8%), more likely to receive radiation therapy alone (71.5% vs 78.2%), and more likely to undergo watchful waiting or observational management alone (64.7% vs 70.4%) ( $P < .001$ ).

Table 3 presents the univariable and multivariable proportional hazards model of the covariates influencing the survival of older men who were diagnosed with locoregional CaP and treated for the disease. In the unadjusted univariable regression, there was a statistically significant difference in the survival of African

Table 2. — Comparison of Treatment Received Among Different Ethnic/Racial Groups in Older Men With Locoregional Prostate Cancer

Treatment	Race/Ethnicity (No. and %)					P Value*
	Caucasians (n = 53,764)	African Americans (n = 6,321)	Hispanics (n = 1,143)	Asians (n = 1,830)	Other (n = 1,417)	
<b>RP</b>						< .001
RP + ADT	1,674 (13.0)	152 (14.2)	51 (15.5)	86 (20.9)	55 (20.1)	
RP alone	11,233 (87.0)	918 (85.8)	277 (84.5)	325 (79.1)	218 (79.9)	
<b>XRT</b>						< .001
XRT + ADT	5,846 (28.5)	536 (21.8)	114 (34.9)	261 (37.5)	141 (29.3)	
XRT alone	14,690 (71.5)	1,927 (78.2)	213 (65.1)	434 (62.5)	340 (70.7)	
<b>RP + XRT</b>						.008
RP/XRT + ADT	234 (19.4)	27 (30.3)	7 (26.9)	15 (26.3)	12 (38.7)	
RP/XRT alone	971 (80.6)	62 (69.7)	19 (73.1)	42 (73.7)	19 (61.3)	
<b>Watchful Waiting</b>						< .001
Watchful waiting + ADT	6,744 (35.3)	798 (29.6)	156 (33.8)	264 (39.6)	242 (38.3)	
Watchful waiting alone	12,372 (64.7)	1,901 (70.4)	306 (66.2)	403 (60.4)	390 (61.7)	
<b>Chemotherapy</b>						< .001
Chemotherapy + ADT	8,497 (89.0)	876 (89.7)	247 (87.6)	436 (95.5)	286 (92.9)	
Chemotherapy alone	1,048 (11.0)	100 (10.2)	35 (12.4)	22 (4.5)	22 (7.1)	

P value for the chi-square on ethnic differences in the distribution of primary therapies and chemotherapy. RP = radical prostatectomy, ADT = androgen deprivation therapy, XRT = external-beam radiation.

**Table 3. — Effects of Covariates on Survival of Older Men With Locoregional Prostate Cancer in Univariable and Multivariable Cox Regression Model**

