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Association Between Androgen Deprivation Therapy and Risk of Dementia

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IMPORTANCE A growing body of evidence supports a link between androgen deprivation therapy (ADT) and cognitive dysfunction, including Alzheimer disease. However, it is currently unknown whether ADT may contribute to the risk of dementia more broadly.

OBJECTIVE To use an informatics approach to examine the association of ADT as a treatment for prostate cancer with the subsequent development of dementia (eg, senile dementia, vascular dementia, frontotemporal dementia, and Alzheimer dementia).

DESIGN, SETTING, AND PARTICIPANTS In this cohort study, a text-processing method was used to analyze electronic medical record data from an academic medical center from 1994 to 2013, with a median follow-up of 3.4 years (interquartile range, 1.0-7.2 years). We identified 9455 individuals with prostate cancer who were 18 years or older at diagnosis with data recorded in the electronic health record and follow-up after diagnosis. We excluded 183 patients with a previous diagnosis of dementia. Our final cohort comprised 9272 individuals with prostate cancer, including 1826 men (19.7%) who received ADT.

MAIN OUTCOMES AND MEASURES We tested the effect of ADT on the risk of dementia using propensity score–matched Cox proportional hazards regression models and Kaplan-Meier survival analysis.

RESULTS Among 9272 men with prostate cancer (mean [SD] age, 66.9 [10.9] years; 5450 [58.8%] white), there was a statistically significant association between use of ADT and risk of dementia (hazard ratio, 2.17; 95% CI, 1.58-2.99; $P < .001$). In sensitivity analyses, results were similar when excluding patients with Alzheimer disease (hazard ratio, 2.32; 95% CI, 1.73-3.12; $P < .001$). The absolute increased risk of developing dementia among those who received ADT was 4.4% at 5 years (7.9% among those who received ADT vs 3.5% in those who did not receive ADT). Analyses stratified by duration of ADT found that individuals with at least 12 months of ADT use had the greatest absolute increased risk of dementia (hazard ratio, 2.36; 95% CI, 1.64-3.38; $P < .001$). Kaplan-Meier analysis demonstrated that ADT users 70 years or older had the lowest cumulative probability of remaining dementia free (log-rank $P < .001$).

CONCLUSIONS AND RELEVANCE Androgen deprivation therapy in the treatment of prostate cancer may be associated with an increased risk of dementia. This finding should be further evaluated in prospective studies.

Invited Commentary

Author Audio Interview

Supplemental content

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Worldwide there are approximately 1.1 million new diagnoses of prostate cancer each year.[1] Androgen deprivation therapy (ADT), which is used to lower male androgens given the androgen dependence of prostate cancer, is a mainstay of treatment for both metastatic and locoregional disease.[2,3] In recent decades, the use of ADT has increased dramatically,[4] with 500 000 males currently receiving ADT for prostate cancer in the United States[5] and 50% of men with prostate cancer in industrialized nations using ADT during their lifetime.[6]

Androgen deprivation therapy has a demonstrated survival benefit in some patients with prostate cancer.[2] However, it also has been linked to several adverse health effects[7,8] with a growing body of evidence now supporting a link between ADT and neurocognitive dysfunction.[9,10] A recent analysis examined the association of ADT and Alzheimer disease[11] given the demonstrated effect of androgens and ADT on accumulation of β-amyloid protein.[12] However, androgens have been also shown to aid in neuron growth and axonal regeneration.[13] In addition, both low testosterone levels and ADT increase the risk of cardiometabolic diseases,[8,14] which are known risk factors for all-cause dementia.[15] Therefore, while ADT may specifically increase the risk of Alzheimer disease, it may also contribute to the risk of dementia more broadly through distinct mechanisms.

Examination of the association between ADT and risk of general dementia is critical to more fully understand the effect of ADT on neurodegenerative diseases. Given that Alzheimer disease accounts for only a portion of the estimated 35 million individuals with dementia worldwide,[16] an association between ADT and dementia may have significant public health implications. In this study, we use an informatics approach, analyzing electronic medical record data from more than 1.2 million patients, to examine the association of ADT with the subsequent development of dementia (eg, senile dementia, vascular dementia, frontotemporal dementia, and Alzheimer dementia) among men with prostate cancer.

