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Androgen Deprivation and Thromboembolic Events in Men with Prostate Cancer

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Abstract

Background—Androgen deprivation therapy (ADT) improves prostate cancer outcomes in specific clinical settings, but is associated with adverse effects, including cardiac complications and possibly thromboembolic complications. Our objective was to estimate the impact of ADT on thromboembolic events (TEs) in a population-based cohort.

Methods—In the linked Surveillance, Epidemiology and End Results (SEER)-Medicare database, we identified men aged over 65 diagnosed with non-metastatic prostate cancer between 1999 and 2005. Medical or surgical ADT was identified by Medicare claims for gonadotropin-releasing hormone agonists or bilateral orchiectomy at any time following diagnosis. TEs included deep venous thrombosis, pulmonary embolism, and arterial embolism. We estimated ADT's impact on the risk of any TE and on total number of events, controlling for patient and tumor characteristics.

Results—Of 154,611 prostate cancer patients, 58,466 (38%) received ADT. During a median follow-up of 52 months, 15,950 men had at least one TE, including 8,829 (55%) who had ADT and 7,121 (45%) with no ADT. ADT was associated with increased risk of a TE (adjusted hazard ratio 1.56, 95% CI: 1.50 to 1.61, $P < 0.0001$), and duration of ADT was associated with the total number of events ($P < 0.0001$).

Conclusion—In this population-based cohort, ADT was associated with increased risk of a TE, and longer durations of ADT were associated with more TEs. Men with intermediate- and low-risk prostate cancer should be assessed for TE risk factors before starting ADT and counseled regarding the risks and benefits of this therapy.

Keywords

prostate cancer; deep vein thrombosis; pulmonary embolism; androgen deprivation; arterial embolism

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Conflicts of interest None

INTRODUCTION

Prostate cancer is the most common malignancy in men, with more than 200,000 new cases in the United States in 2010.¹ The majority of patients diagnosed with prostate cancer have localized disease and a favorable prognosis.² Androgen deprivation therapy (ADT), with gonadotropin-releasing hormone (GnRH) agonists or bilateral orchiectomy, is widely used in the treatment of prostate cancer. The use of ADT has increased steadily in the last two decades among men with all stages and grades of tumor, and primary ADT is the second most common treatment for men with localized prostate cancer.^{3, 4} Its efficacy is clearly supported in men with metastatic disease.⁵ However, the benefit of ADT is less clear in the non-metastatic setting. Evidence from randomized trials supports the use of ADT in patients with high-risk localized prostate cancer treated with radiation therapy.⁴ The role of ADT in the setting of intermediate- and low-risk prostate cancer, however, is not well defined.

For every prostate cancer patient considering ADT, the potential benefits of treatment must be weighed against the risks. Men taking ADT often experience hormonal side effects such as hot flashes, loss of libido, and erectile dysfunction.^{6, 7} ADT is also associated with more serious adverse effects, including skeletal fractures, cardiovascular disease, insulin insensitivity, increased fat mass, and impaired cognition.⁸⁻¹¹ Limited evidence also suggests a relationship between ADT and thromboembolic complications such as deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial embolism (AE).¹² Thromboembolic events (TEs), while treatable, are also potentially life-threatening. If men taking ADT for prostate cancer are at increased risk of thromboembolic disease, this risk must be considered when weighing the potential benefits and harms of treatments. Our objective was to estimate the impact of androgen deprivation on TEs in a population-based cohort of men with non-metastatic prostate cancer.

