

Androgen Deprivation Therapy and Future Alzheimer's Disease Risk

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A B S T R A C T

Purpose

To test the association of androgen deprivation therapy (ADT) in the treatment of prostate cancer with subsequent Alzheimer's disease risk.

Methods

We used a previously validated and implemented text-processing pipeline to analyze electronic medical record data in a retrospective cohort of patients at Stanford University and Mt. Sinai hospitals. Specifically, we extracted International Classification of Diseases-9th revision diagnosis and Current Procedural Terminology codes, medication lists, and positive-present mentions of drug and disease concepts from all clinical notes. We then tested the effect of ADT on risk of Alzheimer's disease using 1:5 propensity score-matched and traditional multivariable-adjusted Cox proportional hazards models. The duration of ADT use was also tested for association with Alzheimer's disease risk.

Results

There were 16,888 individuals with prostate cancer meeting all inclusion and exclusion criteria, with 2,397 (14.2%) receiving ADT during a median follow-up period of 2.7 years (interquartile range, 1.0-5.4 years). Propensity score-matched analysis (hazard ratio, 1.88; 95% CI, 1.10 to 3.20; $P = .021$) and traditional multivariable-adjusted Cox regression analysis (hazard ratio, 1.66; 95% CI, 1.05 to 2.64; $P = .031$) both supported a statistically significant association between ADT use and Alzheimer's disease risk. We also observed a statistically significant increased risk of Alzheimer's disease with increasing duration of ADT ($P = .016$).

Conclusion

Our results support an association between the use of ADT in the treatment of prostate cancer and an increased risk of Alzheimer's disease in a general population cohort. This study demonstrates the utility of novel methods to analyze electronic medical record data to generate practice-based evidence.

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INTRODUCTION

Androgen deprivation therapy (ADT) has been a mainstay of treatment of prostate cancer since the 1940s. Although its use has historically been limited to metastatic disease, randomized evidence supports the use of ADT in combination with external-beam radiation therapy for locoregional disease with high-risk features.^{1,2} Overall the use of ADT has increased dramatically over recent decades,³ with an estimated 500,000 men currently receiving ADT for prostate cancer in the United States.⁴

The goal of ADT is to profoundly lower male androgens, specifically testosterone, secondary to

the androgen dependence of prostate cancer. Although most individuals return to normal testosterone levels post treatment, 20% to 30% have prolonged androgen suppression.^{5,6} Importantly, low testosterone levels have been linked to a number of adverse health effects, including cardiometabolic disease.⁷ Additionally, evidence supports an association between ADT and negative health consequences, including diabetes and cardiovascular disease.^{8,9}

The use of ADT in the treatment of prostate cancer has also been associated with a number of cognitive deficits.^{10,11} Concerningly, ADT has been linked to impairments in visuomotor and executive functioning, which are cardinal features of Alzheimer's disease.¹¹ Additionally, men diagnosed

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with Alzheimer's disease have demonstrated lower levels of circulating and brain testosterone, with low testosterone levels preceding disease onset.¹²⁻¹⁵ Among men with Alzheimer's disease, testosterone supplementation has been shown to improve spatial and verbal memory.¹⁶ Finally, although the majority of cancers have an inverse association with Alzheimer's disease risk, prostate cancer is associated with a significantly increased risk of Alzheimer's disease.¹⁷

Despite these data, there have been limited and conflicting investigations examining the association of ADT with neurocognitive function¹⁰ and no known studies examining the association of ADT with risk of Alzheimer's disease. In the current study we use a novel informatics approach, using electronic medical record data from more than 5 million patients, to examine the association of ADT with the subsequent development of Alzheimer's disease among men with prostate cancer.

METHODS

Data Sources

We used data from Stanford University (1994 to 2013) and Mt. Sinai (2000 to 2013) health systems. There were 1.8 million patients at Stanford and 3.7 million patients at Mt. Sinai, representing 40 million patient encounters with transcriptions of all inpatient and outpatient clinical notes as well as pathology and radiology reports and structured medication lists. Both data sources were accessed under approved institutional review board protocols. Access to Mt. Sinai data was obtained via an institutional research agreement.