Covariates	Univariable HR, 95% CI, and Significance			Multivariable HR, 95% CI, and Significance		
	HR	95% CI	P Value	HR	95% CI	P Value
<b>Race/Ethnicity</b>						
Caucasian	1.00	Referent	Referent	1.00	Referent	Referent
African American	1.26	1.21–1.32	< .001	0.98	0.94–1.03	.51
Hispanic	0.83	0.75–0.92	.001	0.77	0.69–0.86	< .001
Asian	0.72	0.66–0.79	< .001	0.63	0.58–0.69	< .001
<b>Age Group (yrs)</b>						
65–69	1.00	Referent	Referent	1.00	Referent	Referent
70–74	1.48	1.42–1.54	< .001	1.24	1.19–1.29	< .001
75–79	2.60	2.50–2.70	< .001	1.74	1.67–1.82	< .001
≥ 80	5.73	5.50–6.00	< .001	2.98	2.85–3.12	< .001
<b>Marital Status</b>						
Married	1.00	Referent	Referent	1.00	Referent	Referent
Unmarried	1.69	1.64–1.74	< .001	1.29	1.25–1.33	< .001
<b>Education<sup>a</sup></b>						
1st	1.00	Referent	Referent	1.00	Referent	Referent
2nd	1.21	1.16–1.23	< .001	1.07	1.03–1.12	.001
3rd	1.37	1.32–1.43	< .001	1.09	1.04–1.13	< .001
4th	1.54	1.48–1.60	< .001	1.08	1.03–1.14	.001
<b>Income<sup>a</sup></b>						
1st	1.00	Referent	Referent	1.00	Referent	Referent
2nd	1.17	1.12–1.21	< .001	1.07	1.03–1.12	.001
3rd	1.28	1.23–1.33	< .001	1.14	1.09–1.20	< .001
4th	1.47	1.42–1.53	< .001	1.17	1.11–1.23	< .001
<b>Poverty<sup>a</sup></b>						
1st	1.00	Referent	Referent	–	–	–
2nd	1.13	1.09–1.17	< .001	–	–	–
3rd	1.23	1.18–1.28	< .001	–	–	–
4th	1.50	1.44–1.55	< .001	–	–	–
<b>ADT</b>						
No	1.00	Referent	Referent	1.00	Referent	Referent
Yes	1.55	1.50–1.59	< .001	1.02	0.99–1.06	.21
<b>Chemotherapy</b>						
No	1.00	Referent	Referent	1.00	Referent	Referent
Yes	1.27	1.23–1.32	< .001	1.00	0.96–1.05	.90
<b>XRT</b>						
No	1.00	Referent	Referent	–	–	–
Yes	0.79	0.77–0.81	< .001	–	–	–
<b>Radiation + RP</b>						
No	1.00	Referent	Referent	–	–	–
Yes	0.53	0.47–0.59	< .001	–	–	–
<b>Watchful Waiting</b>						
No	1.00	Referent	Referent	–	–	–
Yes	2.93	2.86–3.01	< .001	–	–	–
<b>Primary Therapies</b>						
RP	1.00	Referent	Referent	1.00	Referent	Referent
Radiation	2.41	2.30–2.52	< .001	1.96	1.86–2.06	< .001
Radiation + RP	1.48	1.32–1.66	< .001	1.27	1.14–1.43	< .001
Watchful waiting	5.27	5.04–5.51	< .001	3.12	2.96–3.29	< .001
<b>RP</b>						
No	1.00	Referent	Referent	–	–	–
Yes	0.28	0.27–0.29	< .001	–	–	–
<b>Gleason Score<sup>b</sup></b>						
2–4	1.00	Referent	Referent	1.00	Referent	Referent
5–7	0.87	0.84–0.91	< .001	1.16	1.11–1.21	< .001
8–10	1.49	1.42–1.55	< .001	1.72	1.65–1.80	< .001
<b>Tumor Stage</b>						
I	1.00	Referent	Referent	1.00	Referent	Referent
II	0.88	0.84–0.92	< .001	1.15	1.10–1.21	< .001
III	0.68	0.65–0.71	< .001	1.26	1.20–1.32	< .001
IV	1.33	1.25–1.42	< .001	1.74	1.62–1.86	< .001
<b>Comorbidities<sup>c</sup></b>						
0	1.00	Referent	Referent	1.00	Referent	Referent
1	1.82	1.76–1.87	< .001	1.59	1.54–1.64	< .001
2	2.79	2.68–2.90	< .001	2.19	2.10–2.28	< .001
≥ 3	4.66	4.45–4.88	< .001	3.30	3.15–3.46	< .001

<sup>a</sup>The first quartile represents highest education status, highest income level, and lowest poverty level (high income level); the significance level,  $P < .05$ .

<sup>b</sup>Lower Gleason score (2–3) correlates with better prognosis, while early stage at diagnosis (I) is associated with favorable outcome.

<sup>c</sup>The low comorbidity score (0) is associated with better prognosis; the significance level,  $P < .05$ . HR = hazard ratio, CI = confidence interval, ADT = androgen deprivation therapy, XRT = external-beam radiation, RP = radical prostatectomy.

