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Risk of diabetes complications among those with diabetes receiving androgen deprivation therapy for localized prostate cancer

Marie C. Bradley¹, Yingjun Zhou², Andrew N. Freedman¹, Marianne Ulcickas Yood³, Charles P. Quesenberry⁴, Reina Haque⁵, Stephen K. Van Den Eeden⁴, Andrea E. Cassidy-Bushrow⁶, David Aaronson⁷, Arnold L. Potosky²

¹Clinical and Translational Epidemiology Branch, Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, MD, USA

²Georgetown University Lombardi Comprehensive Cancer Center, Washington, DC, USA

³Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA

⁴Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA

⁵Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA, USA

⁶Department of Public Health Sciences, Henry Ford Health System, Detroit, MI, USA

⁷Kaiser Permanente, Oakland Medical Center, 3600 Broadway, Oakland, CA, USA

Abstract

Purpose—Androgen deprivation therapy (ADT), used increasingly in the treatment of localized prostate cancer, is associated with substantial long-term adverse consequences, including incident diabetes. While previous studies have suggested that ADT negatively influences glycemic control in existing diabetes, its association with diabetes complications has not been investigated. In this study, we examined the association between ADT use and diabetes complications in prostate cancer patients.

Methods—A retrospective cohort study was conducted among men with newly diagnosed localized prostate cancer between 1995 and 2008, enrolled in three integrated health care systems. Men had radical prostatectomy or radiotherapy (curative intent therapy), existing type II diabetes mellitus (T2DM), and were followed through December 2010 ($n = 5,336$). Cox proportional hazards models were used to examine associations between ADT use and diabetes complications (any complication), and individual complications (diabetic neuropathy, diabetic retinopathy, diabetic amputation or diabetic cataract) after prostate cancer diagnosis.

Results—ADT use was associated with an increased risk of any diabetes complication after prostate cancer diagnosis (adjusted hazard ratio, AHR, 1.12, 95% CI 1.03–1.23) as well as an increased risk of each individual complication compared to non-use.

Marie C. Bradley, marie.bradley@nih.gov.

Conflict of interest MB, AP, AF, MUY, XZ, DA, CPQ declare that they have no conflict of interest.

Conclusion—ADT use in men with T2DM, who received curative intent therapy for prostate cancer, was associated with an increased risk of diabetes complications. These findings support those of previous studies, which showed that ADT worsened diabetes control. Additional, larger studies are required to confirm these findings and to potentially inform the development of a risk-benefit assessment for men with existing T2DM, before initiating ADT.

Keywords

Androgen deprivation therapy; Prostate cancer treatment; Diabetes complications; Adverse effects of cancer treatments; Epidemiology

Introduction

Androgen deprivation therapy (ADT) is often the standard of care in men with clinically localized prostate cancer as either adjuvant therapy for radiation-treated locally advanced disease, or as a salvage treatment for recurrence or biochemical failure following locally curative treatment [1–4]. However, while adjuvant ADT with radiotherapy improves survival in men with locally advanced prostate cancer, little evidence exists for salvage ADT (sADT) alone for the treatment of biochemical-only recurrence, signaled by a rising PSA following curative therapies. ADT has substantial long-term adverse consequences on quality of life [5–12]. Given the low probability of prostate cancer-related death in men diagnosed with localized cancer and the high median age at prostate cancer diagnosis, [13] the potential serious adverse effects of ADT warrant careful consideration relative to the benefits.

ADT has been linked to decreased insulin sensitivity [14] and development of incident diabetes [5, 8, 9, 15–17]. In 2010, the FDA mandated labeling changes for ADT products to highlight warnings regarding the risk of diabetes [18]. Despite these concerns, little is known on how ADT affects diabetes control and complications among men with existing type II diabetes mellitus (T2DM). Two small studies examining its use in diabetic prostate cancer patients found that ADT use was associated with increased serum hemoglobin a1c (HbA1c) and fasting serum glucose levels and substantially worsened glycemic control [19, 20]. However, these studies were limited by the lack of an appropriate comparison group (non-ADT users). In a larger cohort study from the Veterans Health Administration (VA) that compared patients with and without ADT use, ADT was associated with worsening glycemic control, defined as both increases in HbA1c levels and the need for additional diabetes medications, in prostate cancer patients with diabetes [21]. However, despite suggestions of worsening glycemic control, the association of ADT with actual diabetes complications has not been investigated.

