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Androgen Deprivation Therapy and Diabetes Control among Diabetic Men with Prostate Cancer

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Abstract

Background—Androgen deprivation therapy (ADT) for prostate cancer is associated with decreased insulin sensitivity and incident diabetes. Few data are available about the effects of ADT on diabetes control among men with diabetes. We examined care for over 7500 men with prostate cancer who had diabetes at the time of diagnosis to assess the effect of ADT on diabetes control, as measured by HbA1c levels and the intensification of diabetes drug therapy.

Methods—We compared hemoglobin A1c (HbA1c) levels and intensification of diabetes pharmacotherapy among 2237 pairs of propensity matched men with prostate cancer and diabetes who were or were not treated with ADT. We calculated the difference-in-difference of HbA1c levels at baseline and 1 and 2 years in the 2 groups, compared using a paired t test. We used a Cox proportional hazards model to estimate time to intensification of diabetes therapy.

Results—The mean (SE) HbA1c at baseline was 7.24 (0.05) for the ADT group and 7.24 (0.04) for the no-ADT group. HbA1c increased at 1 year for men treated with ADT to 7.38 (0.04) and decreased among men not treated with ADT to 7.14 (0.04), for a difference in differences of +0.24 (P=0.008). Results were similar at 2 years (P=.03). Receipt of ADT was also associated with an increased hazard of addition of diabetes medication (adjusted hazard ratio=1.20, 95% CI=1.09-1.32).

Conclusions—ADT is associated with worsening of diabetes control, with both increases in HbA1c levels and the need for additional diabetes medications.

Keywords

prostate cancer; androgen deprivation therapy; diabetes

Previous research suggests that androgen deprivation therapy (ADT) for prostate cancer is associated with decreased insulin sensitivity¹ and development of incident diabetes.²⁻⁵ These findings also suggest that ADT may worsen diabetes control for patients with diabetes. However, few data are available about the impact of ADT on blood sugar control for men with diabetes. One small, single-institution study of 396 prostate cancer patients treated with ADT and followed for a median of 5 years observed that among 77 individuals

with known diabetes at the time of ADT initiation, 19.5% experienced an increase in serum hemoglobin a1c (HbA1c) levels of 10% or more above baseline levels and 29.6% of men had an increase in fasting serum glucose levels of 10% or more above their baseline levels.⁶ Another study of 29 patients with metastatic prostate cancer and diabetes who were treated with ADT found that glycemic control worsened substantially.⁷ These studies were limited, however, by the lack of a control group.

In this study, we examined care for over 7500 men with prostate cancer who had diabetes at the time of diagnosis to assess the effect of ADT on diabetes control, as measured by HbA1c levels and the intensification of diabetes drug therapy.

Patients and methods

Data

We used data from the Veterans Health Administration (VA) for this analysis. Since 1998, the VA Central Cancer Registrar has collected uniformly reported data from each VA medical center on incident cancers diagnosed or receiving their first course of treatment within the VA. We linked registry data from 2001-2004 with administrative data from 2000-2005, including inpatient and outpatient encounter data, pharmacy data on medications administered by the VA and outpatient prescriptions filled, and Medicare administrative data for patients who are also Medicare eligible.

Study cohort

As described previously,³ we identified 37,443 men who were diagnosed with invasive local/regional prostate cancer during 2001-2004, who were not diagnosed at autopsy or by death certificate and who had evidence for claims. We excluded 2016 patients with no administrative data following their cancer diagnosis and 132 patients whose first dose of androgen deprivation therapy was dated more than 30 days before the documented date of diagnosis. From these 35,295 men, we identified 7874 men with evidence for prevalent diabetes at the time of prostate cancer diagnosis, defined as one inpatient admission with a primary diagnosis of diabetes (Appendix) or two or more outpatient visits with a diagnosis of diabetes that appeared more than 30 days apart during the period from 12 months before diagnosis through 6 months after diagnosis.² We then excluded 281 patients with no HbA1c tests during follow up, leaving 7593 men with diabetes and at least one HbA1c.

Androgen deprivation therapy

As previously described, we ascertained receipt of gonadotropin-releasing hormone (GnRH) agonist therapy and orchiectomy using administrative data (Appendix);^{2,3} men were considered continuously treated for 6 months after each GnRH agonist injection, which were nearly all for 3-month or 4-month equivalent doses.