**Table 4. — Cox Proportional Hazards Models for the Covariates Contributing to Racial Variations in Overall Survival of African Americans, Hispanics, and Asians Compared With Caucasians With Locoregional Prostate Cancer**

Variables in Models	HR and 95% CI Compared With Caucasians*		
	African Americans HR (95% CI)	Hispanics HR (95% CI)	Asians HR (95% CI)
<b>Model 1:</b> Race only	1.26 (1.21–1.32)	0.83 (0.75–0.92)	0.72 (0.66–0.79)
<b>Model 2:</b> Race + sociodemographics	1.13 (1.08–1.18)	0.82 (0.74–0.92)	0.66 (0.60–0.72)
<b>Model 3:</b> Race + sociodemographics + tumor characteristics	1.11 (1.06–1.16)	0.81 (0.73–0.90)	0.64 (0.58–0.70)
<b>Model 4:</b> Race + sociodemographics + tumor characteristics + ADT	1.12 (1.07–1.17)	0.81 (0.73–0.90)	0.64 (0.58–0.70)
<b>Model 5:</b> Race + sociodemographics + tumor characteristics + ADT + chemotherapy	1.12 (1.07–1.17)	0.81 (0.73–0.90)	0.64 (0.58–0.70)
<b>Model 6:</b> Race + sociodemographics + tumor characteristics + ADT + chemotherapy + primary therapies	1.06 (1.01–1.10)	0.79 (0.71–0.87)	0.64 (0.58–0.70)
<b>Model 7:</b> Race + sociodemographics + tumor characteristics + ADT + chemotherapy + primary therapies + comorbidities	0.98 (0.94–1.03)	0.77 (0.69–0.86)	0.63 (0.58–0.69)

\* Multiracial model for overall survival of older men treated for locoregional prostate cancer. HR = hazard ratio, CI = confidence interval, ADT = androgen deprivation therapy.

Americans, Hispanics, Asians, and Caucasians ( $\chi^2_{(3)} = 206.6, P < .001$ ; log-rank). Compared with Caucasians, African Americans had a significant 26% increased risk of dying (hazard ratio [HR] = 1.26, 95% confidence interval [CI] = 1.21–1.32,  $P < .001$ ), whereas Hispanics and Asians had a significant 17% and 28% decreased risk of dying (HR = 0.83, 95% CI = 0.75–0.93,  $P < .001$  and HR = 0.72, 95% CI = 0.66–0.79,  $P < .001$ , respectively). Likewise, there was a significant difference in survival by those who received ADT compared with those who did not ( $\chi^2_{(1)} = 923.5, P < .001$ ; log-rank). ADT significantly increased the risk of dying (HR = 1.55, 95% CI = 1.50–1.59,  $P < .001$ ). Higher education level, younger age at diagnosis, early-stage tumor, low Gleason score, marriage, higher income, lower comorbidity index, lower poverty level, radical prostatectomy (RP), radiation therapy (XRT), and XRT plus RP were significantly associated with survival advantage ( $P < .001$ ). In contrast, chemotherapy received and observational management, also termed watchful waiting, were significantly associated with poorer survival ( $P < .001$ ). Whereas XRT was associated with a significant 21% decreased risk of dying (HR = 0.79, 95% CI = 0.77–0.81,  $P < .001$ ), the use of XRT plus RP was associated with a significant 47% decreased risk of dying in this cohort (HR = 0.53, 95% CI = 0.47–0.59,  $P < .001$ ). In the multivariable Cox model, the impact of the covariates (sociodemographics, ADT, chemotherapy, primary therapies, and

comorbidities) on the survival of this cohort persisted. However, the significant racial difference in survival between African Americans and Caucasians was removed after controlling for these covariates (HR = 0.98, 95% CI = 0.94–1.03,  $P < .001$ ).