Among the 29.1 million Americans with diabetes, diabetes complications such as diabetic neuropathy, diabetic retinopathy, diabetic amputation, and diabetic cataracts result in vast morbidity, disability, and mortality and account for around 35% of the total estimated \$92 billion in medical expenditures for this disease [22].

Given the high prevalence of T2DM in the US population, the serious risk of diabetes complications and the growing numbers of prostate cancer survivors,[23] determining the risk of diabetes complications associated with ADT use may help to more fully inform

treatment decisions regarding the appropriate use of adjuvant or sADT in this subgroup of higher risk men.

In this study, we examined the effect of ADT on diabetes complications among men receiving curative therapies for localized prostate cancer who had existing T2DM at the time of their cancer diagnosis.

Methods

Data sources

A retrospective cohort study was conducted among men with newly diagnosed clinically localized prostate cancer between 1995 and 2008. All men were enrolled in one of three integrated health care systems within the Health Care Systems Research Network (HCSRN)—Kaiser Permanente Northern California (KPNC), Kaiser Permanente Southern California (KPSC), and Henry Ford Health System (HFHS) in Detroit. These integrated health care systems have comprehensive electronic medical record (EMR) data including inpatient and outpatient encounters containing diagnoses and procedures, laboratory test values, pharmacy data, and cancer registry data.

Study cohort

A total of 37,818 men newly diagnosed with localized prostate cancer and treated with primary radical prostatectomy (RP) ($n = 15,231$) or radiotherapy (RT) ($n = 16,058$) were assessed for eligibility. Only men with existing T2DM diagnosed before their prostate cancer were included (5,336 men) in this study. T2DM was defined as either (1) one inpatient primary diagnosis, (2) two outpatient diagnoses at least 30 days apart, (3) antidiabetic medication prescriptions, and (4) at least one HbA1c test result greater than 7%. If men met more than one of these conditions, the earliest recorded diagnosis date was chosen. All patients were followed up through December 21, 2010 or until censoring due to first diabetic complication (after prostate cancer diagnosis), death, or disenrollment. Only those with T2DM, and not type I diabetes mellitus (T1DM), were included as the effects of ADT on glycemic control are believed to be related to metabolic syndrome which has been implicated in type II diabetes.

Exposures

ADT—Exposure to ADT was defined as ever use of either a GnRH analog (e.g., leuprolide, goserelin, or triptorelin) or GnRH antagonists (e.g., abarelix or degarelix), with or without an oral anti-androgen (flutamide, bicalutamide, or nilutamide) for combined androgen blockade in prostate cancer at any time after initial diagnosis. Due to possible incomplete PSA data in some health plans, adjuvant ADT and sADT exposures were defined in the entire cohort based on the timing relative to primary prostate cancer therapy. Adjuvant ADT was defined as ADT initiated just before or within 6 months following primary prostatectomy for men with pathologically regional summary stage or within 6 months following the last date of primary radiotherapy. sADT was defined as either (1) ADT after primary prostatectomy for men with pathologically localized summary stage; (2) initiation of ADT after a period of 6 months or more following primary prostatectomy for men with pathologically regional

summary stage, or after 6 months or more following the last dose of primary radiotherapy; or (3) ADT after 12 or more months following the last date of adjuvant ADT. We required at least 12 months of an ADT-free period in this latter definition to reduce the possibility of misclassifying adjuvant ADT as sADT. Exposure to either adjuvant ADT or sADT at any time during follow-up was considered.