Key Points

Questions Is there evidence of an association between use of androgen deprivation therapy in the treatment of prostate cancer and future dementia and can applied clinical informatics tools help identify relevant population cohorts?

Findings This cohort study applied a novel text-processing analytic approach to the electronic medical records of 9272 individuals with prostate cancer. There was a statistically significant association between androgen deprivation therapy and increased risk of dementia.

Meaning Future prospective studies are needed to further investigate the association of androgen deprivation therapy and risk of dementia.

Methods

Data Source

We used data from the Stanford University health system (1994-2013) accessed under a protocol approved by the Stanford Human Subjects Research Institutional Review Board, which waived the requirement for patient consent as the data mining studies were deemed not to involve human participants. This study included data for 1.2 million patients representing 19 million encounters, 35 million coded *International Classification of Disease, Ninth Revision* (*ICD-9*) diagnoses, and a combination of pathologic studies, radiologic images, and transcription reports totaling more than 11 million unstructured clinical notes. We used a previously validated[17] and implemented[11,18] text-processing method to analyze clinical data. Briefly, we extracted *ICD-9* diagnosis and *Current Procedural Terminology* (*CPT*) codes, medication lists, and positive-present mentions of drug and disease concepts from all clinical notes. We removed uninformative phrases based on term frequency analysis of more than 50 million clinical documents[19] and suppressed terms having fewer than 4 characters because most of these terms are ambiguous abbreviations. We used NegEx regular expressions to flag negative mentions (eg, "ruled out prostate cancer") and to determine if a term was mentioned in the history or family history section of the clinical note.[20] The result is a list of present, positive mentions of biomedical concepts, which are converted into a patient-feature matrix for analysis.

Definition of Outcomes and Covariates

Prostate cancer was defined as the following: (1) *ICD-9 code* 185; (2) billing code for radical prostatectomy (*ICD-9* 60.5 or *CPT* codes 55810-55815 and 55840-55845) plus either use of ADT (in medication lists or clinical text) or clinical text evidence of prostate cancer diagnosis (eTable 1 in the Supplement); or (3) clinical text evidence of prostate cancer diagnosis and use of ADT (in medication lists or clinical text), as previously described.[11] The use of ADT was defined using data from clinical notes and medication lists, including pharmacy orders. Specific medication names used in the search are detailed in the eAppendix in the Supplement. Duration of ADT was calculated using time-stamp data at each determined instance of ADT use.

New-onset dementia was defined using terms from clinical notes (eTable 1 in the Supplement) and *ICD-9* diagnostic codes 290.0 through 290.9, 331.0 through 331.2, or 294.1 through 294.21.[21] Among those receiving ADT, incident dementia was ascertained after initiation of ADT and at least 180 days after prostate cancer diagnosis. Among those not using ADT, incident dementia was ascertained 180 days after prostate cancer diagnosis and after the median time to use of ADT in our study.

Adjustment covariates included were age at prostate cancer diagnosis; race/ethnicity; smoking status; use of antiplatelet, anticoagulant, antihypertensive, and statin medications; and a history of cardiovascular disease, type 1 or 2 diabetes, stroke, or malignant neoplasms. All covariates were binary except age (continuous). Race/ethnicity was defined as recorded in the electronic medical record. We used *ICD-9* diagnostic codes, clinical text data, medication lists, and pharmacy records to define each covariate with further details

(eTable 2 in the Supplement). Medication use and a history of diabetes or malignant neoplasm were determined using data from 365 days prior through 180 days after prostate cancer diagnosis. A history of cardiovascular disease was determined using data from 365 days prior through 180 days after prostate cancer diagnosis, with the exception of myocardial infarction, for which only data prior to prostate cancer diagnosis were used. A history of stroke was determined using data only prior to prostate cancer diagnosis.