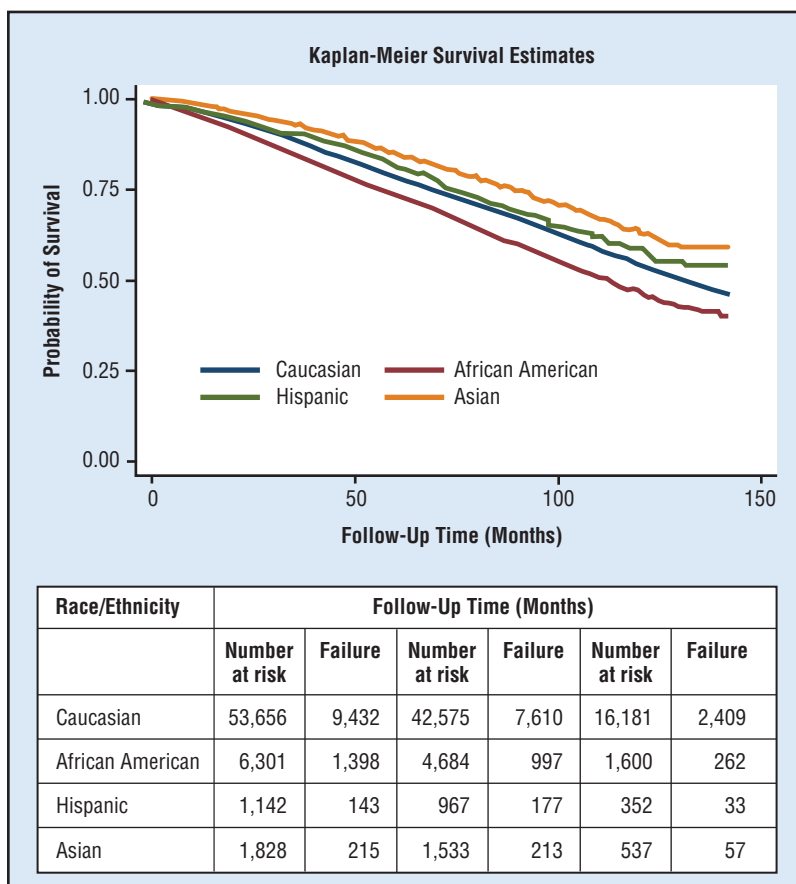


Fig 1. — The Kaplan-Meier survival function illustrates the unadjusted overall survival by race and ethnicity, indicating the survival disadvantage of older African American males (lowest curve) and the survival advantage of older Asian males (highest curve) diagnosed with locoregional prostate cancer and treated for the disease.

Table 4 presents seven models used to assess the effects of ADT, primary therapies, and other prognostic factors such as education as socioeconomic proxy on racial disparities in the survival of older men treated for locoregional disease. The crude HR of dying was 26%, 52%, and 76% higher in African Americans relative to Caucasians (HR = 1.26, 95% CI = 1.21-1.32,  $P < .001$ ), Hispanics (HR = 1.52, 95% CI = 1.36-1.70,  $P < .001$ ) and Asians (HR = 1.76, 95% CI = 1.60-1.94,  $P < .001$ ) (Fig 1). Model 2 adjusted for sociodemographics, namely age at diagnosis, marital status, education and income. After controlling for these covariates, there was a significant 13% increased risk of mortality among African Americans compared with Caucasians (HR = 1.13, 95% CI = 1.08-1.18,  $P < .001$ ). Model 3 adjusted for all the covariates controlled in model 2 as well as tumor characteristics (tumor stage and Gleason score). There was a significant 11% increased risk of dying among African Americans relative to Caucasians (HR = 1.11, 95% CI = 1.06-1.16,  $P < .001$ ). Model 4 adjusted for all the covari-

