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Influence of Age on Incident Diabetes and Cardiovascular Disease in Prostate Cancer Survivors Receiving Androgen Deprivation Therapy

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Abstract

Purpose—Observational data suggest that androgen deprivation therapy increases the risk of diabetes and cardiovascular disease. Using data from the population based PCOS we evaluated whether age at diagnosis and comorbidity impact the association of androgen deprivation therapy with incident diabetes and cardiovascular disease.

Materials and Methods—We identified men with nonmetastatic prostate cancer diagnosed from 1994 to 1995 who were followed through 2009 to 2010. We used multivariable logistic regression models to assess the relationship of androgen deprivation therapy exposure (2 or fewer years, greater than 2 years or none) with incident diabetes and cardiovascular disease, adjusting for age at diagnosis, race, stage and comorbidity.

Results—Of 3,526 eligible study participants 2,985 without diabetes and 3,112 without cardiovascular disease comprised the cohorts at risk. Androgen deprivation therapy was not associated with an increased risk of diabetes or cardiovascular disease in men diagnosed with prostate cancer before age 70 years. Prolonged androgen deprivation therapy and increasing age at diagnosis in older men was associated with an increased risk of diabetes (at age 76 years OR 2.1, 95% CI 1.0–4.4) and cardiovascular disease (at age 74 years OR 1.9, 95% CI 1.0–3.5). Men with

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comorbidities were at greater risk for diabetes (OR 4.3, 95% CI 2.3–7.9) and cardiovascular disease (OR 8.1, 95% CI 4.3–15.5) than men without comorbidities.

Conclusions—Prolonged androgen deprivation therapy exposure increases the risk of cardiovascular disease and diabetes in men diagnosed with prostate cancer who are older than approximately 75 years, especially those with other comorbidities. Older men who receive prolonged androgen deprivation therapy should be closely monitored for diabetes and cardiovascular disease.

Keywords

prostatic neoplasms; antiandrogens; cardiovascular diseases; diabetes mellitus; risk

Prostate cancer is the most common noncutaneous malignancy in American men.¹ ADT is the most frequently used systemic therapy for prostate cancer. More than 600,000 men are receiving treatment with ADT in the United States and up to 50% of men receive ADT during the course of the disease.^{2,3} Some studies suggest that ADT is associated with an increased risk of DM and cardiovascular complications, although this remains controversial.^{3–7} Understanding this risk is a critical aspect of delivering quality care to prostate cancer survivors.

Although numerous studies of prostate cancer survivors demonstrate an association between ADT exposure and the risk of incident DM or CVD, controversy remains. Studies in men older than 65 years or with a greater comorbid burden, such as Medicare enrollees and veterans, suggest an increased risk of DM, cardiovascular morbidity and cardiovascular death in men treated with ADT compared to those who are not.^{4–7} In contrast, analysis of data from clinical trials and Canadian administrative data, which include younger and healthier men, fail to show an increased risk of cardiovascular mortality associated with ADT.^{8–12}

We hypothesized that there is an association between the duration of ADT exposure, increasing age at diagnosis, the comorbidity burden and the risk of DM or CVD. To assess this we analyzed the development of DM and CVD in men in PCOS, a population based cohort of patients diagnosed with prostate cancer in 1994 to 1995 who were followed longitudinally for up to 15 years.

MATERIALS AND METHODS

Design

PCOS enrolled men with prostate cancer from 6 participating SEER sites in Connecticut, Utah and New Mexico, and the metropolitan areas of Atlanta, Georgia, Los Angeles, California, and Seattle-Puget Sound, Washington, between October 1, 1994 and October 31, 1995. Men between ages 39 and 89 years at diagnosis were identified by rapid case ascertainment, resulting in a random sampling of 5,672 from the 11,137 who were eligible for analysis. To ensure a representative cohort a prespecified sampling strategy was used to oversample Hispanic, black and younger men.^{13,14} The study was approved by the institutional review board at all participating sites.

Within 6 months after enrollment participants completed a self-administered survey including questions on clinical and sociodemographic factors, comorbid conditions, health related quality of life, age at diagnosis, race/ethnicity, marital status, income level, education level and insurance type.^{15,16} We collected information on the primary treatment for prostate cancer (surgery, radiation, hormonal therapy, no therapy or any combination of therapies) and tumor characteristics (Gleason score, highest PSA and disease stage) from a detailed 1-year medical record review as described previously. Information was coded according to SEER guidelines.^{13,14,17} Participants were asked 1, 2, 5 and 14 to 15 years after diagnosis to complete a survey containing items on further prostate cancer treatment, including past or current ADT, incident comorbid conditions and clinical outcomes. Cause of death data were obtained from vital status records.