Inclusion and Exclusion Criteria

All individuals with prostate cancer who were 18 years or older at diagnosis with data in the electronic health record were eligible for study inclusion. Patients with exposure to ADT were included only if they had follow-up after initiation of ADT. To control for differential frequency of follow-up, patients without exposure to ADT were included only if they had follow-up visits after the median time to use of ADT in the exposed group. Patients with a previous diagnosis of dementia were excluded. Individuals who received ADT but developed dementia before starting ADT were also excluded.

Statistical Analysis

For all analyses, the start of the follow-up period was defined as either the initiation of ADT or, for those who did not receive ADT, the time of prostate cancer diagnosis plus the median time to use of ADT in our study. The end of the follow-up period was that of the last available record, either inpatient or outpatient, or the time of dementia diagnosis. Baseline patient characteristics were compared for those receiving ADT and those not receiving ADT using a *t* test or χ^2 test.

Hazard ratios (HRs) were calculated using propensity score-matched and traditional multivariable adjusted Cox proportional hazards regression models to test the effect of ADT on risk of dementia. We used 1:1 nearest-neighbor propensity score matching without replacement. Variables included in propensity score matching and in traditional multivariable adjusted Cox proportional hazards regression analyses included age at prostate cancer diagnosis; race/ethnicity; smoking status; use of antiplatelet, anticoagulant, antihypertensive, and statin medications; and a history of cardiovascular disease, diabetes, stroke, or malignant neoplasms. Variables associated with cardiometabolic disease and age were included as they have been shown to increase risk of dementia[15,22] and, along with prior malignant neoplasms, may contribute to patients' likelihood of receiving radiotherapy and therefore ADT, if, for example, they are poor candidates for surgery. We additionally accounted for race/ethnicity, given known racial/ethnic disparities in stage at diagnosis and access to definitive cancer treatment.[23,24]

Kaplan-Meier curves were constructed to examine the cumulative probability of remaining dementia free in the propensity score-matched and unmatched cohorts. Kaplan-Meier curves were compared in the propensity score-matched and unmatched cohorts using the log-rank test for equality. We calculated the cumulative probability of developing dementia at 5 years using the Kaplan-Meier method in the propensity score-matched cohort. The duration of ADT use was also tested for association with risk of dementia. Specifically, we examined risk of dementia among those with fewer than 12 months of ADT use and 12 months or more of ADT use compared with those not receiving ADT using Cox proportional hazards regression models in the propensity score-matched cohort. We additionally conducted a test for trend of the risk of dementia with increasing duration of use of ADT across categories (ie, no use, <12 months or ≥12 months).

We examined the effect of ADT on dementia according to age at diagnosis. We also stratified our analysis with age 70 years selected as the cutoff, given recommendations for comprehensive geriatric assessment of all patients with cancer who are 70 years or older.[25-27] Propensity score-matched Kaplan-Meier curves were compared using log-rank tests for (1) those younger than 70 years who did not use ADT, (2) ADT users younger than 70 years, (3) those 70 years or older who did not use ADT, and (4) ADT users 70 years or older. A test for interaction was conducted between age and ADT using the Wald test. We additionally calculated the cumulative probability of developing dementia at 5 years using the Kaplan-Meier method in the age-stratified propensity score-matched cohort.

We conducted sensitivity analyses excluding men who received chemotherapy, given evidence for chemotherapy-associated cognitive dysfunction[28] in addition to excluding dementia diagnoses within the first 2 years of follow-up to control for inclusion of prevalent disease diagnosed after study entry. We included Gleason score as an adjustment covariate in the sensitivity analysis in 4360 patients with available data. We additionally evaluated the association of ADT with dementia excluding 94 patients with Alzheimer disease, given previous data supporting an association between ADT and Alzheimer disease.[11] Finally, we evaluated whether an association between ADT and dementia might be secondary to unmeasured physician or patient characteristics by using falsification analyses.[29] Specifically, we selected 3 outcomes to test for association with ADT with no known or hypothesized association: tuberculosis, allergic rhinitis, and abdominal aortic aneurysm.