Diabetes control

We assessed two measures of diabetes control over time. First, we assessed glycosylated hemoglobin (A1c) values from the laboratory data. Second, we assessed initiation of a new diabetes medication (based on starting diabetes medications if not already on them, or adding a medication from a new class).

We documented the HbA1c value for each quarter of observation during follow up. Guidelines recommend testing HbA1c at least twice yearly in patients with controlled diabetes, or quarterly in patients whose therapy has changed or who are not meeting glycemic goals.⁸ HbA1c measures glucose control over several months,⁹ thus, 3-month

periods are likely to be the minimum timing for meaningful changes in values and any changes in medications.

In any given quarter, 31.4% to 49.5% of non-censored men had a HbA1c value (in the infrequent case that there were 2 or more values in any quarter, these were averaged). We used multiple imputation to impute a HbA1c value for each quarter.¹⁰ The multiple imputation models were based on patient characteristics (age at diagnosis, year of diagnosis, race/ethnicity, marital status, Census division, median household income and average proportion of residents who are high school graduates in the zip code of residence at diagnosis, tumor stage, tumor grade, type of primary treatment (surgery, radiation, or neither [Appendix]), and individual comorbid illnesses identified using coding from the Klabunde modification of the Charlson comorbidity index.¹¹ We also included prostate specific antigen (PSA) levels at diagnosis, HbA1c in other quarters, diabetes medications, ADT, and any blood glucose levels in the laboratory data. In sensitivity analyses we also repeated analyses using complete data for A1c at baseline, and 1 and 2 year time points.

To assess initiation of a new drug class, we assessed for start of a drug that was in a class that the patient had not been on after baseline. Drug classes available during the study period included metformin, sulfonamides (glyburide, glypizide, glimepiride, tolazamide, tolbutamide), other oral drugs (acarbose, miglitol, pioglitazone, rosiglitazone, nateglinide, repaglinide), and insulins (short or long acting).

Analyses

After describing characteristics of the cohorts, we used propensity score analyses to match men treated with ADT with similar men who were not treated with ADT based on all observed characteristics. For men treated with ADT, we characterized baseline variables, such as age and comorbid illness, at the time ADT was started (rather than the time of diagnosis). We matched these men to men who were not treated with ADT who had similar characteristics, including age and comorbid illness, characterized at the time of diagnosis, since we were able to characterize comorbid illness for all men at that time.

To conduct the propensity score matching, we first used a logistic regression model to predict receipt of ADT. The propensity score model included race/ethnicity, marital status, U.S. Census division, median household income and proportion of high school graduates in the zip code of residence, tumor grade, prostate specific antigen level at diagnosis, primary treatment received, as well as variables defined as of the date of initiation of ADT (for the ADT group) or diagnosis (for the no-ADT group), including age, specific comorbid illnesses defined based on the Charlson comorbidity index¹¹ and also including hypertension and obesity,¹² year, baseline HbA1c, and baseline diabetes medications. Variables were categorized as in Table 1. Then, for each man treated with ADT, we sought to match, without replacement, one man with a similar propensity to receive ADT (within 0.6 standard deviations of the propensity score). We successfully matched 2237 of the 3156 men treated with ADT with a patient who did not receive ADT. The characteristics of the matched cohort are very similar (Table 1).

We then calculated the difference in differences and used paired t-tests to compare the change in HbA1c from baseline (the quarter before diagnosis or start of ADT) through 1 year (quarter +4) among men who were not censored. We also similarly compared change in HbA1c from baseline through 2 years (quarter +8) for men who did and did not receive ADT for men who were not censored. In sensitivity analyses, we repeated the HbA1c analyses only among patients with non-missing HbA1c values in the quarters of interest. We also repeated these analyses restricting to men (and matched pairs) who were treated continuously with ADT for at least 1 year and for at least 2 years. Analyses of the HbA1c

imputed data were conducted using the MIANALYZE procedure in SAS software, version 9.2 (SAS Institute).

To assess for changes in diabetes medications, we calculated the incidence rates of the event of initiating diabetes pharmacotherapy or increasing the number of diabetes drug classes for the matched cohorts of men who were and were not treated with ADT. We then used a Cox proportional hazards regression model in the propensity matched data to assess if ADT was associated with initiating or adding a new class of diabetes drugs, adjusting for all other covariates.