Electronic Medical Record Processing

We used a previously validated¹⁸ and implemented¹⁹⁻²¹ text-processing pipeline²² to analyze clinical data. We extracted International Classification of Diseases-9th revision (ICD-9) diagnosis and Current Procedural Terminology 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 documents²³ and suppressed terms having fewer than four characters because the majority of these 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 note.²⁴ The result is a list of present, positive mentions of biomedical concepts, which are converted into a patient-feature matrix for analysis (Appendix Fig A1, online only).

These methods have been compared against advanced natural language-processing methods in a functional evaluation, which showed little impact on the accuracy of association detection in large data sets.²² As further validation, in drug safety studies, the sensitivity and specificity in detecting 25 different conditions via methods used in this study were 0.74 and 0.96, respectively.¹⁸

Definition of Outcomes and Covariates

Prostate cancer was defined as (1) ICD-9 code (185), (2) billing code for radical prostatectomy (ICD-9 60.5 or CPT code 55810-55815, 55840-55845) plus either ADT use (in medication lists or clinical text) or clinical text evidence of prostate cancer diagnosis (Appendix Table A1), or (3) clinical text evidence of prostate cancer diagnosis and ADT use (in medication lists or clinical text). In essence, in the absence of an ICD-9 code for prostate cancer, two data points specific for prostate cancer were required. This approach was used to identify prostate cancer diagnoses not reflected in billing codes (eg, only clinical notes were available or data were from visits not resulting in billing for prostate cancer) while limiting misclassification.

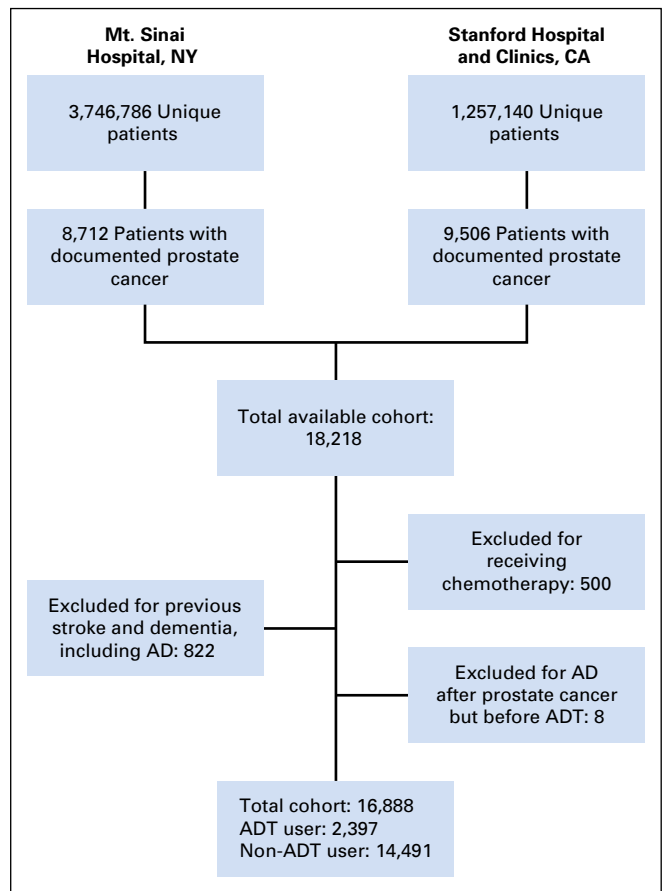


Fig 1. Flow diagram of cohort selection. AD, Alzheimer's disease; ADT, androgen deprivation therapy.

The use of ADT was defined using data from clinical notes and medication lists including pharmacy orders. Specific medication names are detailed in the Appendix. Duration of ADT was calculated using timestamp data at each determined instance of ADT use.

New-onset Alzheimer's disease was defined using terms from clinical notes (Appendix Table A1) and ICD-9 diagnostic code 331.0. Among ADT users, incident Alzheimer's disease was ascertained after initiation of ADT and at least 180 days after prostate cancer diagnosis to limit inclusion of prevalent disease. Among non-ADT users, incident Alzheimer's disease was ascertained starting 180 days after the time of prostate cancer diagnosis and after the median time to ADT use in our study.