Cox proportional hazards regression assumptions were evaluated by Schoenfeld residuals tests. Tests were considered significant with a 2-sided $P < .05$. Analyses were performed using Stata, version 12.0 (StataCorp), and R, version 3.2 (R Foundation for Statistical Computing).

Results

We identified 9455 individuals with prostate cancer who were 18 years or older at diagnosis with data recorded in the electronic health record and eligible follow-up. We excluded 183 patients with a previous diagnosis of dementia. No patients receiving ADT developed dementia prior to starting ADT. There were 9272 individuals with prostate cancer meeting all inclusion criteria, including 1826 men (19.7%) who received ADT. There were 314 new cases of dementia during a median follow-up of 3.4 years (interquartile range, 1.0-7.2 years), with a median time to dementia diagnosis of 4.0 years (interquartile range, 1.8-7.9 years). In the unmatched cohort, individuals

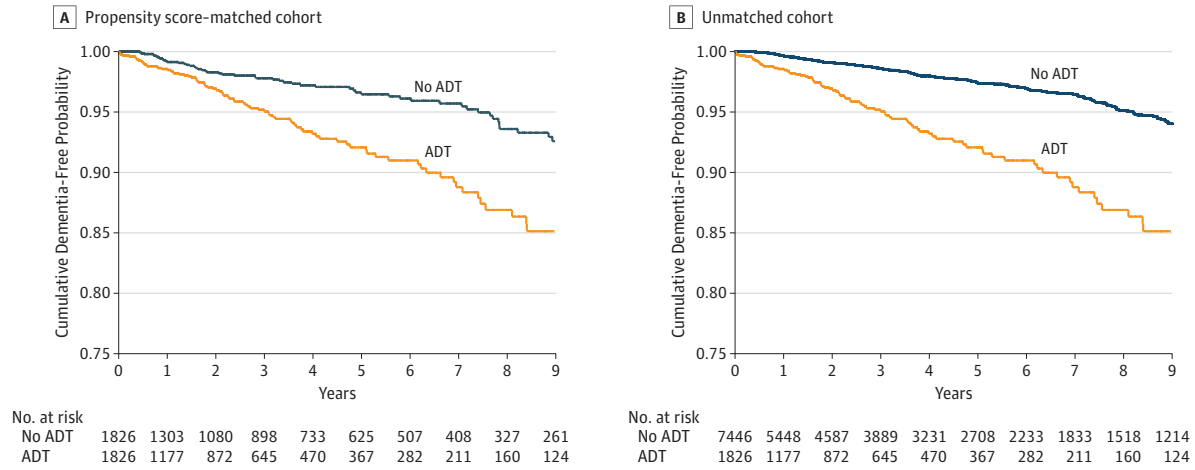
Table 1. Demographic Characteristics

Characteristic	Value[a]					
	Full Cohort			Propensity Score-Matched Cohort		
	ADT Users (n = 1826)	Non-ADT Users (n = 7446)	*P* Value for Difference	ADT Users (n = 1826)	Non-ADT Users (n = 1826)	*P* Value for Difference
Age, mean (SD), y	69.9 (11.0)	66.2 (10.8)	<.001	69.9 (11.0)	69.8 (11.3)	.81
White	993 (54.4)	4457 (59.9)	<.001	993 (54.4)	1028 (56.3)	.24
Ever smoker	799 (43.8)	2835 (38.1)	<.001	799 (43.8)	811 (44.4)	.69
Medication use						
Antiplatelet	579 (31.7)	1786 (24.0)	<.001	579 (31.7)	588 (32.2)	.75
Anticoagulant	250 (13.7)	871 (11.7)	.02	250 (13.7)	227 (12.4)	.26
Antihypertensive	832 (45.6)	2493 (33.5)	<.001	832 (45.6)	827 (45.3)	.87
Statin	334 (18.3)	1069 (14.4)	.06	334 (18.3)	312 (17.1)	.34
Prior cardiovascular disease	490 (26.8)	1406 (18.9)	<.001	490 (26.8)	477 (26.1)	.63
Prior type 1 or 2 diabetes	369 (20.2)	1096 (14.7)	<.001	369 (20.2)	363 (19.9)	.80
Prior stroke	21 (1.2)	70 (0.9)	.42	21 (1.2)	17 (0.9)	.51
Prior malignant neoplasm	89 (4.9)	629 (8.4)	<.001	89 (4.9)	74 (4.1)	.23