All tests of statistical significance were two-sided. We used SAS statistical software, version 9 (SAS Institute, Inc., Cary, North Carolina) for analyses. The study was approved by the Institutional Review Boards of the Durham Veterans Affairs Medical Center and Harvard Medical School.

Results

Of 7593 men diagnosed with local/regional prostate cancer during 2001-2004 and followed through 2005, 3156 were treated with ADT at some point. Characteristics of the men who were treated and not treated with ADT are included in Table 1. We successfully matched 2237 men who were treated with ADT with an equal number of men not treated with ADT. Characteristics of the matched cohorts were evenly distributed (Table 1).

Table 2 presents the HbA1c values at baseline and 1 year for patients who were not censored before the end of 1 year as well as the values for at baseline and 2 years for patients not censored by 2 years. The mean (SE) HbA1c at baseline for men in the 1 year cohort was 7.24 (0.05) for the ADT group and 7.24 (0.04) for the group not treated with ADT. HbA1c increased at 1 year for men treated with ADT to 7.38 (0.04) and decreased among men not treated with ADT to 7.14 (0.04), for a difference in differences of +0.24 ($P=0.008$). Similarly, among the 2-year cohort, the mean HbA1c increased during follow up among men treated with ADT and decreased among men not treated with ADT (difference in differences 0.18, $P=0.03$). Overall, 19.2% of men on ADT had a HbA1c increase of 1.0% at one year vs. 11.9% of men not treated with ADT.

Table 3 demonstrates the use of diabetes medications at baseline among matched cohorts of men who were and were not treated with ADT. Approximately 82% of both groups were taking at least some form of medications, with about 27% on metformin, 40% on sulfonylureas, and 19% on insulin. Most patients at baseline were treated with a single agent.

The unadjusted rates per 1000 person-years for initiating or increasing a class of diabetes drugs are included in Table 4. We found a higher unadjusted rate for initiating or increasing a new drug class for men on ADT with 248.6 per 1000 person-years (95% CI=233.2-265.0) than for men not on ADT with 209.6 per 1000 person-years (95% CI=195.9-224.4; $P<0.001$).

Table 5 displays the results of the Cox proportional hazards model assessing time to initiating or adding a new class of diabetes medication. Receipt of ADT was associated with an increased hazard of addition of diabetes medication (adjusted hazard ratio=1.20, 95% CI=1.09-1.32). Other factors associated with increased intensity of the diabetes regimen included higher baseline levels of HbA1c and residing in areas with higher levels of educational attainment.

In sensitivity analyses, we repeated the analyses assessing HbA1c over time including only patients with complete data on HbA1c values at baseline and 1 year (N=2268 patients) and 2 years (N=1295 patients). Results were similar to the findings reported (data not shown). We also repeated analyses among patients who were continuously treated with ADT for 1 year or more (N=2770) or 2 years or more (N=1278), and results demonstrated a stronger association between ADT and difference in HbA1c (data not shown).

Discussion

ADT is frequently prescribed for the treatment of local or regional prostate cancer.^{13,14} However, recent research has found that ADT is associated with metabolic changes, including decreased insulin sensitivity¹ and development of incident diabetes.²⁻⁵ This research suggest that ADT may also worsen diabetes control for patients with diabetes. However, to date there has been limited information about the effect of ADT on diabetes control for men with diabetes.

We studied a large cohort of men with local/regional prostate cancer in the VA who had diabetes at the time of their prostate cancer diagnosis. We found that ADT was associated with worsening diabetes control despite the intensification of pharmacologic therapy for diabetes. Although the increases in HbA1c were modest (an increase in 0.14%), in light of improved control of HbA1c in the control group, the net change in HbA1c was a quarter of a percent. Nearly 20% of men treated with ADT had an increase in HbA1c of at least 1.0 percentage points, compared with only 12% of men not treated with ADT. At the same time, there was a 20% increase in the risk for new diabetes medications being added. This often involved addition of insulin to one's regimen, or requirement for multiple classes of medications, which can lead to problems with weight gain or hypoglycemia, and can increase health care costs to patients.