METHODS

Data

The primary data source was the Surveillance, Epidemiology, and End Results (SEER)-Medicare database which links information from the National Cancer Institute (NCI)'s SEER cancer registry program with Medicare claims and enrollment records. The SEER program collects data from 17 population-based cancer registries in selected states and metropolitan areas covering 26% of the US population. Medicare is the primary health insurer for 97% of Americans 65 years and older, covering inpatient hospital care (Part A) and outpatient care and physician services (Part B). For all incident cancers, the SEER registries collect information regarding site and extent of disease, first course of cancer-directed therapy, and sociodemographic characteristics, with active follow-up for vital status and cause of death.¹³

Compared with the population of all US adults age 65 years and older, the SEER-Medicare population has a similar age and sex distribution but has more residents of urban and affluent areas and a smaller proportion of nonwhite individuals.¹³ The SEER-Medicare files were used in accordance with a data-use agreement from NCI, and the study was approved by the Institutional Review Board at Memorial Sloan-Kettering Cancer Center.

Study Cohort

We identified all cases of non-metastatic prostate cancer in the SEER-Medicare database diagnosed between 1999 and 2005. The cohort was restricted to patients 66 years or older and who had been enrolled in Parts A and B of Medicare for at least one year before diagnosis, because information from the year prior to diagnosis was necessary for estimating comorbidity. Patients diagnosed only at the time of death were excluded, as were patients

who participated in a Medicare managed care plan at the time of diagnosis or any time thereafter. Men who had metastatic disease at the time of diagnosis were excluded, based on clinical extent-of-disease information in SEER.

Treatment

Medical and surgical ADT were identified by Current Procedural Terminology (CPT) codes for GnRH agonists and bilateral orchiectomy in Medicare claims at any time following diagnosis. Duration of ADT was categorized as less than 1 year, 1 to less than 3 years, and 3 or more years, based on the interval between first and last claim for GnRH agonist. Surgical ADT was included in the category of longest ADT duration (≥ 3 years). Other prostate cancer treatments identified in Medicare claims included surgery and radiation therapy (see codes in Appendix).

Outcomes

The primary endpoint was a TE, identified in Medicare claims by ICD-9 diagnosis codes for DVT, PE, or AE. When a patient had a single claim with multiple diagnosis codes indicating PE and one of DVT or AE, the event was classified as a PE. If a claim indicated both DVT and AE without PE, the event was classified as an AE. For analysis of the cumulative number of events per patient, unique events were defined as those occurring at least 6 months apart.

Covariates

We examined several characteristics hypothesized to predict receipt of ADT or risk of TE and potentially confound the relationship between the two. Demographic characteristics from SEER included age at diagnosis, race, marital status, urban/rural location, and median income in the census tract of residence. Disease characteristics included clinical tumor stage, Gleason score, PSA, and lymph node involvement. Comorbidity was estimated using a modification of the Charlson comorbidity index based on inpatient, outpatient, and physician claims in the year before prostate cancer diagnosis.^{14, 15} We also identified patients at elevated risk for TEs specifically based on the presence of a diagnosis code for stroke, ischemic heart disease, or a TE in the year prior to cancer diagnosis.

Statistical Analysis

Unadjusted associations between exposure to ADT and patient characteristics were examined using chi-square statistics. The impact of ADT on the risk of any TE was evaluated in a time-to-event framework, where the time origin was the date of prostate cancer diagnosis and patients who did not have an event were censored at the time of death or end of follow-up. Multivariable Cox proportional hazards regression was used to estimate the impact of ADT on TEs, controlling for demographic, disease, and health characteristics. In regression analysis, receipt of ADT and other treatments were analyzed as time-dependent variables, with exposure to each treatment identified at the time of the first Medicare claim for that treatment. Hazard ratios (HR), 95% confidence intervals (CI), and two-sided *P*-values were estimated for each covariate. We performed stratified analyses to assess whether the relationship between ADT exposure and the risk of a TE varied by age at diagnosis, disease stage and grade, and type of ADT. We also repeated the analysis separating venous TEs (PE and DVT) from arterial TEs (AE).