Adjustment covariates included were age at prostate cancer diagnosis; race; smoking status; use of antiplatelet, anticoagulant, antihypertensive, and statin medications; and a history of cardiovascular disease, diabetes, or malignancy. Gleason score was included as a covariate in sensitivity analysis in those patients with available data (n = 4,373). We used ICD-9 diagnostic codes, clinical text data, medication lists, and pharmacy records to define each covariate with further details outlined in Appendix Table A2. Medication use and a history of diabetes or malignancy were determined using data from 365 days before through 180 days after prostate cancer diagnosis. A history of cardiovascular disease was determined using data from 365 days before through 180 days after prostate cancer diagnosis with the exception of myocardial infarction, which used data only before prostate cancer diagnosis.

Inclusion and Exclusion Criteria

All individuals with prostate cancer and data on all defined covariates who had follow-up data for at least 180 days after prostate cancer diagnosis

were eligible for study inclusion (Fig 1). Patients with exposure to ADT were only included if they had follow-up after initiation of ADT. Men who received chemotherapy were excluded, given evidence for chemotherapy-associated cognitive dysfunction and an expected high correlation between receipt of chemotherapy and ADT use.²⁵ Those with a history of dementia, including Alzheimer's disease, frontotemporal dementia, and Lewy body dementia, as well as stroke, were also excluded, given concern for misclassification of Alzheimer's disease (see Appendix Table A2 for variable definition). A history of dementia was determined using data from 365 days before through 180 days after prostate cancer diagnosis to limit misclassification of prevalent disease. A history of stroke was determined using only data before prostate cancer diagnosis. Individuals who received ADT but developed Alzheimer's disease before starting ADT were also excluded.

Statistical Methods

For all analyses, the start of the follow-up period was defined as either the initiation of ADT for ADT users or, for non-ADT users, the time of prostate cancer diagnosis plus the median time to ADT use 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 Alzheimer's disease diagnosis. Baseline patient characteristics were compared for ADT and non-ADT users using a *t* test or χ^2 test. All included variables were binary except age.

Hazard ratios were calculated using propensity score–matched and traditional multivariable-adjusted Cox proportional hazards models to test the effect of ADT on risk of Alzheimer's disease. Specifically, we used 1:5 nearest-neighbor propensity score matching with replacement. We then analyzed the propensity score–matched data set using weighted Cox proportional hazards models as previously described.²⁶

Propensity score–matched analyses and traditional multivariable-adjusted Cox regression analyses were adjusted for age at prostate cancer diagnosis; race; smoking status; use of antiplatelet, anticoagulant, antihypertensive, and statin medications; and a history of cardiovascular disease, diabetes, or malignancy. We adjusted for cardiometabolic disease–associated variables and age, as they have been shown to increase Alzheimer's disease risk^{27,28} and, along with prior malignancy, contribute to patients' likelihood of receiving radiation therapy and therefore ADT, if, for example, they are poor surgical candidates. We additionally accounted for race given known racial disparities in stage at diagnosis and access to definitive cancer treatment.^{29,30} Further sensitivity analyses were conducted including individuals receiving chemotherapy, among only those with at least 5 years of follow-up, and using shared-frailty models to account for the matched nature of the data.

Results were compared between Stanford and Mt. Sinai. Kaplan-Meier curves were constructed to examine the cumulative probability of remaining Alzheimer's disease–free in the full cohort and in the propensity score–matched cohort. Kaplan-Meier curves were compared in the full and propensity score–matched cohorts using log-rank and Cox regression–based tests for equality, respectively. The duration of ADT use was also tested for association with Alzheimer's disease risk using Cox regression models. Specifically, we examined Alzheimer's disease risk among those with less than 12 months ADT use and greater than or equal to 12 months ADT use compared with non-ADT users. We additionally conducted a test for trend of the risk of Alzheimer's disease with increasing duration of ADT use across categories (ie, no ADT, < 12 months, \geq 12 months). Finally, we evaluated whether an association between ADT and Alzheimer's disease might be secondary to unmeasured physician or patient characteristics by using falsification analysis.³¹ Specifically, we selected five outcomes to test for association with ADT with no known or hypothesized association: anaphylaxis, rhabdomyolysis, tuberculosis, allergic rhinitis, and abdominal aortic aneurysm.