ates controlled in model 3 plus ADT. There was a significant 12% increased risk of dying among African Americans compared with Caucasians (HR = 1.12, 95% CI = 1.07-1.17,  $P < .001$ ). Fig 2 illustrates the effect of race/ethnicity on the survival of older men with locoregional prostate cancer, while controlling for ADT. Model 5 controlled for all the covariates adjusted in model 4 as well as chemotherapy. There was no difference in the risk of dying in this model relative to model 4. Model 6 controlled for the covariates adjusted in model 5 as well as primary therapies (surgery, radiation, and watchful waiting). There was a significant 6% increased risk of dying among African Americans compared with Caucasians (HR = 1.06, 95% CI = 1.01- 1.10,  $P < .001$ ). Finally, model 7 adjusted for all the covariates controlled in previous models plus comorbidities. There was no significant difference in mortality between African Americans and Caucasians (HR = 0.98, 95% CI = 0.94-1.03,  $P = .51$ ). The Kaplan-Meier survival function curve shows the survival advantage of both Hispanics and Asians compared

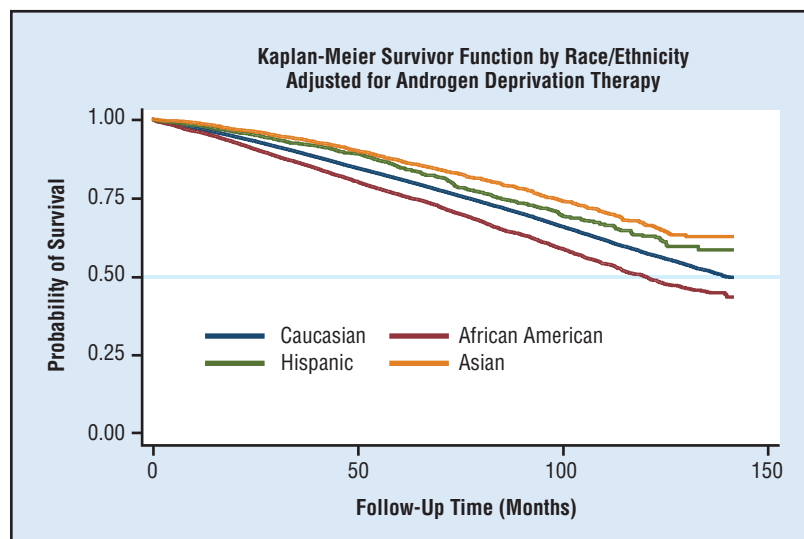


Fig 2. — Kaplan-Meier survival curve for the effect of race/ethnicity on the survival, adjusted for androgen deprivation therapy (ADT). The Kaplan-Meier curves are parallel after the adjustment, indicative of the insignificant effect of ADT on the racial/ethnic differences in the survival of older men diagnosed with locoregional disease and treated for the disease.

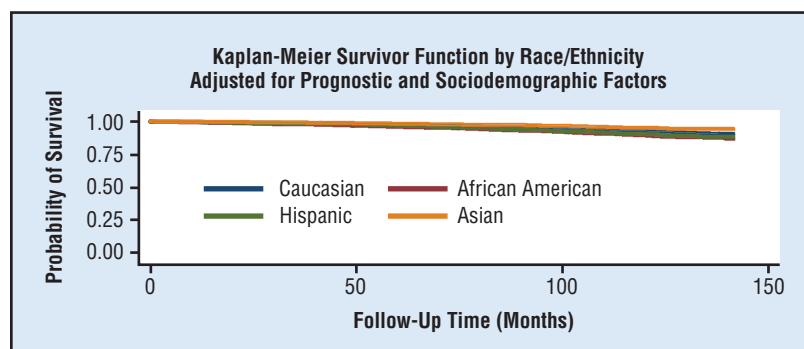


Fig 3. — The Kaplan-Meier survival curve of the effect of race/ethnicity on the survival experience of older men diagnosed with locoregional prostate cancer, after adjustment for tumor prognostic factors including treatment and sociodemographic factors. The curves are not parallel, indicative of statistically insignificant differences in survival by race/ethnicity.

with Caucasians and African Americans (Fig 1). This survival advantage persisted after adjustment for all the covariates (model 7). Thus, Hispanics and Asians had significant 23% and 37% decreased risks of dying (HR = 0.77, 95% CI = 0.69-0.86,  $P < .001$  and HR = 0.63, 95% CI = 0.58-0.69,  $P < .001$ , respectively) compared with Caucasians (Fig 3).