Diabetes drugs—Exposure to diabetes drugs including oral agents (metformin, sulfonylureas [glyburide, glipizide, glimepiride, tolazamide, tolbutamide, acarbose, miglitol, pioglitazone, rosiglitazone, nateglinide, repaglinide]) and insulins (ever/never use) from 1 year prior to prostate cancer diagnosis date until the end of follow-up was determined from electronic pharmacy records.

Outcomes

Data on the incidence and date of diabetes complications, that occurred after the date of first prostate cancer diagnosis, including diabetic neuropathy (ICD 9 code-250.6x), diabetic retinopathy (ICD9 code-250.5x), diabetic amputation (ICD9 code-84.xx) or cataracts (ICD 9 code-366.xx) were obtained from all inpatient and outpatient clinical encounter data in the integrated health systems' EMRs.

Covariates

Information on covariates related to prostate cancer were obtained from the health care systems' tumor registries that operate in accordance with national registry standards and are the primary sources for data transmitted to the NCI's Surveillance, Epidemiology, and End Results program. Data on age at diagnosis, race-ethnicity, tumor stage, primary treatment, total serum PSA level (ng/mL) at baseline (defined as the closest value within the 6 months before prostate cancer diagnosis), and the two-value summed Gleason score from the first biopsy leading to the prostate cancer diagnosis were extracted. Based on patients' T-stage, PSA level, and Gleason sum, risk groups were computed as low, intermediate, or high based on American Urological Association (AUA) definitions: low risk defined as PSA ≤ 10 , Gleason score ≤ 6 , and stages T1c–T2a; intermediate risk defined as PSA 11–20 or Gleason score = 7 or stage T2b; and high risk defined as PSA > 20 , Gleason score ≥ 8 , or clinical stage T2c–3a [24]. For other clinical covariates, we constructed the Elixhauser comorbidity index [25] using electronic health records from 2 years before prostate cancer diagnosis date. For each condition, an inpatient diagnosis and/or at least two outpatient diagnoses codes were required at least 30 days apart to minimize false-positives. Availability of baseline HbA1c values varied over time by health system, thus we did not have complete data on baseline HbA1c levels and were unable to include it as a confounder.

Statistical analysis

Descriptive statistics were used to compare population characteristics according to ADT use. Due to varying lengths of follow-up available for men in the cohort, rates of diabetic complications by ADT use status were computed. Cox Proportional Hazard (PH) models were used to estimate the association (expressed as hazard ratios) between ADT use (ever use and time between first and last prescription) and time to first diabetes complications adjusting for all other clinical and socio-demographic variables. Five separate models were

constructed for the different types of diabetes complications. The first related to the first incidence of any complication type while the other models related to the first incidence of four specific complications (diabetic neuropathy, diabetic retinopathy, diabetic amputation, or diabetic cataract).

For each model, follow-up began on the date of prostate cancer diagnosis with incidence of diabetes complications as the outcome event or censoring defined as disenrollment from the health plans, death, or end of study period (July 31, 2010), whichever came first. Each modeled outcome was adjusted for patients socio-demographic factors (age at diagnosis, race/ethnicity, health plan), clinical prognostic factors (AUA risk group, radiation or surgery as primary treatment), and comorbidities, measured using the Elixhauser comorbidity index. Diabetes severity was approximated using data on diabetes drug use from 1 year prior to prostate cancer diagnosis date until end of follow-up (no diabetes medications were classified as less severe T2DM, use of oral agents only represented intermediate severity, and insulin with or without oral agents indicated more severe T2DM) and included in the model as a fixed variable. Ever use of ADT was modeled as a time-dependent variable where patients were classed as unexposed until the start of the first ADT treatment, after which they were considered exposed until event occurrence or end of follow-up, whichever came first. Follow-up ended with first diabetes complication, thus ADT use after the first complication did not contribute towards ADT-associated complication risk. A post hoc analysis adjusting the original Cox model for prior history of diabetes complications as a time varying covariate was performed. All tests of statistical significance were two-sided. SAS statistical software, version 9 (SAS Institute, Inc., Cary, North Carolina) was used for all analyses.