Although comprehensive guidelines are not currently available about management of diabetes for men on ADT, a scientific advisory sponsored by the American Heart Association recommend that patients with cardiac disease who are treated with ADT receive appropriate secondary preventive measures including glucose lowering therapies to reduce glucose and glycosylated hemoglobin levels for patients with diabetes as recommended by other national guidelines.¹⁵ Guidelines of the National Comprehensive Cancer Network currently not that ADT is associated insulin resistance and an increased risk for diabetes and recommend intervention to prevent/treat diabetes in men receiving ADT.¹⁶ Although it remains uncertain whether strategies for screening, prevention, and treatment of diabetes in men receiving ADT should differ from the general population, strategies such as exercise, weight loss, and healthy eating, as well as monitoring of glycemic control and intensifying medication as needed, are likely to be helpful in maintaining diabetes control for men with diabetes who require ADT.

Our study's strengths include the large population of men from across the U.S. with prostate cancer and diabetes who were diagnosed and treated before evidence about the association of ADT with insulin resistance or diabetes was published. In addition, we had rich clinical, pharmacy, and laboratory data that allowed us to examine very similar men who were and were not treated with ADT using propensity score methods. Our study also has some limitations. First, our study included only men with prostate cancer treated in the VA during 2000-2005; however, we had rich data that included prescription and laboratory data, and we have no reason to believe that our findings would not generalize to other populations. Second, we ascertained use of ADT based on administrative data. Previous research in the VA has demonstrated that administrative data are highly valid for ascertaining cancer treatments such as chemotherapy and radiation. Third, we compared diabetes control and

medication use among propensity matched cohorts of similar men in the time period after ADT initiation for the ADT group and after diagnosis for the control group. We have no reason to expect that this would bias our findings. Even if there was intensity of diabetes care in the period following diagnosis in the control group which could have potentially caused the control group's diabetes control to improve, we would have also expected to see more diabetes medications in the control group.

In conclusion, ADT is associated with worsening of diabetes control, with both increases in HbA1c levels and the need for additional diabetes medications. Men with diabetes who start ADT should be counseled about the potential need for intensification of diabetes therapy and should have their HbA1c levels monitored during therapy, especially if they continue on long-term ADT. Their diabetes control should also be monitored when ADT is finished. Physicians should continue to weigh potential benefits and risks of treatment when making decisions about the use of ADT, particularly when used in settings for which the benefits have not been clearly established.

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Appendix

Diagnosis or Procedure	ICD-9 Diagnosis	HCPCS	CPT	ICD-9 Procedure	Comments
Diabetes ^{2,17-19}					Required two or more outpatient encounters with a primary or secondary diagnosis code or one hospitalization with a primary diagnosis of diabetes
Diabetes mellitus	250.xx				
Diabetic polyneuropathy	357.2				
Diabetic retinopathy	362.0-362.0x				
Diabetic cataract	366.41				
Leuprolide injection [*]		J9217, J9218, J9219, J1950			
Goserelin injection [*]		J9202			
Orchiectomy			54520, 54521, 54522, 54530, 54535, 54690, 49510	62.3, 62.4, 62.41, 62.42	
Radical prostatectomy [†]			55810-55815, 55840-55845	60.5	
Radiation therapy [†]	V58.0, V67.1, V66.1		77261-77431, 77499, 77750-77799	92.2-92.29	

^{*} To calculate duration of use, we added the number of months on therapy. We considered men continuously on therapy for 6 months after each dose.

[†] Radical prostatectomy and radiation therapy were identified based on claims in the 6 months after diagnosis or data from the VA-registry data indicating use of these treatments.^{20,21}

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Table 1
Patient characteristics and receipt of androgen deprivation therapy (ADT) before and after propensity score matching