We examined the impact of duration of ADT on both time to first TE and total number of TEs. In both analyses duration of ADT was categorized as <1 year, $1-<3$ years or ≥ 3 years, based on the interval between first and last claim for ADT. In the time-to-event framework, ADT duration was treated as a time-dependent characteristic, varying for each patient based

on his cumulative months of ADT exposure at each month, and the impact of ADT duration was estimated using multivariable Cox proportional hazards regression. The impact of ADT on the total number of TEs was estimated using multivariable negative binomial regression, stratified by total cumulative ADT exposure. All analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC). Results are reported in adherence with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.¹⁶

RESULTS

Cohort Characteristics

The study cohort included 154,611 men diagnosed with non-metastatic prostate cancer between 1999 and 2005, of whom 58,466 (38%) received ADT. In men who had ADT the median time from prostate cancer diagnosis to initiation of ADT was 1.3 months, and 83% of those who received ADT initiated therapy within 6 months of diagnosis. Men who received ADT were older and more likely to live in non-metropolitan areas and areas with lower median income than men not receiving ADT (Table 1). They also had higher clinical stage and Gleason score, greater comorbidity and were more likely to have an elevated risk for a TE due to a diagnosis of stroke, ischemic heart disease, or TE in the year before cancer diagnosis. Men who had ADT were also more likely to have received radiation at some point following diagnosis. Only 2% of men who received any ADT underwent orchiectomy. Among the 57,009 men who had medical ADT, 56% received ADT for <1 yr, 26% for 1 to <3 yrs, and 19% for 3 yrs or more. The median number of Medicare claims for GnRH agonist therapy was 2, 7 and 14 in each of these categories, respectively.

Thromboembolic Events

During a median follow-up of 52 months, 15,950 men (10.3%) had at least one TE, including 8,829 (15%) of those who had ADT and 7,121 (7%) of those with no ADT (Table 2). In men with a TE, 30% had more than one event, and half of all TEs were DVTs. About one-fourth of all events were associated with an inpatient hospital stay. At 4 years after diagnosis, TE-free survival was 87% in men who had ADT and 94% in those who did not (log-rank $P < .0001$). Controlling for patient and tumor characteristics, comorbidity, and other cancer treatment, exposure to ADT increased the risk of a TE by more than 50% (adjusted HR 1.56, 95% CI 1.50 to 1.61, $P < 0.0001$). The risk of a TE was also significantly increased among older men, black men, those who received surgery or radiation therapy, those with greater comorbidity, and men who had had a diagnosis of stroke, ischemic heart disease, or a TE in the year prior to cancer diagnosis (Table 3).

ADT had a similar impact on the risk of a TE in men younger than 75 years at diagnosis (adjusted HR 1.54, 95% CI 1.46 to 1.62) and in men 75 and older (adjusted HR 1.59, 95% CI 1.51 to 1.67). Results were also similar when the cohort was stratified by prognosis. Controlling for other factors associated with ADT increased the risk of a TE by 55% (95% CI 1.49 to 1.60) in men with a low risk of disease progression (clinical stage T2 and Gleason score ≤6) and by 83% (95% CI 1.71 to 1.96) in men with a higher risk of disease progression (stage >T2 or Gleason score >6).

Patients who had surgical rather than medical ADT should have the highest risk for TEs, because these patients are exposed to constant castrate levels of androgen. Consistent with this hypothesis, we found that the impact of ADT on the risk of a TE was greater in men who had orchiectomy (adjusted HR compared with no ADT 1.97, 95% CI 1.72 to 2.26) than in men who had androgen suppression by GnRH agonist (adjusted HR compared with no ADT 1.54, 95% CI 1.49 to 1.60). ADT exposure was associated with both venous and arterial thromboembolic events, although the magnitude of the relationship was somewhat

attenuated when these endpoints were analyzed separately. Controlling for other factors, ADT increased the risk of a DVT or PE by 27% (95% CI 1.21 to 1.32) while it increased the risk of an AE by 18% (95% CI 1.10 to 1.32).