Results

Population characteristics

The cohort included 5,336 men newly diagnosed with localized prostate cancer who had pre-existing T2DM. ADT users contributed 6,379 years of study follow-up while non-users contributed 19,196 years. ADT users were more often in the “high” risk group according to the AUA definition and were diagnosed with prostate cancer at an older age (Table 1).

Diabetes complications and ADT use

Cataracts were the most common outcome in the cohort, followed by neuropathy, retinopathy, and amputations. The incidence rate for any diabetes complication was 249.3 per 1,000 person years in ADT users and 231.9 per 1,000 person years in non-users (Table 2). Multivariate analyses showed ADT use was associated with a 12% increased risk of a diabetes complication post diagnosis compared to non-use; adjusted hazard ratio [AHR], (1.12 95% CI 1.03–1.23) (Table 2). ADT use was associated with a 17% increased risk of diabetic retinopathy (AHR 1.17, 95% CIs 0.92–1.47), a 14% increased risk of diabetic neuropathy (AHR 1.14, 95% CI 1.02–1.28), and more than twofold increase in diabetic amputations (AHR 2.06, 95% CIs 1.28–3.31) compared to non-use (Table 2). The results did not change substantially when we adjusted for prior history of complications.

Discussion

In this study of men with localized prostate cancer and T2DM, we found that ADT use was associated with a 12% increased risk of experiencing any diabetes complication (cataract, diabetic retinopathy, diabetic neuropathy, or diabetic amputation) as well as increased risks of diabetic neuropathy and amputation, specifically. These findings are consistent with previous studies showing that ADT induces metabolic changes such as insulin resistance, [14] which have been associated with increasing hyperglycemia in patients with diabetes [26, 27]. These metabolic changes may lead to worsening diabetes control (indicated by increases in HBA1c level), despite intensification of pharmacotherapy, as demonstrated in a recent VA study [21]. A UK-based prospective diabetes study demonstrated that increasing HBA1C predicts poorer diabetes control and has been associated with an increased risk of diabetes complications [28]. ADT users were slightly older than non-users (mean age 68 vs. 65); however, the assumption that older men are more likely to have microvascular diabetes complications may not be correct, according to a large and well-known diabetes and aging study. In this study it was reported that, “for a given duration of diabetes, rates of hypoglycemia, cardiovascular complications, and mortality increased steeply with advancing age, while rates of microvascular complications remained stable or declined.” [29].

Diabetes is the sixth leading cause of death in the U.S. Mortality risk increases as the degree of diabetes complications increases [30]. Severe microvascular complications such as severe diabetic retinopathy, early and severe diabetic nephropathy, peripheral vascular disease, hyperglycemia, and metabolic abnormalities increase mortality. In addition, these complications are responsible for significant morbidity and disability in patients with diabetes [22]. Considering all of these risks and the fact that diabetes complications account for more than 35% of almost \$92 billion in medical expenditures for diabetes, reducing the risk of diabetes complications is critical for improving quality of care and patient outcomes in those with T2DM, and also for cost control [22].

The National Comprehensive Cancer Network (NCCN) has developed guidelines aimed at reducing the risks associated with ADT use in prostate cancer patients [31]. However, diabetes prevention recommendations are vague and similar to those advocated for routine prevention in the general population. There is no additional consideration given to the potential implications of ADT use in men with existing diabetes.