Proportional hazards assumptions were evaluated by Schoenfeld residuals tests. Tests were considered significant if the two-sided *P* value was less than .05. Analyses were performed using Stata version 12.0 (StataCorp, College Station, TX) and R version 3.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

There were 16,888 individuals with prostate cancer meeting all inclusion and exclusion criteria (Fig 1). Of these, 2,397 (14.2%) received ADT, with a median time from prostate cancer diagnosis to ADT use of 35.6 days. Before propensity score matching, individuals receiving ADT were statistically significantly older and more likely to be white, smokers, on antiplatelet, anticoagulant and antihypertensive medications, and have a history of cardiovascular disease and diabetes (Table 1). No statistically significant differences existed among measured baseline covariates in the propensity score–matched cohort. There were 125 new diagnoses of Alzheimer's disease during a median follow-up period of 2.7 years (interquartile range, 1.0 to 5.4 years). The median time to Alzheimer's disease diagnosis was 4.0 years (interquartile range, 2.0 to 7.4 years). Gleason score was available for a subset of patients

Table 1. Demographic Characteristics

Characteristic	Full Cohort			1:5 Propensity Score–Matched Cohort		
	ADT Users (n = 2,397)	Non-ADT Users (n = 14,491)	<i>P</i> for Difference	ADT Users (n = 2,397)	Non-ADT Users (n = 11,985)	<i>P</i> for Difference
Age, mean (SD), years	70.9 (10.8)	66.7 (10.5)	< .001	70.9 (10.8)	70.9 (12.6)	.974
White	1,243 (52)	8,426 (58)	< .001	1,243 (52)	6,487 (54)	.115
Ever smoker	890 (37)	3,420 (24)	< .001	890 (37)	4,553 (38)	.539
Antiplatelet medication use	802 (33)	3,394 (23)	< .001	802 (33)	3,871 (32)	.393
Anticoagulant medication use	420 (18)	1,885 (13)	< .001	420 (18)	1,950 (16)	.248
Antihypertensive medication use	1,205 (50)	5,775 (40)	< .001	1,205 (50)	6,015 (50)	.954
Statin use	559 (23)	3,135 (22)	.064	559 (23)	2,651 (22)	.321
Prior cardiovascular disease	679 (28)	3,072 (21)	< .001	679 (28)	3,288 (27)	.491
Prior diabetes	514 (21)	2,295 (16)	< .001	514 (21)	2,499 (21)	.616
Prior malignancy	166 (7)	1,057 (7)	.519	166 (7)	679 (6)	.073

NOTE. Data presented as No. (%) unless otherwise noted.
Abbreviations: ADT, androgen deprivation therapy; SD, standard deviation.

(n = 4,373), of whom 58% had a Gleason score less than 7, 29% had a Gleason score of 7, and 13% had a Gleason score greater than 7 (Appendix Table A3).

Validating Known Risk Factors

Age and a history of cardiovascular disease showed statistically significant associations with Alzheimer's disease risk using traditional multivariable Cox regression models (Table 2). The results of the falsification analyses (Appendix Table A4) showed no statistically significant associations ($P > .1$).

Association of ADT Use and Development of Alzheimer's Disease

Kaplan-Meier curves demonstrated a lower cumulative probability of remaining Alzheimer's disease-free among ADT users in the full ($P = .001$) and the propensity score-matched ($P = .021$) cohorts (Fig 2).

Propensity score-matched Cox regression analysis (Table 3) supported a statistically significant positive association between ADT use and Alzheimer's disease risk (hazard ratio [HR], 1.88; 95% CI, 1.10 to 3.20; $P = .021$), as did traditional multivariable-adjusted Cox regression analysis (HR, 1.66; 95% CI, 1.05 to 2.64; $P = .031$). This association did not differ by location in the propensity score-matched Cox regression analysis ($P = .700$). Analyses stratified by duration of ADT use (Table 4) demonstrated that individuals with at least 12 months of ADT use had the greatest risk of subsequent Alzheimer's disease (HR, 2.12; 95% CI, 1.11 to 4.03; $P = .011$). We also showed a statistically significant increased risk of Alzheimer's disease by category of increasing ADT duration (P for trend = .016). Schoenfeld residuals tests demonstrated that the proportional hazards assumption was met for all models.

