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

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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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Study received institutional review board approval at each participating site.

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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 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.

Key Words: prostatic neoplasms, antiandrogens, cardiovascular diseases, diabetes mellitus, risk

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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 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]