Abbreviation: ADT, androgen deprivation therapy.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

Figure 1. Kaplan-Meier Curves Examining the Cumulative Probability of Remaining Dementia Free



A, Propensity score–matched cohort. B, Unmatched cohort. ADT indicates androgen deprivation therapy.

receiving ADT were statistically significantly older and less likely to be white, as well as more likely to be smokers; taking antiplatelet, anticoagulant, and antihypertensive medications; and have a history of cardiovascular disease, diabetes, or prior malignant neoplasms (**Table 1**). No statistically significant differences existed in the propensity score-matched cohort. Among 4360 patients with available Gleason scores, 2562 (58.8%) had a Gleason score of 6 or less, 1224 (28.1%) had a Gleason score of 7, and 574 (13.2%) had a Gleason score of 8 or more (eTable 3 in the Supplement).

Kaplan-Meier analyses demonstrated that those receiving ADT had a lower cumulative probability of remaining dementia free in the propensity score-matched (log-rank $P < .001$) and unmatched (log-rank $P < .001$) cohorts (**Figure 1**). The absolute increased risk of developing dementia among those receiving ADT was 4.4% at 5 years (7.9% among those receiving ADT vs 3.5% among those not receiving ADT). There was a statistically significant positive association between use of ADT and dementia in the propensity score-matched (HR, 2.17; 95% CI, 1.58-2.99; $P < .001$) and traditional multivariable adjusted (HR, 2.21; 95% CI, 1.72-2.83; $P < .001$) Cox proportional hazards regression analyses (**Table 2**).

Stratification by duration of use of ADT showed that individuals who had been receiving ADT for at least 12 months had the greatest risk of dementia (HR, 2.36; 95% CI, 1.64-3.38; $P < .001$), with a statistically significant increased risk of dementia by category of increasing ADT duration ($P < .001$ for trend) (**Table 3**). Age-stratified propensity score-matched (**Figure 2**) and unmatched (eFigure in the Supplement) Kaplan-Meier analyses demonstrated a lower cumulative probability of remaining dementia free among those younger than 70 years who received ADT vs those younger than 70 years who did not

receive ADT (log-rank $P = .02$) and a lower cumulative probability of remaining dementia free among those 70 years or older who received ADT vs those 70 years or older who did not receive ADT (log-rank $P < .001$). We did not find evidence of an interaction between use of ADT and age (Wald 0.29; $P = .59$). We found that the cumulative probabilities of developing dementia at 5 years were 13.7%, 6.6%, 2.3%, and 1.0% among those 70 years or older who received ADT, those 70 years or older who did not receive ADT, those younger than 70 years who received ADT, and those younger than 70 years who did not receive ADT, respectively.

In sensitivity analyses, results were similar when excluding individuals who received chemotherapy (HR, 2.35; 95% CI, 1.82-3.03; $P < .001$), when excluding patients diagnosed with dementia within the first 2 years of eligible follow-up (HR, 2.39; 95% CI, 1.78-3.21; $P < .001$), and when excluding those with Alzheimer disease (HR, 2.32; 95% CI, 1.73-3.12; $P < .001$). Subgroup analysis adjusted for Gleason score demonstrated similar results (HR, 2.16; 95% CI, 1.46-3.22; $P < .001$). The results of the falsification analyses (eTable 4 in the Supplement) showed no statistically significant associations. Schoenfeld residuals tests demonstrated that the Cox proportional hazards regression assumption was met for all models.

Discussion

We used an informatics-based approach to demonstrate an association between the use of ADT in the treatment of prostate cancer and an increased risk of dementia. We support this association using both propensity score–matched and traditional multivariable regression models adjusted for a wide range of potential confounding factors. We show a dose-response effect between greater duration of use of ADT and increased risk of dementia. Finally, we find that use of ADT increases the risk of dementia regardless of age, but that older men receiving ADT were the least likely to remain dementia free.