## Discussion

There are five relevant findings from this study. (1) Substantial variations were seen in the receipt of ADT alone and primary therapies (RP, radiation, and observational management or watchful waiting) among different ethnic/racial groups. (2) RP alone and combined XRT and RP significantly improved survival of older men treated for locoregional disease irrespective of race/ethnicity. (3) African Americans were less likely to receive ADT alone and RP alone and were more likely to receive observational management alone than Caucasians, whereas Hispanic and Asian men were more likely to receive ADT alone and RP alone. (4) African Americans were more likely to have a higher comorbidity index, indicative of poor tumor prognosis. (5) Racial/ethnic disparities in survival were not affected by ADT alone but were substantially reduced after adjusting for racial differences in primary therapies, and these disparities no longer persisted after controlling for comorbidities.

This study demonstrated racial/ethnic variance in the survival of older men diagnosed with CaP and treated for the disease. We examined the differences in ADT alone and other treatments for possible explanations of the persistent racial/ethnic differences in CaP mortality. Though we used a multi-race model, our main focus was on African Americans because this ethnic/racial group has the highest incidence and mortality rates of CaP in the United States.<sup>1-4</sup> Further, we considered a number of explanations for the racial differences in survival and observed that ethnic/racial difference in all cause mortality in older men treated for locoregional CaP is explained not by racial variance in ADT but largely by primary therapies, mainly RP and comorbidities.

African Americans had more advanced-stage disease at diagnosis as defined by the Gleason score, and they were less likely to receive aggressive therapy, which has been associated with improved survival in previous studies.<sup>37-44</sup> Although it is unclear why African Americans received less aggressive therapy, it is possible that the selection of a particular therapy is driven by patient factors such as concerns about side effects of the treatment or bias among medical professionals not to recommend aggressive treatments for African Americans.<sup>45-47</sup> Therefore, it is plausible to assume that physicians may have empirically treated African Americans as being more likely to have advanced-stage disease by withholding RP and offering either conservative management or radiation therapy.<sup>48,49</sup>

We have demonstrated a statistically significant difference in the receipt of ADT by race, with African Americans less likely to receive ADT compared with Caucasians and other ethnic groups. We have also shown that ADT does not explain the survival differences observed between African Americans and Caucasians. There are conflicting results on the role of androgen in prostate carcinogenesis<sup>14,50-59</sup> and therapeutics. Because CaP is heterogeneous, with hormone-sensitive and hormone-refractory subtypes, hormonal manipulation in CaP is not clearly understood. Generally, ADT, or rather maximum androgen blockade, competitively antagonizes the androgen receptors and therefore blocks the action of androgens from any source. This action may result in the blockade of ligand-independent activation receptors.<sup>14,60</sup> CaP is initially androgen-dependent or androgen-sensitive and loses this sensitivity as the tumor progresses or after long-term treatment with antiandrogens, thus becoming androgen-independent and incurable.<sup>60</sup>

Racial and ethnic disparities in CaP survival have been documented.<sup>21,39,44,61-64</sup> This variation has been associated with disparities in socioeconomic status,<sup>37</sup> socioeconomic differences,<sup>17,21,62,64</sup> response to chemotherapy,<sup>60,65</sup> and tumor stage.<sup>9,63,64</sup> This study focused on ADT and other treatments received in explaining the