Results were similar in propensity score-matched analyses that included individuals who received chemotherapy (HR, 1.96; 95% CI, 1.13 to 3.40; $P = .016$) and when accounting for within-propensity score-matched group correlation (HR, 1.73; 95% CI, 1.09 to 2.75; $P = .019$). Among those with at least 5 years of follow-up we observed a consistent proportion of ADT use (15.6%) and a similar risk of Alzheimer's disease among ADT users (HR, 1.89; 95% CI, 1.11 to 3.21; $P = .018$). Subgroup analysis adjusted for Gleason score demonstrated a similar magnitude of

effect (HR, 1.84; 95% CI, 0.78 to 4.32; $P = .161$) but had significantly decreased power secondary to few patients with Alzheimer's disease (n = 47).

DISCUSSION

We used a novel informatics approach to demonstrate an association between the use of ADT in the treatment of prostate cancer and an increased future risk of Alzheimer's disease. We support this association using both propensity score-matched and traditional multivariable regression models adjusted for a wide range of potential confounding factors. We also show an association between greater duration of ADT use and increased risk of Alzheimer's disease, which is significant given that length of ADT use is associated with a longer period of testosterone suppression.⁵ Our findings did not differ across two separate electronic medical record data sets in a large patient population consisting of a diverse group of individuals. Additionally, we support the validity of our study by showing no association between ADT and five distinct outcomes as falsification tests³¹ as well as replicating known associations between age and cardiovascular disease with Alzheimer's disease. Use of the electronic medical record in this way allows rapid investigation of a rich data source to study a broad range of postmarketing outcomes, including those unlikely to be seen in smaller clinical trials.¹⁹

There are a number of plausible mechanisms to explain a neuropathic effect of androgen deficiency in the etiology of Alzheimer's disease. Androgens have been shown to aid in neuron growth and axonal regeneration.³² Androgens also modulate β -amyloid protein accumulation, the main component of amyloid plaques.³² ADT use in the treatment of prostate cancer has been shown to result in elevated circulating β -amyloid protein levels.³³ Additionally, low testosterone levels and ADT have been associated with a number of cardiometabolic derangements, including subsequent diabetes, coronary heart disease, myocardial infarction, and peripheral arterial disease.^{8,34-36} Interestingly, cardiometabolic diseases have been shown to increase Alzheimer's disease risk,^{27,28} which we demonstrate in the current analysis with a positive association between cardiovascular disease and future Alzheimer's disease. Furthermore, the combination of atherosclerosis and the possession of the Alzheimer's disease risk genotype, apolipoprotein-E $\epsilon 4$, may interact to further increase Alzheimer's disease risk.³⁷

Despite these data, limited direct research has been conducted regarding the association of ADT with cognitive impairment, and existing studies have yielded mixed results. Individual analyses have shown that 47% to 69% of men receiving ADT develop deficits in at least one cognitive area characteristic of Alzheimer's disease, including visuospatial abilities and executive functioning.¹¹ A 2014 meta-analysis examined the literature across seven cognitive domains and found that patients receiving ADT had a statistically significant impairment of visuomotor ability compared with control participants.¹⁰ No known studies have specifically examined the association of ADT use in the treatment of prostate cancer with future Alzheimer's disease risk.

Table 2. Traditional Multivariable Cox Regression for the Association of Covariates With Alzheimer's Disease

Characteristic	HR (95% CI)	P
Age	1.06 (1.04 to 1.08)	< .001
White	1.30 (0.88 to 1.91)	.182
Ever smoker	1.11 (0.72 to 1.73)	.635
Antiplatelet medication use	0.68 (0.43 to 1.10)	.114
Anticoagulant medication use	0.82 (0.47 to 1.45)	.499
Antihypertensive medication use	1.46 (0.94 to 2.26)	.093
Statin use	1.54 (0.93 to 2.53)	.091
History of cardiovascular disease	1.60 (1.04 to 2.44)	.031
History of diabetes	1.45 (0.91 to 2.30)	.121
History of malignancy	1.18 (0.60 to 2.31)	.627

Abbreviation: HR, hazard ratio.