Previous studies have shown that systemic cancer treatments have a detrimental effect on cognitive function.[9,30] Androgen deprivation therapy in particular has been linked with impairments in visuomotor and executive functioning.[10,31] In a prospective evaluation, men treated with ADT were more likely to demonstrate impaired cognitive performance as early as 6 months after starting ADT compared with matched controls.[9] Men diagnosed with dementia have demonstrated reduced levels of testosterone, including prior to onset of dementia.[32-34] Among men with Alzheimer disease, testosterone supplementation has been shown to improve spatial and verbal memory.[35] However, a previous study showed an association between a luteinizing hormone-releasing hormone agonist and a decreased risk of death from Alzheimer disease.[36]

This study extends previous work showing an association between ADT and Alzheimer disease.[11] That study focused on Alzheimer disease given specific mechanisms to explain an association with ADT. Androgens may affect the risk of Alzheimer disease through modulation of accumulation of β-amyloid protein with use of ADT in the treatment of prostate cancer having been shown to increase circulating levels of β-amyloid protein.[12] In addition, the combination of cardiovascular disease and possession of the ε4 allele of the apolipoprotein E gene (OMIM 107741) may directly interact to increase risk of Alzheimer disease.[37]

However, there are several plausible mechanisms that may explain an association between ADT and dementia in general. Androgens have a demonstrated role in neuron health and growth.[13] Testosterone analogues have shown neuroprotective effects directly through their interaction with androgen receptors.[38] Testosterone also may be converted to estrogen, which has well-defined neuroprotective properties.[39] Low testosterone levels and ADT also have been shown to increase the risk of cardiometabolic diseases,[8,14] which are also known risk factors for dementia.[15] Finally, previous studies have suggested that carriers of polymorphisms in certain genes may be at an increased risk of cancer and cognitive changes associated with cancer treatment.[40,41]

Table 2. Analyses of the Association of Use of ADT With Risk of Dementia

Exposure	HR (95% CI)	*P* Value
Propensity Score–Matched Analysis		
No ADT use	1 [Reference]	1 [Reference]
ADT use	2.17 (1.58-2.99)	<.001
Multivariable Adjusted Analysis[a]		
No ADT use	1 [Reference]	1 [Reference]
ADT use	2.21 (1.72-2.83)	<.001
Unadjusted Analysis		
No ADT use	1 [Reference]	1 [Reference]
ADT use	3.00 (2.34-3.84)	<.001

Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio.

[a] Adjusted for age; race/ethnicity; smoking status; anticoagulant, antiplatelet, antihypertensive, and statin therapy; and history of cardiovascular disease, type 1 or 2 diabetes, stroke, or malignant neoplasm.

Table 3. Propensity Score–Matched Cox Proportional Hazards Regression Analysis[a]

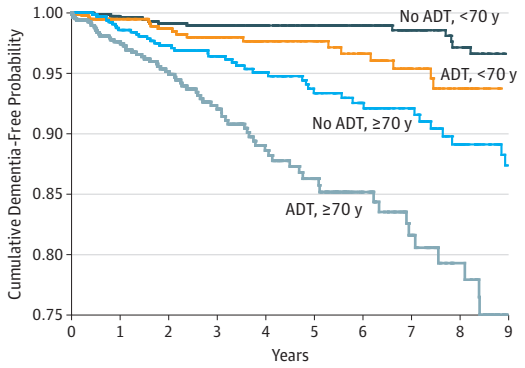
Duration of ADT Use	HR (95% CI)	*P* Value	*P* Value for Trend[b]
None	1 [Reference]	1 [Reference]	
ADT use, mo			<.001
<12	1.95 (1.31-2.89)	.001	
≥12	2.36 (1.64-3.38)	<.001	

Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio.

[a] Adjusted for age; race/ethnicity; smoking status; anticoagulant, antiplatelet, antihypertensive, and statin therapy; and history of cardiovascular disease, type 1 or 2 diabetes, stroke, or malignant neoplasm.

[b] By category of ADT duration.