While our findings suggest only a modestly increased risk of diabetes complications, given the recent controversy regarding the survival benefit of ADT in localized prostate cancer, a careful risk–benefit assessment for men with existing T2DM, may be appropriate before initiating ADT. At a minimum for these men, more intensive and/or frequent monitoring of glycemic control, promoting physical activity and, if indicated, use of additional diabetes therapy may be considered. However, each of these requires further study. This study has a number of strengths: To our knowledge this is the first study to examine the association of ADT use and risk of diabetes complications among men with prostate cancer with pre-existing T2DM. The study population was drawn from three large diverse health care systems increasing the generalizability of the findings to the whole US population. Comprehensive follow-up data were available from the EMRs in these health care systems

allowing reliable ascertainment of ADT use and many important covariates. Study limitations include the possibility of residual confounding, particularly from unmeasured factors associated with ADT treatment choice (patient and physician factors) that might have influenced the risk of diabetes complications, BMI, and health behaviors (e.g., physical activity), which were not available or complete in the EMR. While the proportion of diabetes complications observed was substantial, the actual number of prostate cancer cases with diabetes in this study was small and there are other diabetes complications that were not assessed. The findings of this study may not be generalizable to prostate cancer patients who did not receive RP or RT or those who used ADT as a primary therapy. We did not have detailed data on ADT dose or duration of use due to the early practice in two of the three integrated health plans, contributing EHR data for our study, of only recording the initial ADT (LHRH agonists) injection rather than each ADT/LHRH agonist injection given over the course of time. Therefore, it was not possible to estimate a dose–response effect and this may require further study. Further, we did not adjust for baseline HbA1C levels or diabetes duration, a marker of diabetes severity, as we did not have complete data for all study participants. However, we did adjust for insulin use, a recognized indicator of severity, and prior history of diabetes complications.

Conclusion

ADT use in men with T2DM who received curative intent therapy for prostate cancer was associated with an increased risk of diabetes complications particularly diabetic neuropathy and amputation. These findings support those of previous studies which showed that ADT worsened diabetes control and increased HbA1c levels. Additional, larger studies are required to confirm these findings and to potentially inform the development of a risk–benefit assessment for men with existing T2DM, before initiating ADT.

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References

1. Cooperberg MR, Grossfeld GD, Lubeck DP et al. (2003) National practice patterns and time trends in androgen ablation for localized prostate cancer. *J Natl Cancer Inst* 95(13):981–989 [PubMed: 12837834]
2. Kawakami J, Cowan JE, Elkin EP et al. (2006) Androgen-deprivation therapy as primary treatment for localized prostate cancer: data from Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE). *Cancer* 106(8):1708–1714 [PubMed: 16544313]
3. Keating NL, O'Malley AJ, McNaughton-Collins M et al. (2008) Use of androgen deprivation therapy for metastatic prostate cancer in older men. *BJU Int* 101(9):1077–1083 [PubMed: 18190632]
4. Zeliadt SB, Etzioni R, Ramsey SD et al. (2007) Trends in treatment costs for localized prostate cancer: the healthy screenee effect. *Med Care* 45(2):154–159 [PubMed: 17224778]