Characteristic	Before Propensity Score Matching (N = 7593)			After Propensity Score Matching (N = 4474)*		
	ADT	No ADT	PValue	ADT	No ADT	PValue
Total	3156	4437		2237	2237	
Age (Mean (SD))	70.2 (7.7)	66.0 (7.7)	<0.001	68.9 (7.6)	68.8 (7.4)	0.64
Race			<0.001			0.48
White	1888 (59.8)	2761 (62.2)		1373 (61.4)	1403 (62.7)	
Black	885 (28.0)	1287 (29.0)		634 (28.3)	609 (27.2)	
Hispanic	281 (8.9)	256 (5.8)		164 (7.3)	148 (6.6)	
Other or unknown	102 (3.2)	133 (3.0)		66 (3.0)	77 (3.4)	
Marital status			0.81			0.94
Married	1872 (59.3)	2609 (58.8)		1320 (59.0)	1331 (59.5)	
Unmarried	1216 (38.5)	1738 (39.2)		871 (38.9)	861 (38.5)	
Unknown	68 (2.2)	90 (2.0)		46 (2.1)	45 (2.0)	
Census division			<0.001			0.90
New England	129 (4.1)	152 (3.4)		90 (4.0)	79 (3.5)	
Mid Atlantic	328 (10.4)	494 (11.1)		233 (10.4)	258 (11.5)	
South Atlantic	929 (29.4)	1010 (22.8)		599 (26.8)	571 (25.5)	
East North Central	316 (10.0)	516 (11.6)		240 (10.7)	247 (11.0)	
West North Central	250 (7.9)	389 (8.8)		188 (8.4)	183 (8.2)	
East South Central	262 (8.3)	344 (7.8)		184 (8.2)	181 (8.1)	
West South Central	441 (14.0)	630 (14.2)		322 (14.4)	317 (14.2)	
Mountain	130 (4.1)	193 (4.4)		89 (4.0)	97 (4.3)	
Pacific	371 (11.8)	709 (16.0)		292 (13.1)	304 (13.6)	
Median household income in zip code of residence at diagnosis			<0.001			0.99
Quartile 1 (lowest)	821 (26.0)	984 (22.2)		556 (24.9)	554 (24.8)	
Quartile 2	771 (24.4)	1035 (23.3)		546 (24.4)	554 (24.8)	
Quartile 3	739 (23.4)	1066 (24.0)		526 (23.5)	516 (23.1)	
Quartile 4 (high)	675 (21.4)	1131 (25.5)		506 (22.6)	506 (22.6)	
Missing	150 (4.8)	221 (5.0)		103 (4.6)	107 (4.8)	

Characteristic	Before Propensity Score Matching (N = 7593)			After Propensity Score Matching (N = 4474)*		
	ADT	No ADT	PValue	ADT	No ADT	PValue
% High school graduates in census tract of residence at diagnosis			0.002			0.72
Quartile 1 (lowest)	741 (23.5)	1065 (24.0)		535 (23.9)	565 (25.3)	
Quartile 2	806 (25.5)	999 (22.5)		551 (24.6)	517 (23.1)	
Quartile 3	770 (24.4)	1034 (23.3)		547 (24.5)	539 (24.1)	
Quartile 4 (high)	689 (21.8)	1118 (25.2)		501 (22.4)	509 (22.7)	
Missing	150 (4.8)	221 (5.0)		103 (4.6)	107 (4.8)	
Tumor grade (Gleason score)			<0.001			0.04
Well differentiated (2-4)	79 (2.5)	224 (5.1)		74 (3.3)	71 (3.2)	
Moderately differentiated (5-7)	1474 (46.7)	3038 (68.5)		1267 (56.9)	1360 (60.8)	
Poorly or undifferentiated (8-10)	1471 (46.6)	1009 (22.7)		788 (35.2)	704 (31.5)	
Unknown	132 (4.2)	166 (3.7)		108 (4.8)	102 (4.6)	
Prostate-specific antigen level at diagnosis (ng/mL)			<0.001			0.24
< 5.00	341 (10.8)	1167 (26.3)		327 (14.6)	327 (14.6)	
5.00 – 7.49	644 (20.4)	1429 (32.2)		590 (26.4)	620 (27.7)	
7.50 – 9.99	437 (13.9)	635 (14.3)		361 (16.1)	376 (16.8)	
10.00	1335 (42.3)	675 (15.2)		643 (28.7)	576 (25.8)	
Unknown	399 (12.6)	531 (12.0)		316 (14.1)	338 (15.1)	
Primary treatment received in the 6 months after diagnosis			<0.001			0.90
Radical prostatectomy	180 (5.7)	1233 (27.8)		179 (8.0)	183 (8.2)	
Radiation therapy	1434 (45.4)	1711 (38.6)		1057 (47.3)	1068 (47.7)	
Neither	1542 (48.9)	1493 (33.6)		1001 (44.7)	986 (44.1)	
Comorbidity						
MI	44 (1.4)	35 (0.8)	0.01	27 (1.2)	23 (1.0)	0.57
Old MI	79 (2.5)	84 (1.9)	0.07	57 (2.6)	60 (2.7)	0.78
CHF	309 (9.8)	268 (6.0)	<0.001	206 (9.2)	208 (9.3)	0.92
Peripheral vascular disease, dx	214 (6.8)	204 (4.6)	<0.001	132 (5.9)	144 (6.4)	0.46
Peripheral vascular disease, surgical	12 (0.4)	12 (0.3)	0.40	5 (0.2)	8 (0.4)	0.41
Cerebrovascular disease	197 (6.2)	168 (3.8)	<0.001	121 (5.4)	122 (5.4)	0.95
COPD	387 (12.3)	404 (9.1)	<0.001	249 (11.1)	261 (11.7)	0.57
Dementia	20 (0.6)	15 (0.3)	0.06	8 (0.4)	13 (0.6)	0.27