Figure 2. Propensity Score–Matched Kaplan-Meier Curves Examining the Age-Stratified Cumulative Probability of Remaining Dementia Free



No. at risk

No ADT, <70 y	971	711	601	501	418	365	295	236	200	162
ADT, <70 y	925	587	448	337	251	205	171	129	102	83
No ADT, ≥70 y	855	592	479	397	315	260	212	172	127	99
ADT, ≥70 y	901	590	424	308	219	162	111	82	58	41

The cumulative probabilities of developing dementia at 5 years were 13.7%, 6.6%, 2.3%, and 1.0% among those 70 years or older who received androgen deprivation therapy (ADT), those 70 years or older who did not receive ADT, those younger than 70 years who received ADT, and those younger than 70 years who did not receive ADT, respectively. Each curve was independently statistically significantly different from all other curves ($P < .05$).

Examination of the association between ADT and all-cause dementia more fully characterizes the effect of ADT on neurocognitive function. In our study, Alzheimer disease accounted for only 30% of dementia cases, and sensitivity analyses excluding these patients supported a strong association between ADT and dementia not associated with Alzheimer disease. In addition, we found a clinically meaningful 7.1% absolute increased risk of dementia at 5 years among patients 70 years or older who received ADT. An association between use of ADT and dementia in general may therefore have significant public health implications.

Limitations

This study has limitations that warrant consideration. We used clinical text documentation and billing codes to determine diagnosis of dementia, which may introduce bias into our analysis. We therefore used established methods in accessing administrative health data for dementia diagnosis.[21] Patients also may be more likely to receive definitive radiotherapy and therefore ADT if they are poor candidates for surgery secondary to medical comorbidities, such as cardiometabolic diseases, which are also risk factors for dementia.[35] Therefore, we adjusted for a range of comorbidities and conducted propensity score-matched analyses. More important, in this study, we were not sufficiently powered to undertake subgroup analysis by type of ADT. Given that the various forms of ADT have complex effects on the hypothalamic-pituitary-gonadal axis, future studies should prioritize stratification by type of ADT.

A further limitation is that we were only able to adjust for characteristics specific to prostate cancer (ie, Gleason score) in a subset of patients. However, adjustment for Gleason score in the subgroup of patients with available data continued to show a statistically significant association between use of ADT and risk of dementia. Similarly, we were unable to reliably delineate use of ADT in the setting of definitive vs metastatic prostate cancer. Future studies should examine the effect of use of ADT on risk of dementia in the setting of definitive prostate cancer, in particular, among men for whom the benefit of ADT may be unclear. Our analysis, while in a general population cohort, was limited to a single institution and therefore may not be generalizable to all individuals. Finally, our analysis was retrospective and does not establish a causal association between the use of ADT and risk of dementia.

Conclusions

As survival rates following cancer diagnoses continue to improve, the population of older, long-term cancer survivors is expected to increase.[42] Therefore, the chronic health implications of cancer therapies will become of increasing importance. Here, we demonstrate an association between the use of ADT and increased risk of dementia in a general population cohort of men with prostate cancer. Our study extends previous work supporting an association between use of ADT and Alzheimer disease and suggests that ADT may more broadly affect neurocognitive function. This finding should be investigated in prospective studies given significant individual patient and health system implications if there are higher rates of dementia among the large group of patients undergoing ADT.

ARTICLE INFORMATION

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Author Contributions: Drs Nead and Shah had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: Nead, Gaskin, Swisher-McClure, Shah.
Drafting of the manuscript: Nead, Gaskin, Swisher-McClure, Leeper.
Critical revision of the manuscript for important intellectual content: Nead, Chester, Swisher-McClure, Leeper, Shah.
Statistical analysis: Nead.
Obtained funding: Shah.
Administrative, technical, or material support: Chester.
Study supervision: Nead, Leeper, Shah.

Conflict of Interest Disclosures: Dr Shah reported holding patent US13/273,038 pending, patent US13/420,402 pending, patent US13/424,375 pending, and patent US13/424,376 pending related to the use of text-mining methods in clinical data. No other disclosures were reported.

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