Duration of ADT exposure was associated with both the risk of a first TE and the total number of TEs (Figure 1). Cumulative ADT exposure of <1 year increased the risk of TE by 40% (95% CI 1.33 to 1.45), 1-<3 years of ADT increased the risk by 66% (95% CI 1.57 to 1.75), and 3 or more years of ADT doubled the risk (95% CI 1.90 to 2.19), compared with no ADT, controlling for patient and disease characteristics, comorbidity and other cancer treatment (Figure 1, Panel A). The incidence rate ratio (IRR) for the impact of ADT on total number of TEs varied from 2.05 (95% CI 1.89 to 2.23) in men exposed to less than 1 year of ADT to 2.94 (95% CI 2.61 to 3.32) in those with more than 3 years of ADT or bilateral orchiectomy (Figure 1, Panel B).

DISCUSSION

In this large, population-based study of men diagnosed with non-metastatic prostate cancer, we found that ADT was associated with the risk of TEs. Men exposed to ADT, defined as GnRH agonist therapy or bilateral orchiectomy, had a greater risk of any TE after controlling for demographic and disease characteristics and other cancer treatments. Moreover, the risk of any TE and the total number of TEs both increased with longer durations of ADT.

Our results reinforce the findings of several prior studies. In another population-based study using the Swedish National Prostate Cancer Registry, men with advanced prostate cancer had an increased risk of TEs compared to a matched group of men without prostate cancer.¹² Among the men with prostate cancer, those receiving primary ADT had the highest risk of venous thrombosis.

The association of androgen deprivation with increased risk of TEs has also been investigated in other clinical settings. GnRH agonists have been associated with adverse metabolic effects, including increased fat mass and decreased insulin sensitivity.¹⁷⁻¹⁹ In addition, androgen deprivation from GnRH agonist therapy or orchiectomy has been associated with an increased risk of developing diabetes.^{9, 20} The impact of these adverse physiologic effects can alter serum lipoproteins and lead to obesity and increased arterial stiffness which may increase the risk of TEs.²¹ In preliminary experimental studies, the androgen receptor on megakaryocytic cells has been shown to regulate platelet activation and androgen has been shown to inhibit arterial thrombosis.^{23, 24}

In addition to ADT, both malignancy itself and host factors have been associated with increased risk of thromboembolic disease.²⁵⁻²⁹ TEs are also common complications after surgical intervention, affecting 0.5% to 40% of patients in the perioperative period.³⁰ Although we could not observe disease recurrences in the SEER-Medicare dataset, we excluded patients with metastatic disease at diagnosis and we controlled for important tumor characteristics including clinical stage, histological grade, preoperative PSA, and lymph node status; patient characteristics such as age, general comorbidity, and specific conditions associated with thromboembolic disease; and other cancer treatments including surgery. Adjusting for all of these factors, ADT had an independent effect on the risk of thromboembolic complications, increasing the risk of any event as well as the total number of events. Death due to prostate cancer was observed in less than 5% of patients who had a TE, suggesting that tumor progression is unlikely to confound the relationship between ADT and TE in this cohort.

The benefit of ADT, and thus the benefit-risk tradeoff, varies by disease severity. Men with high-risk prostate cancer, defined by multifactorial risk prediction algorithms, have a significantly greater likelihood of biochemical relapse compared to those with more favorable disease characteristics. Several randomized clinical trials have demonstrated that ADT improves disease-specific survival in men with high-risk prostate cancer treated with radiation therapy.³¹⁻³⁴ However, subgroup analyses suggest no statistically significant survival benefit in patients with low-risk disease.³⁵ In men with intermediate-risk prostate cancer, ADT improves prognosis, but survival differences appear to be mitigated by a patient's level of comorbidities.³⁵ In patients treated with radical prostatectomy, neoadjuvant ADT may decrease the rate of positive surgical margins, but it has not been shown to improve disease-free or overall survival.³⁶ Separate from its effect on survival, the impact of ADT on quality of life may be mixed. In a population-based sample of men with localized prostate cancer who received neither surgery nor radiation therapy, those treated with ADT reported greater satisfaction with their treatment decision, but greater physical discomfort than men who had no ADT.³⁷