Characteristic	Before Propensity Score Matching (N = 7593)			After Propensity Score Matching (N = 4474)*		
	ADT	No ADT	PValue	ADT	No ADT	PValue
Paralysis	21 (0.7)	19 (0.4)	0.16	14 (0.6)	12 (0.5)	0.69
Chronic renal failure	177 (5.6)	155 (3.5)	<0.001	118 (5.3)	114 (5.1)	0.79
Various cirrhodites	13 (0.4)	11 (0.3)	0.21	8 (0.4)	7 (0.3)	0.80
Moderate-severe liver disease	4 (0.1)	5 (0.1)	0.99	1 (0.0)	2 (0.1)	0.99
Ulcers1	28 (0.9)	35 (0.8)	0.64	21 (0.9)	19 (0.9)	0.75
Ulcers2	13 (0.4)	10 (0.2)	0.15	7 (0.3)	8 (0.4)	0.80
Rheumatism	32 (1.0)	39 (0.9)	0.55	24 (1.1)	21 (0.9)	0.65
AIDS	9 (0.3)	9 (0.2)	0.47	5 (0.2)	6 (0.3)	0.76
HTN	2343 (74.2)	2874 (64.8)	<0.001	1611 (72.0)	1597 (71.4)	0.64
Obesity	301 (9.5)	425 (9.6)	0.95	233 (10.4)	234 (10.5)	0.96
Year of diagnosis or starting ADT			<0.001			0.94
2001	555 (17.6)	958 (21.6)		428 (19.1)	420 (18.8)	
2002	775 (24.6)	1078 (24.3)		550 (24.6)	538 (24.1)	
2003	748 (23.7)	1140 (25.7)		549 (24.5)	562 (25.1)	
2004/2005	1078 (34.2)	1261 (28.4)		710 (31.7)	717 (32.0)	
Baseline diabetes medications						
Metformin	825 (26.1)	1309 (29.5)	0.001	610 (27.3)	621 (27.8)	0.71
Sulfonylurea	1294 (41.0)	1758 (39.6)	0.23	917 (41.0)	889 (39.7)	0.39
Other oral hypoglycemic agents	193 (6.1)	227 (5.1)	0.06	134 (6.0)	137 (6.1)	0.85
Insulin	656 (20.8)	729 (16.4)	<0.001	428 (19.1)	431 (19.3)	0.91
Baseline hemoglobin A1c level			0.77			0.98
< 6.00%	504 (16.0)	643 (14.5)		340 (15.2)	322 (14.4)	
6.00 – 6.49%	465 (14.7)	668 (15.1)		323 (14.4)	338 (15.1)	
6.50 – 6.99%	487 (15.4)	694 (15.6)		346 (15.5)	348 (15.6)	
7.00 – 7.49%	382 (12.1)	540 (12.2)		285 (12.7)	279 (12.5)	
7.50 – 8.49%	478 (15.2)	676 (15.2)		336 (15.0)	333 (14.9)	
8.50%	457 (14.5)	663 (14.9)		332 (14.8)	332 (14.8)	
Unknown	383 (12.1)	553 (12.5)		275 (12.3)	285 (12.7)	
Followed-up duration			<0.001			0.92
Less than one year	244 (7.7)	154 (3.5)		132 (5.9)	126 (5.6)	

Characteristic	Before Propensity Score Matching (N = 7593)			After Propensity Score Matching (N = 4474)*		
	ADT	No ADT	PValue	ADT	No ADT	PValue
One year	897 (28.4)	1040 (23.4)		601 (26.9)	607 (27.1)	
Two years	802 (25.4)	1235 (27.8)		599 (26.8)	614 (27.5)	
Three years and longer	1213 (38.4)	2008 (45.3)		905 (40.4)	890 (39.8)	

* Propensity score model included all variables in the table; 2237 of the 3156 men who were treated with androgen deprivation therapy were matched one to one with a patient who was not treated with androgen deprivation therapy without replacement.