Population

Of the initial 3,718 PCOS participants who completed a baseline survey 3,526 (94.8%) survived at least 2 years and were included in analysis. We identified men without a diagnosis of DM (2,985) or CVD (3,112) at baseline (fig. 1).

Statistical Analysis

We categorized participants into 3 ADT exposure subgroups, including no ADT, short-term ADT (duration 2 years or less) and prolonged ADT (duration greater than 2 years) based on 1-year medical record review data and self-reported ADT at 6 months, 1, 2, 5 and 14 to 15 years after diagnosis. We defined short-term ADT in this way because it was more reliably defined in our data than shorter durations used in some studies.^{15–17}

A combination of patient report and cause of death data were used to identify incident comorbid disease. In each survey participants were queried on whether a physician told them that they had DM or CVD. We considered insulin use equivalent to a report of DM and a report of coronary artery bypass surgery, heart attack or congestive heart failure equivalent to a report of CVD. A participant was deemed to have incident disease at survey completion if he did not report that illness in preceding surveys. Previous assessment showed that the reliability of patient reported comorbid disease in men in PCOS was approximately 93% for DM and 96% for reports of heart attack and heart failure.¹⁸ Vital status data were used to identify deaths from DM or CVD that occurred between survey administrations.

We calculated descriptive statistics to compare baseline characteristics and outcome variables between ADT exposure groups. We assessed the relationship of the reported duration of ADT exposure with DM and CVD using weighted multivariable logistic regression adjusted for age at diagnosis, race, modified Charlson comorbidity score, Gleason score and stage. An ADT and age interaction term was included. Sample weights were calculated as the inverse of the sampling proportions in each region-race-age group stratum. All multivariable analyses were adjusted for sampling weights. To account for 18 (0.5% of the total cohort), 217 (6%) and 518 patients (15%) for stage, highest PSA and grade information, respectively, we performed single imputation to account for missing data. We used certain variables to perform imputation, including registry, age, treatment, grade, stage,

race, comorbidity score, PSA, education, insurance, marital status and employment status. All tests of statistical significance were 2-sided with $p < 0.05$ considered statistically significant. We used R, version 2.15 (<http://www.R-project.org/>) and the associated survey package for our analyses.¹⁹

RESULTS

Population

Mean age at diagnosis in the entire cohort was 67 years and median followup was 5 years. We found significant differences in sociodemographic and clinical categories between participants in the ADT exposure groups, although most differences were small (supplementary table 1, <http://jurology.com/>, and see table). As expected, fewer men reporting low grade (Gleason score 6 or less) or clinically localized disease reported ADT. A greater percent of men reporting radiation plus ADT or surgery plus ADT reported ADT for 2 years or less than men reporting more than 2 years of ADT exposure or no ADT (supplementary table 1, <http://jurology.com/>, and see table). Median highest PSA was 7.0, 14.0 and 12.1 ng/ml in patients with no ADT, and 2 or less and greater than 2 years of ADT (Kruskal-Wallis test $p < 0.001$).

Outcome

The baseline prevalence of DM and CVD in the entire cohort was 15% and 12%, respectively. By study end incident DM and CVD had developed in 455 (15%) and 538 men (14%), respectively. Of identified incident disease cases 26 (6%) of DM and 123 (23%) of CVD were identified based on data derived from death certificates.

We used weighted multivariable logistic regression analysis to evaluate the association of the duration of ADT exposure with incident DM and CVD (supplementary tables 2 and 3, <http://jurology.com/>). An increasing comorbid disease burden was associated with increasing odds of incident DM and CVD compared to the odds in men with no comorbidities (1, 2 and 3 or more comorbidities vs none DM OR 2.5, 95% CI 1.6–3.9, OR 2.4, 95% CI 1.4–4.1 and OR 4.3, 95% CI 2.3–7.9, and CVD OR 2.0, 95% CI 1.3–3.1, OR 2.3, 95% CI 1.4–3.9 and OR 8.1, 95% CI 4.3–16, respectively). ADT exposure duration, race, Gleason grade and stage did not significantly affect the odds of DM or CVD.

To evaluate the interaction between age at diagnosis and the duration of ADT exposure we calculated the odds of incident DM or CVD by year after diagnosis (figs. 2 and 3). Short-term ADT did not increase the odds of DM or CVD in men at any age. In contrast, prolonged ADT was associated with increased odds of DM in men older than 76 years at diagnosis (at age 76 years OR 2.1, 95% CI 1.0–4.4) and CVD in men older than 74 years at diagnosis (at age 74 years OR 1.9, 95% CI 1.0–3.5, figs. 2 and 3). The odds of DM or CVD increased yearly across these threshold ages.