Even when the benefits of ADT are likely to outweigh the risks, the optimal duration of therapy is uncertain. One randomized trial found greater overall survival with 36 months of ADT compared to 6 months in men with high-risk prostate cancer patients treated with radiation therapy.³⁸ However, a pooled analysis of patients enrolled in three randomized trials and treated with long-term or short-term ADT and radiation therapy concluded that a longer duration of ADT was not associated with improved survival.³⁹ Moreover, in a randomized trial of radiation therapy with or without ADT, patients who received long-term ADT had a higher rate of non-cancer deaths than patients on short-term ADT.⁴⁰

While our findings are relevant to clinical decision-making for individual patients, they also have important implications for public health and the economic burden of prostate cancer. Although prostate cancer accounts for a substantial fraction of new cancer cases and deaths each year, most men are diagnosed at an early stage with a favorable prognosis. More than 45% of patients will die of causes other than prostate cancer and TEs are the second most common cause of death among all cancer patients.^{41, 42} In 1999, ADT was given to half of all prostate cancer patients and accounted for one third of Medicare expenditures for prostate cancer treatment.³ However, use of ADT appears sensitive to the level of reimbursement for physicians. Two studies showed a substantial decline in utilization after Medicare payments for ADT administration were reduced.^{43, 44}

Several limitations of our analysis should be noted. In this observational study, our findings demonstrate an association between ADT and TEs, but we are limited in our ability to infer causality. Although we were able to control for numerous potential confounders, we could not control for smoking history or body mass index, two factors associated with thromboembolic complications. We also had no information regarding patient preferences or physician recommendations for treatment, or other factors which may be associated with both receipt of ADT and with the underlying risk of TE. During the years of our study, we could not identify another potential confounder, oral anticoagulant therapy, in Medicare claims. Finally, our results may not be generalizable to prostate cancer patients younger than 66 years.

Our results add to an expanding body of literature which suggests that concerns regarding ADT are warranted, and they emphasize the importance of identifying those men at highest risk for complications and implementing strategies to prevent treatment-related morbidity. The implications of these findings prompt several recommendations for prostate cancer patients and their physicians. First, men considering ADT should be assessed for TE risk factors, such as obesity, smoking, prolonged immobility, and personal history of stroke or

TEs, before starting therapy. Second, for men who initiate ADT, they and their physicians need to be aware of and vigilant for thromboembolic complications. Most importantly, the treatment decision-making process should include a careful discussion, tailored to the individual patient based on his health and the characteristics of his disease, of the expected benefits and potential harms of ADT and other treatment options.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Adjusted impact of ADT duration on thromboembolic events

Panel A shows the adjusted impact of ADT duration on risk of first TE with ADT duration analyzed as a time-dependent characteristic, varying for each patient based on his cumulative months of ADT exposure at each month. Men who had surgical ADT were assumed to have continuous ADT exposure from the time of orchiectomy. Each category of ADT duration was compared with no ADT.

Panel B shows the adjusted impact of ADT on total number of TEs, estimated with negative binominal regression, stratified by total cumulative ADT exposure. Men who had surgical ADT were included in the group with 3 or more years of ADT exposure. Each category of ADT duration was compared with no ADT. All incidence rate ratios were statistically significant at