Table 2

Change in HbA1c over time for men with and without ADT treatment

	N	Baseline HbA1c		One Year HbA1c		Change in HbA1c from baseline to 1 year		Difference	P Value
1 Year									
		HbA1c, %	SE	HbA1c, %	SE	ΔHbA1c, %	SE		
ADT	2105	7.24	0.05	7.38	0.04	0.13	0.07	0.24	0.008
No ADT	2111	7.24	0.04	7.14	0.04	-0.11	0.04	Reference	-
	N	Baseline HbA1c		Two Year HbA1c		Change in HbA1c from baseline to 2 years		Difference	P Value
2 Years									
		HbA1c, %	SE	HbA1c, %	SE	ΔHbA1c, %	SE		
ADT	1504	7.25	0.06	7.35	0.05	0.10	0.08	0.18	0.03
No ADT	1504	7.24	0.05	7.16	0.06	-0.08	0.06	Reference	-

* Based on paired t test comparing difference in difference from baseline to 1 or 2 years of follow up for the two groups. The cohorts were based on 2237 propensity-score matched pairs of patients who were or were not treated with ADT. The cohort N's reflect the number of patients not yet censored by the 1 or 2 year follow up time points.

ADT = androgen deprivation therapy; HbA1c = glycosylated hemoglobin

Table 3

Diabetes medications at baseline among propensity-matched cohorts*

	ADT		No ADT		All	
	N = 2237	(%)	N = 2237	(%)	N = 4474	(%)
Diabetes pharmacotherapy						
Yes	1826	(81.6)	1824	(81.5)	3650	(81.6)
No	411	(18.4)	413	(18.5)	824	(18.4)
Number of diabetes drug classes						
1	1578	(70.5)	1590	(71.1)	3168	(70.8)
2	233	(10.4)	215	(9.6)	448	(10.0)
3	15	(0.7)	19	(0.8)	34	(0.8)
Diabetes drugs						
Metformin	610	(27.3)	621	(27.8)	1231	(27.5)
Sulfonylurea	917	(41.0)	889	(39.7)	1806	(40.4)
Other oral hypoglycemic	134	(6.0)	137	(6.1)	271	(6.1)
Insulin	428	(19.1)	431	(19.3)	859	(19.2)

* The baseline prescription with diabetes drugs was defined as the latest prescription during the one-year period before cancer diagnosis for patients without ADT or the latest one since one year before starting ADT through the day of starting ADT for patients with ADT.

ADT = androgen deprivation therapy

Unadjusted rates of initiation of a diabetic medication or adding a new class of diabetes medication for propensity matched cohorts of men who were or were not treated with ADT*

Table 4

	ADT (N=2237)			No ADT (N=2237)			P value [†]
	Events	Person-years	Rate	Events	Person-years	Rate	
Initiation of a diabetic medication	189	696.2	271.4	180	713.1	252.4	0.45
Addition of a new diabetes drug class	749	3076.8	243.4	652	3255.4	200.3	<0.001
Initiation or addition of a diabetes drug class	938	3773.0	248.6	832	3968.5	209.6	<0.001

* ADT = androgen deprivation therapy; Rate = number of events per 1000 person-years.

[†] P values were based on two-sample z tests that evaluated whether the rate of each outcome for men with ADT differed from the rate under no ADT.