5. Alibhai SM, Duong-Hua M, Sutradhar R et al. (2009) Impact of androgen deprivation therapy on cardiovascular disease and diabetes. *J Clin Oncol* 27(21):3452–3458 [PubMed: 19506162]
6. Barry MJ, Delorenzo MA, Walker-Corkery ES et al. (2006) The rising prevalence of androgen deprivation among older American men since the advent of prostate-specific antigen testing: a population-based cohort study. *BJU Int* 98(5):973–978 [PubMed: 16879443]
7. D'Amico AV, Denham JW, Crook J et al. (2007) Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. *J Clin Oncol* 25(17): 2420–2425 [PubMed: 17557956]
8. Keating NL, O'Malley AJ, Freedland SJ et al. (2010) Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. *J Natl Cancer Inst* 102(1):39–46 [PubMed: 19996060]
9. Keating NL, O'Malley AJ, Smith MR (2006) Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 24(27):4448–4456 [PubMed: 16983113]
10. Moul JW, Banez LL, Freedland SJ (2007) Rising PSA in non-metastatic prostate cancer. *Oncology* 21(12):1436–1445 1454. [PubMed: 18077992]
11. Shahinian VB, Kuo YF, Freeman JL et al. (2005) Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 352(2):154–164 [PubMed: 15647578]
12. Wei JT, Gross M, Jaffe CA et al. (1999) Androgen deprivation therapy for prostate cancer results in significant loss of bone density. *Urology* 54(4):607–611 [PubMed: 10510915]
13. Lu-Yao G, Stukel TA, Yao SL (2004) Changing patterns in competing causes of death in men with prostate cancer: a population based study. *J Urol* 171(6 Pt 1):2285–2290 [PubMed: 15126804]
14. Smith MR, Lee H, Nathan DM (2006) Insulin sensitivity during combined androgen blockade for prostate cancer. *J Clin Endocrinol Metab* 91(4):1305–1308 [PubMed: 16434464]
15. Lage MJ, Barber BL, Markus RA (2007) Association between androgen-deprivation therapy and incidence of diabetes among males with prostate cancer. *Urology* 70(6):1104–1108 [PubMed: 18158027]
16. Tsai HK, D'Amico AV, Sadetsky N et al. (2007) Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. *J Natl Cancer Inst* 99(20):1516–1524 [PubMed: 17925537]
17. Tsai HT, Keating NL, Van Den Eeden SK et al. (2015) Risk of diabetes among patients receiving primary androgen deprivation therapy for clinically localized prostate cancer. *J Urol* 193(6):1956–1962 [PubMed: 25524243]
18. US Food and Drug Administration. Review of GnRH agonists and notification to manufacturers of GnRH agonists to add new safety information to labeling regarding increased risk of diabetes and certain cardiovascular diseases, 2011 Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm229986.htm>
19. Derweesh IH, Diblasio CJ, Kincade MC et al. (2007) Risk of new-onset diabetes mellitus and worsening glycaemic variables for established diabetes in men undergoing androgen-deprivation therapy for prostate cancer. *BJU Int* 100(5):1060–1065 [PubMed: 17868420]
20. Haidar A, Yassin A, Saad F et al. (2007) Effects of androgen deprivation on glycaemic control and on cardiovascular biochemical risk factors in men with advanced prostate cancer with diabetes. *Aging Male* 10(4):189–196 [PubMed: 18033628]
21. Keating NL, Liu PH, O'Malley AJ et al. (2014) Androgen-deprivation therapy and diabetes control among diabetic men with prostate cancer. *Eur Urol* 65(4):816–824 [PubMed: 23453420]
22. Young BA, Lin E, Von Korff M et al. (2008) Diabetes complications severity index and risk of mortality, hospitalization, and healthcare utilization. *Am J Manag Care* 14(1):15–23 [PubMed: 18197741]
23. Centers for Disease Control. National Diabetes Statistics Report 2014 (2014) Department of Health and Human Services, Atlanta <https://www.cdc.gov/diabetes/pdfs/data/2014-report-estimates-of-diabetes-and-its-burden-in-the-united-states.pdf>
24. Thompson I, Thrasher JB, Aus G et al. (2007) Guideline for the management of clinically localized prostate cancer: 2007 update. *J Urol* 177(6):2106–2131 [PubMed: 17509297]
25. Elixhauser A, Steiner C, Harris DR et al. (1998) Comorbidity measures for use with administrative data. *Med Care* 36(1):8–27 [PubMed: 9431328]

26. Shahani S, Braga-Basaria M, Basaria S (2008) Androgen deprivation therapy in prostate cancer and metabolic risk for atherosclerosis. *J Clin Endocrinol Metab* 93(6):2042–2049 [PubMed: 18349064]
27. Allan CA, Collins VR, Frydenberg M et al. (2014) Androgen deprivation therapy complications. *Endocr Relat Cancer* 21(4):T119–29 [PubMed: 24872511]
28. King P, Peacock I, Donnelly R (1999) The UK prospective diabetes study (UKPDS): clinical and therapeutic implications for type 2 diabetes. *Br J Clin Pharmacol* 48(5):643–648 [PubMed: 10594464]
29. Huang ES, Laiteerapong N, Liu JY et al. (2014) Rates of complications and mortality in older patients with diabetes mellitus: the diabetes and aging study. *JAMA Intern Med* 174(2):251–258 [PubMed: 24322595]
30. Cusick M, Meleth AD, Agron E et al. (2005) Associations of mortality and diabetes complications in patients with type 1 and type 2 diabetes: early treatment diabetic retinopathy study report no. 27. *Diabetes Care* 28(3):617–625 [PubMed: 15735198]
31. National Comprehensive Cancer Network. Practice Guidelines in Oncology, v.3.2012, Prostate cancer. http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf

Demographic and clinical characteristics of 5,336 men, with existing T2DM, diagnosed with clinically localized prostate cancer from 1995 to 2008

Table 1

Characteristic	Non-user (<i>n</i> = 3,651)		ADT user (<i>n</i> = 1,685)		<i>p</i>
	No. of patients	%	No. of patients	%	
Age at diagnosis in years					
Mean (SD)	65 (7)		68 (7)		
Race/ethnicity					
Non-Hispanic White	1,803	49	879	52	
Hispanic	648	18	258	15	
Non-Hispanic black	822	23	356	21	
All others or unknown	378	10	192	12	0.05
Year of diagnosis					
1995–2000	628	17	449	27	
2001–2005	1,508	41	739	43	
2006–2011	1,515	42	497	29	< 0.001
AUA risk group ^a					
Low	1,134	31	261	15	
Intermediate	1,240	34	657	39	
High	1,277	35	767	46	< 0.001
Primary treatment					
Radical prostatectomy	1,662	46	366	22	
Radiation therapy	1,989	54	1,319	78	< 0.001
Comorbidity count (Elixhauser index, 2 years before diagnosis date)					
1	3,155	87	1,412	84	
2	328	9	178	11	
3	13	0	7	0	
Unknown/missing	155	4	88	5	0.138
Ever use of antidiabetic drugs					
Never	884	24	310	18	
Ever	2,767	76	1,375	82	< 0.001
Antidiabetic drug type					

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Characteristic	Non-user (<i>n</i> = 3,651)		ADT user (<i>n</i> = 1,685)		<i>p</i>
	No. of patients	%	No. of patients	%	
None	884	24	310	18	
Oral only	2,149	59	928	55	
Insulin	618	17	447	27	<0.001
ADT type					
Adjuvant ADT only			1,100	65	
Salvage ADT only			388	23	
Adjuvant & salvage ADT			197	12	

^a†Risk group is defined as low (pre-treatment PSA level 10 ng/mL, Gleason score 6, and a clinical tumor stage of T2a), intermediate (10 ng/mL PSA 20 ng/mL, Gleason score of 7, or T2b), or high (PSA 20 ng/mL, Gleason score 8–10, or T2c–T3a)

Table 2

Risk of diabetes complications associated with ADT use, among men diagnosed with localized prostate cancer, who received primary treatment with RP or RT

Post-diagnostic diabetes complications	Event rate per 1,000 person years in ADT users	Event rate per 1,000 person years in ADT non-users	Unadjusted HR (95% CIs)	Adjusted HR ^a (95% CIs)
Any complication	249.3	231.9	1.26 (1.17–1.37)	1.12 (1.03–1.23)
Diabetic cataracts	153	136.6	1.27 (1.16–1.38)	0.98 (0.90–1.08)
Diabetic neuropathy	75.8	76.9	1.23 (1.11–1.36)	1.14 (1.02–1.28)
Diabetic retinopathy	12.7	24.8	0.63 (0.52–0.77)	1.17 (0.92–1.47)
Diabetic amputation	4.3	1.9	2.20 (1.45–3.35)	2.06 (1.28–3.31)

ADT androgen deprivation therapy, HR hazard ratio

^a Adjusted in a multivariable analysis using Cox proportional hazards models for ethnicity, health plan, AUA risk group, comorbidity according to the Elixhauser index, prostate cancer treatment (RP or RT), age at diagnosis (years), and diabetes severity. Ever use of ADT modeled as time varying