ADT: androgen deprivation therapy

TE: thromboembolic event

Table 1

Characteristics of cohort by receipt of androgen deprivation therapy

	All patients		ADT		No ADT		P-value
	No. Pts	%	No. Pts	%	No. Pts	%	
Total	154,611	—	58,466	—	96,145	—	
Age at diagnosis							<0.001
66-69	39,209	25%	10,337	18%	28,872	30%	
70-74	48,487	31%	16,855	29%	31,632	33%	
75-59	38,098	25%	16,563	28%	21,535	22%	
80-84	19,789	13%	9,970	17%	9,819	10%	
85+	9,028	6%	4,741	8%	4,287	4%	
Race							<0.001
White	126,039	82%	47,950	82%	78,089	81%	
Black	15,330	10%	5,703	10%	9,627	10%	
Other	13,074	8%	4,741	8%	8,333	9%	
Unknown	168	<1%	72	<1%	96	<1%	
Census tract median income							<0.0001
1st quartile	37,191	24%	15,816	27%	21,375	22%	
2nd quartile	37,224	24%	14,138	24%	23,086	24%	
3rd quartile	37,208	24%	13,180	23%	24,028	25%	
4th quartile	37,217	24%	13,043	22%	24,174	25%	
Unknown	5,771	4%	2,289	4%	3,482	4%	
Urban-rural residence							<0.0001
Metropolitan	136,821	88%	49,533	85%	87,288	91%	
Non-metropolitan	17,790	12%	8,933	15%	8,857	9%	
Region							<0.0001
Northeast	30,062	19%	15,287	26%	14,775	15%	
South	20,872	13%	9,351	16%	11,521	12%	
Midwest	19,532	13%	9,130	16%	10,402	11%	
West	84,145	54%	24,698	42%	59,447	62%	
Married							<0.0001
Yes	106,740	69%	38,684	66%	68,056	71%	
No	31,234	20%	12,011	21%	19,223	20%	
Unknown	16,637	11%	7,771	13%	8,866	9%	
Clinical stage							<0.0001
T1	66,895	43%	21,370	37%	45,525	47%	
T2	83,180	54%	34,440	59%	48,740	51%	
T3	3,589	2%	2,104	4%	1,485	2%	
T4	947	1%	552	1%	395	<1%	
Gleason score							<0.0001
2-4	4,864	3%	1,293	2%	3,571	4%	
5-7	97,617	63%	31,713	54%	65,904	69%	

	All patients		ADT		No ADT		P-value
	No. Pts	%	No. Pts	%	No. Pts	%	
8+	46,960	30%	23,624	40%	23,336	24%	<0.0001
Unknown	5,170	3%	1,836	3%	3,334	3%	
Preoperative PSA							
Elevated	111,296	72%	42,656	73%	68,640	71%	<0.0001
Borderline	8,415	5%	2,183	4%	6,232	6%	
Normal	7,958	5%	3,004	5%	4,954	5%	
Unknown	26,942	17%	10,623	18%	16,319	17%	<0.0001
Lymph node involvement							
Positive	43,801	28%	15,135	26%	28,666	30%	<0.0001
Negative	92,968	60%	36,015	62%	56,953	59%	
Unknown	17,842	12%	7,316	13%	10,526	11%	
Charlson comorbidity score							<0.0001
0	121,672	79%	40,181	69%	81,491	85%	
1	21,689	14%	11,971	20%	9,718	10%	
2+	11,250	7%	6,314	11%	4,936	5%	<0.0001
Elevated TE risk *							
Yes	35,102	23%	19,270	33%	15,832	16%	
No	119,509	77%	39,196	67%	80,313	84%	<0.0001
Year of diagnosis							
1999	12,679	8%	4,869	8%	7,810	8%	<0.0001
2000	24,645	16%	9,837	17%	14,808	15%	
2001	25,774	17%	10,273	18%	15,501	16%	
2002	25,696	17%	10,079	17%	15,617	16%	<0.0001
2003	22,914	15%	8,830	15%	14,084	15%	
2004	22,171	14%	7,935	14%	14,236	15%	
2005	20,732	13%	6,643	11%	14,089	15%	<0.0001
Other prostate cancer treatment							
Surgery only	15,208	10%	2,560	4%	12,648	13%	<0.0001
RT only	56,104	36%	33,836	58%	22,268	23%	
Surgery + RT	2,840	2%	1,429	2%	1,411	1%	
Neither	80,459	52%	20,641	35%	59,818	62%	<0.0001
Type of ADT							
Medical	57,009	37%	57,009	98%	N/A		
Surgical	1,457	1%	1,457	2%	N/A		