DISCUSSION

Treatment with prolonged ADT was associated with an increased risk of incident DM at ages greater than 76 years and of CVD at ages greater than 74 years compared to younger

men. Men younger than these ages and men treated with short-term ADT did not experience this increased risk. The risk of DM or CVD was higher in men with at least 1 comorbid illness compared to men with no comorbidities. To our knowledge our analysis of the modifying effect of age on the association between ADT exposure and incident DM or CVD is the first to specifically evaluate this relationship in a prospective, nonmilitary, nonMedicare, population based cohort. The PCOS cohort included the full range of ages and comorbidity profiles found in the general population of patients with prostate cancer. This enables us to identify the effect of patient age and the duration of ADT exposure on the risk of incident DM and CVD.

Our findings are in agreement with those of several previous studies showing an increased risk of DM or cardiovascular outcomes in men treated with prolonged ADT, particularly older men.^{4,5,7,12} In 2 such studies Medicare cohorts were evaluated in which more than 70% of participants were older than 70 years.^{4,7} These studies and a Veterans Health Administration analysis assessed cohorts that included a larger proportion of elderly participants who were exposed to ADT.^{4,5,7} A retrospective cohort study of a Canadian administrative registry cohort showed that an increased risk of DM was associated with ADT exposure in a cohort with a mean age of 75 years.¹² We postulate that these groups reached conclusions similar to ours because the evaluated populations were predominantly elderly with a greater comorbid burden.

We also found that the increasing burden of comorbid illness was associated with higher odds of incident DM and CVD. This is in agreement with data suggesting that cardiovascular risk factors are particularly associated with DM or myocardial infarction in Medicare enrollees with prostate cancer independent of ADT exposure.²⁰ Finding an association between the comorbidity burden and the risk of incident CVD or DM is especially important because older men with a greater comorbidity burden may be more likely to receive primary ADT for localized disease. Recent data demonstrated a lack of benefit from primary ADT in this population.²¹

Our findings disagree with previously reported analyses of the effect of ADT on cardiovascular outcomes. Multiple clinical trials and a meta-analysis of 8 clinical trials in men with prostate cancer revealed no association between ADT and cardiovascular mortality.^{8–10} Several factors may explain this discrepancy. 1) Clinical trial participants in those studies may have been fundamentally different from the population based PCOS cohort evaluated in this study. Clinical trial participants tend to be younger with fewer comorbid illnesses than individuals who do not participate in clinical trials.²² 2) The cardiovascular end point in many clinical trials was cardiovascular death, a more restrictive end point than the development of CVD, as defined in our study. That more restrictive definition of CVD may have inadequately assessed the cardiovascular risk associated with ADT because many cardiac disorders, including myocardial infarction, heart failure and coronary artery disease, present and are treated before cardiovascular death.

Our findings differ from those of the recently reported study by Alibhai et al from Canada, which showed no increased risk of CVD or sudden cardiac death associated with ADT.¹² The differences may be due to differences in ADT exposure between the studies. Alibhai et

al evaluated cardiovascular outcomes in men with 6 months or more of ADT compared to no ADT. In contrast, we compared cardiovascular outcomes in men exposed to ADT for greater than 2 years (prolonged ADT) or for 2 years or less (short-term ADT) to outcomes in men with no ADT exposure. The duration of ADT in the Canadian study was similar to the definition of short-term ADT in our study. We found no increased cardiovascular risk in those men.

Our study highlights several important issues relevant to the care of men with prostate cancer. The data suggest that short-term exposure to ADT does not increase the risk of DM or CVD. In contrast, the risk of incident DM or CVD in men exposed to prolonged ADT increases with age at diagnosis. Younger men are not at increased risk for incident DM or CVD even when treated with prolonged courses of ADT while older men exposed to prolonged ADT are at increased risk for these illnesses. This is of critical importance to tens of thousands of younger men who are weighing the risks of ADT for curative or palliative treatment. These men do not appear to be at increased risk for DM or CVD due to ADT.

Although we present several clinically relevant findings, we acknowledge that our study has limitations. Our analysis may underestimate the incidence of DM and CVD since we relied on patient report and death certificate data to identify these outcomes. If DM or CVD developed and a man did not report it, we did not identify it. There is also the issue of participant loss to followup, which may have introduced respondent bias into the analysis. Despite this neither the duration of ADT exposure nor increasing age after prostate cancer diagnosis should be associated with failure to identify disease, particularly by death certificate data. Therefore, we would expect the true association between increasing age, ADT exposure and incident disease to be stronger than the association reported. Additionally, our surveys and analysis did not include risk factors known to influence the development of CVD or DM, including obesity, hyperlipidemia, dietary factors, family history and smoking status. Furthermore, our data set did not include specific dates indicating ADT initiation, cessation or intermittent treatment. Finally, given the number of statistical tests performed, there is some risk of type I error in the analysis and the reader should remain cognizant of this when considering the results.

Despite these limitations our analysis identifies a possible interaction between increasing age and the duration of ADT exposure in a diverse population reflective of men who receive treatment for prostate cancer today.