Table 5

Association between ADT and time to increasing number of classes of diabetes medications (N=4474)*

Characteristic	Adjusted Hazard Ratio	95% CI	P Value
ADT	1.20	1.09 to 1.32	<0.001
Age (year)	0.98	0.97 to 0.99	<0.001
Race			
White	Reference		
Black	0.92	0.82 to 1.03	0.15
Hispanic	1.17	0.96 to 1.42	0.12
Other or unknown	0.88	0.67 to 1.17	0.39
Marital status			
Married	Reference		
Unmarried	1.06	0.96 to 1.17	0.24
Unknown	1.10	0.78 to 1.54	0.58
Census division			
Pacific	Reference		
New England	0.95	0.72 to 1.24	0.69
Mid Atlantic	1.04	0.85 to 1.25	0.72
South Atlantic	0.96	0.82 to 1.13	0.62
East North Central	0.92	0.75 to 1.11	0.38
West North Central	0.91	0.73 to 1.14	0.43
East South Central	0.81	0.65 to 1.02	0.07
West South Central	1.15	0.96 to 1.37	0.14
Mountain	0.84	0.64 to 1.10	0.20
Median household income in zip code of residence at diagnosis			
Quartile 1 (lowest)	Reference		
Quartile 2	0.95	0.82 to 1.10	0.46
Quartile 3	0.93	0.79 to 1.09	0.35
Quartile 4 (high)	0.90	0.74 to 1.09	0.27
Missing	0.99	0.78 to 1.26	0.94
% High school graduates in census tract of residence at diagnosis			
Quartile 1 (lowest)	Reference		
Quartile 2	1.10	0.95 to 1.27	0.21
Quartile 3	1.17	1.00 to 1.36	0.04
Quartile 4 (high)	1.27	1.05 to 1.52	0.01
Tumor grade (Gleason score)			
Well differentiated (2-4)	Reference		
Moderately differentiated (5-7)	1.28	0.95 to 1.73	0.11
Poorly or undifferentiated (8-10)	1.15	0.85 to 1.57	0.37
Unknown	1.35	0.94 to 1.95	0.11
Prostate-specific antigen level at diagnosis (ng/mL)			
< 5.00	Reference		

Characteristic	Adjusted Hazard Ratio	95% CI	P Value
5.00 – 7.49	1.01	0.86 to 1.17	0.93
7.50 – 9.99	0.92	0.78 to 1.09	0.35
10.00	0.96	0.82 to 1.12	0.62
Unknown	1.07	0.89 to 1.28	0.46
Comorbidity			
MI	0.94	0.56 to 1.60	0.83
Old MI	1.02	0.75 to 1.40	0.90
CHF	0.92	0.77 to 1.11	0.37
Peripheral vascular disease, dx	0.84	0.67 to 1.05	0.12
Peripheral vascular disease, surg	0.97	0.35 to 2.67	0.96
Cerebrovascular disease	0.93	0.74 to 1.17	0.54
COPD	0.94	0.80 to 1.10	0.43
Dementia	1.59	0.85 to 2.99	0.15
Paralysis	0.65	0.30 to 1.39	0.26
Chronic renal failure	0.49	0.36 to 0.65	<0.001
Various cirrhodites	1.46	0.65 to 3.29	0.36
Moderate-severe liver disease	0.78	0.11 to 5.63	0.81
Ulcers1	1.21	0.75 to 1.94	0.44
Ulcers2	1.24	0.51 to 3.05	0.63
Rheumatism	0.87	0.51 to 1.48	0.60
AIDS	0.81	0.26 to 2.52	0.71
HTN	1.07	0.96 to 1.19	0.20
Obesity	1.15	0.99 to 1.34	0.06
Year of diagnosis or starting ADT			
2001	Reference		
2002	1.10	0.96 to 1.26	0.19
2003	1.09	0.95 to 1.26	0.23
2004/2005	1.09	0.94 to 1.26	0.25
Primary treatment received in the 6 months after diagnosis			
Neither	Reference		
Radical prostatectomy	1.14	0.95 to 1.37	0.17
Radiation therapy	1.04	0.93 to 1.15	0.50
Baseline HbA1c level (%)			
< 6.00	Reference		
6.00 – 6.49	1.67	1.34 to 2.09	<0.001
6.50 – 6.99	2.14	1.73 to 2.64	<0.001
7.00 – 7.49	2.50	2.02 to 3.09	<0.001
7.50 – 8.49	3.20	2.61 to 3.93	<0.001
8.50	3.44	2.81 to 4.22	<0.001
Unknown	2.79	2.25 to 3.44	<0.001

* Using Cox proportional hazards model including all variables in the table, among propensity-matched cohorts of men with prostate cancer who were or were not treated with ADT.

ADT=androgen deprivation therapy; HbA1c=glycosylated hemoglobin