ADT: Androgen deprivation therapy

TE: Thromboembolic event

PSA: prostate-specific antigen

RT: Radiation therapy

* Stroke, ischemic heart disease, or TE in year prior to prostate cancer diagnosis

Table 2

Frequency of thromboembolic events by ADT exposure ADT No ADT

	ADT (N = 58,466)			No ADT (N = 96,145)		
	No. Pts	% of Pts	No. Events	No. Pts	% of Pts	No. Events
Thromboembolic events						
Any event	8,829	15%	13,330	7,121	7%	10,318
Deep venous thrombosis	4,360	7%	6,623	3,564	4%	5,191
Arterial embolism	2,574	4%	3,834	2,011	2%	2,874
Pulmonary embolism	1,895	3%	2,873	1,546	2%	2,253

Table 3

Predictors of time to first thromboembolic event

Characteristic	Adjusted HR (95% CI)	P-value
Androgen deprivation *		
No	Reference	
Yes	1.54 (1.48 - 1.59)	<0.0001
Prostate cancer surgery *		
No	Reference	
Yes	1.53 (1.45 - 1.62)	<0.0001
Radiation therapy *		
No	Reference	
Yes	1.34 (1.29 - 1.39)	<0.0001
Age at diagnosis		
66-69	Reference	
70-74	1.13 (1.08 - 1.18)	<0.0001
75-79	1.30 (1.24 - 1.36)	
80-84	1.54 (1.45 - 1.62)	
85+	1.62 (1.50 - 1.75)	
Race		
White	Reference	
Black	1.32 (1.26 - 1.39)	<0.0001
Other/Unknown	0.73 (0.68 - 0.79)	
Census tract median income		
1st quartile	Reference	
2nd quartile	0.93 (0.89 - 0.97)	<0.0001
3rd quartile	0.89 (0.85 - 0.94)	
4th quartile	0.89 (0.84 - 0.93)	
Unknown	1.09 (1.00 - 1.18)	
Urban-rural residence		
Metropolitan	Reference	
Non-Metropolitan	0.88 (0.84 - 0.93)	<0.0001
Geographic area		
Northeast	Reference	
South	0.89 (0.84 - 0.94)	<0.0001
Midwest	1.14 (1.09 - 1.20)	
West	0.80 (0.77 - 0.83)	
Married		
No/Unknown	Reference	
Yes	0.93 (0.90 - 0.96)	<0.0001
Gleason score		
2 - 7	Reference	<0.001
8 - 10	1.02 (0.98 - 1.06)	

Characteristic	Adjusted HR (95% CI)	P-value
Unknown	1.19 (1.10 - 1.29)	
Clinical stage		
T1	Reference	
T2	0.98 (0.95 - 1.01)	<0.0001
T3/T4	1.20 (1.10 - 1.30)	
Lymph node involvement		
Negative	Reference	
Positive	1.04 (0.98 - 1.11)	NS
Unknown	0.99 (0.95 - 1.04)	
Preoperative PSA		
Normal	Reference	
Borderline	1.03 (0.94 - 1.14)	<0.0001
Elevated	0.99 (0.92 - 1.06)	
Unknown	1.17 (1.07 - 1.25)	
Elevated TE risk		
No	Reference	
Yes	1.76 (1.69 - 1.82)	<0.0001
Charlson comorbidity score		
0	Reference	
1	1.52 (1.46 - 1.58)	<0.0001
2+	2.16 (2.06 - 2.27)	
Year of diagnosis	1.02 (1.00 - 1.03)	< .02

HR: Hazard ratio

TE: Thromboembolic event

PSA: prostate-specific antigen

P-value for adjusted association between characteristic and hazard of first TE

* All prostate cancer treatments analyzed as time-dependent characteristics