To our knowledge this study is the first to demonstrate the interaction between increasing age at diagnosis, duration of exposure to ADT and its effect on the development of DM and CVD in men with prostate cancer. We believe that this population based study with long-term followup offers generalizable findings that can be applied to routine clinical practice. It provides further evidence that older men, especially those with multiple comorbidities, may face more risk than benefit when ADT is not clearly indicated.

CONCLUSIONS

In this prospective cohort study older men with prostate cancer treated with prolonged ADT (greater than 2 years) were at increased risk for DM (ages 76 years or greater) or CVD (ages 74 years or greater) compared to men not exposed to ADT. Younger men treated with prolonged ADT and men treated with short-term ADT (2 years or less) did not experience these outcomes. Comorbid illness increased the odds of DM and CVD in men treated with prolonged ADT. Physicians should carefully monitor men who receive prolonged ADT and recognize that older men, especially those with comorbidities, are at increased for DM and CVD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms

ADT	androgen deprivation therapy
CVD	cardiovascular disease
DM	diabetes
PCOS	Prostate Cancer Outcomes Study
PSA	prostate specific antigen
SEER	Surveillance, Epidemiology and End Results

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Figure 1.
CONSORT diagram of PCOS participants included in DM and CVD analyses

Figure 2. Odds of DM by age at diagnosis of prostate cancer and ADT exposure. Solid curve indicates odds of DM. Dashed curves indicate 95% CI.

Figure 3.
Odds of CVD by age at diagnosis of prostate cancer and ADT exposure. Solid curve indicates odds of CVD. Dashed curves indicate 95% CI.

Baseline characteristics of patients with prostate cancer by ADT exposure group in DM cohort

	% ADT (No. pts)			
	None*	2 Yrs or Less	Greater than 2 Yrs	
Overall	(2,033)	(692)	(260)	
SEER site:				
CT	17 (353)	21 (144)	19 (50)	
NM	14 (285)	8 (53)	10 (27)	
Seattle	11 (230)	10 (71)	10 (26)	
UT	19 (384)	19 (131)	20 (52)	
Atlanta	13 (258)	11 (77)	5 (14)	
Los Angeles	26 (523)	31 (216)	35 (91)	
Age:				
49 or Less	3 (64)	2 (14)	0 (1)	
50–59	24 (496)	16 (111)	21 (55)	
60–69	40 (820)	34 (236)	33 (87)	
70–79	28 (573)	34 (236)	40 (105)	
80 or Greater	4 (80)	14 (95)	5 (12)	
Race:				
White	72 (1,466)	65 (453)	73 (190)	
Black	13 (273)	20 (139)	15 (38)	
Hispanic	14 (294)	14 (100)	12 (32)	
Primary treatment:				
Watchful waiting	19 (377)	6 (44)	14 (37)	
Surgery only	56 (1,138)	7 (50)	22 (56)	
Radiation only	22 (451)	3 (24)	19 (49)	
Hormonal therapy only	0 (0)	44 (302)	28 (72)	
Surgery + radiation	3 (67)	0 (1)	2 (6)	
Surgery + hormonal therapy	0	22 (150)	7 (19)	
Radiation + hormonal therapy	0	16 (113)	7 (18)	
Surgery, radiation + hormonal therapy	0	1 (8)	1 (3)	

% ADT (No. pts)				
	None *	2 Yrs or Less	Greater than 2 Yrs	
Stage:				
Clinically localized	97 (1,964)	73 (504)	82 (212)	
Regionally advanced	3 (56)	13 (92)	12 (30)	
Metastatic	1 (13)	14 (96)	7 (18)	
Gleason grade:				
6 or Less	73 (1,476)	49 (338)	47 (121)	
7	20 (409)	32 (219)	38 (99)	
8 or Greater	7 (148)	20 (135)	15 (40)	
Comorbidity index:				
0	53 (1,074)	44 (305)	42 (110)	
1	30 (602)	33 (225)	39 (101)	
2	11 (216)	14 (98)	11 (29)	
3 or Greater	7 (141)	9 (64)	8 (20)	
Marital status:				
Married	72 (1,463)	72 (498)	78 (203)	
Single	16 (318)	20 (140)	21 (55)	
Unknown	12 (252)	8 (54)	1 (2)	
Insurance status:				
Medicare	41 (831)	49 (226)	47 (121)	
Private or military	49 (1,004)	40 (274)	46 (120)	
Medicaid or other	1 (30)	1 (10)	1 (3)	
No insurance	0 (10)	1 (9)	0 (1)	
Unknown	8 (158)	9 (63)	6 (15)	

* SEER site, age, race, primary treatment, stage, comorbidity index, Gleason grade, marital and insurance status no ADT vs 2 or less, or greater than 2 years of ADT each Pearson chi-square test p <0.001.