observed racial/ethnic variation in this cohort. Our results indicate that African Americans have a 20% decreased risk of dying after controlling for sociodemographics, tumor characteristics, ADT, chemotherapy, and primary therapies (model 6). Therefore, in older men treated for locoregional CaP, the racial disparities between African Americans and Caucasians were narrowed to some extent but not removed by primary therapies. However, these racial disparities did not persist after adjustment for comorbidities (HR = 0.98, 95% CI = 0.94-1.03,  $P < .001$ ), which confirms previous observations on survival disadvantage of cancer patients with increasing comorbidities.<sup>17,21,62,64</sup> African Americans are more likely to be hypertensive and to be prescribed hydrochlorothiazide, which had been implicated in prostate carcinogenesis by increasing calcium and suppressing circulating levels of dihydroxyvitamin D (1,25 (OH)<sub>2</sub>D), a potential protective factor for CaP.<sup>66</sup> Therefore, racial differences in comorbidities as well as the treatment of these comorbidities (not measured by our data) may explain to some degree the racial differences in survival of older men with locoregional CaP treated for the disease.

In addition, we have shown that Asians have the highest survival in this large sample of older men with locoregional disease (model 7). Compared with Caucasians, Asians had a 37% decreased risk of dying after adjustment for sociodemographics, tumor characteristics, ADT, chemotherapy, primary therapies, and comorbidities (HR = 0.63, 95% CI = 0.58-0.69,  $P < .001$ ). Since the differences between Asians and Caucasians persisted after adjustment, it is plausible to suggest that gene-environment interaction such as differences in the dietary pattern (implying variation in tumor biology or molecular factors),<sup>10,67,68</sup> which was not assessed and controlled for in our analysis, might explain these disparities. Similarly, Hispanics presented with a survival advantage relative to Caucasians and African Americans. After adjustment for all covariates (model 7) compared with Caucasians, Hispanics had 23% decreased mortality risk. The survival advantage of Hispanics in this sample of older men treated for locoregional disease, albeit the aggressive treatment received, remains to be explored, which may include differences in the biologic behavior, tumor virulence, or simply the Hispanic paradox.

Generally, racial variance in survival is a complex phenomenon. There is a possibility that race is related to CaP screening and frequency of medical examination, which in turn may be associated with education, comorbidities, or access to and utilization of care. In interpreting the results of this study, several limitations should be considered. First, though we adjusted for several possible confounders of the effect of race on CaP survival, other confounders were not available in our dataset for possible adjustment, typically oral hormonal agents, dietary profile, concurrent disease, and their treatments. Also, as with any epidemiologic investigation, we cannot

exclude the possibility of unmeasured or residual confounding influencing our results. Second, we were unable to separate LHRH-A and orchiectomy, LHRH-A and antiandrogens, or regional and localized tumor for separate group analysis. Likewise, having data on separate tumor stage (for example, local stage alone) would provide a better assessment of the role of ADT in CaP since CaP tends to be androgen-insensitive with locally advanced stage, indicative of poor prognosis with ADT in advanced disease. Third, men aged 65 years and younger and those who were members of an HMO with incident CaP were not included in our sample. We surmise that the distribution and effect of ADT would be different in this age group; therefore, these results may not be generalizable to younger cases and to men utilizing HMO. Also, because we did not assess the effect of other hormonal agents, care must be exercised to avoid generalizing these findings to all androgen-blocking agents and procedures. Finally, we used census tract for education, income, and poverty because information on individual level measures of these covariates were not available; measures of the latter type might minimize misclassification and allow more precise estimates of socioeconomic status.<sup>69,70</sup>

## Conclusions

Among older men treated for locoregional CaP, marked racial variations were seen in the receipt of ADT, in primary therapies, and in comorbidities. However, racial disparities in survival were not affected by racial variations in ADT but were explained substantially by variations in primary therapies and by racial differences in comorbidities. Additional research is necessary not only to assess whether the racial variation in comorbidities is associated with the racial variations in the treatment of comorbidities, but also to determine whether the treatment received for locoregional CaP is due to preference by African Americans for conservative therapy or to clinicians' bias to not recommend aggressive and beneficial therapy to older African American men.

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## Disclosures

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