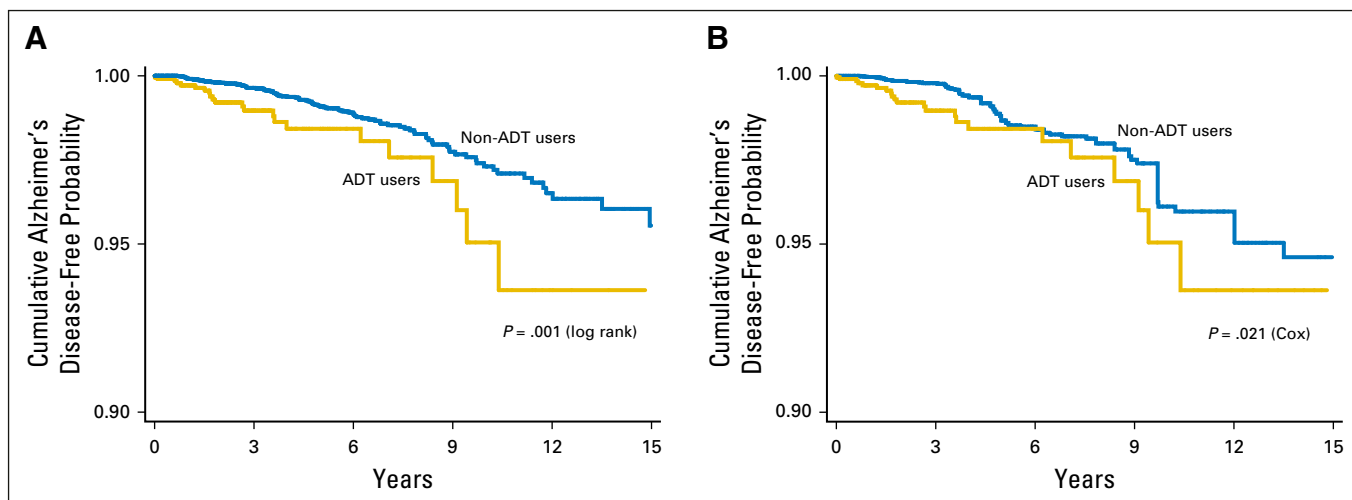


Fig 2. Kaplan-Meier curves according to androgen deprivation therapy (ADT) use for the cumulative probability of remaining Alzheimer’s disease-free (y-axis) from the initiation of ADT, for ADT users, or from the time of prostate cancer diagnosis plus the median time to ADT use, for non-ADT users (x-axis), in the full (A) and propensity score-matched (B) cohorts. AD, Alzheimer’s disease; ADT, androgen deprivation therapy.

The current study has a number of limitations that warrant discussion. Our criteria for Alzheimer’s disease were limited to billing codes and clinical note documentation. The use of billing records in the diagnosis of Alzheimer’s disease introduces a potential for bias,³⁸ as may the incorporation of clinical text data. Even in a controlled setting, the diagnosis of Alzheimer’s disease remains clinical and susceptible to misclassification. However, data support a high degree of accuracy in the clinical diagnosis of Alzheimer’s disease compared with autopsy results.^{39,40} Although we cannot exclude the presence of prevalent Alzheimer’s disease in this study, we have no reason to suspect a differential misclassification that would introduce bias into our analysis.

Additionally, individuals may be more likely to receive definitive radiation therapy and ADT if they are poor surgical candidates secondary to a high number of comorbidities, such as cardiovascular disease, which are also risk factors for Alzheimer’s disease.²⁷ We therefore adjusted for a broad range of comorbidities and conducted propensity score-matched analyses. However, given the retrospective nature of this study and the limitations of data available from the electronic medical

record, we were unable to account for all possible risk factors, such as laboratory values (eg, lipids), family history, and other biometric data (eg, systolic blood pressure). Similarly, we were only able to extract Gleason score for a minority of patients; despite demonstrating a similar magnitude of effect, the analysis was underpowered, and therefore no conclusion can be drawn about the effect of disease stage based on our data. Future studies may be needed to fully account for stage of disease and to characterize the nature of this association across prostate cancer risk groups.

Finally, we calculated ADT duration from clinical notes as well as medication and pharmacy records. It is probable that some individuals received a different duration of ADT than was documented. We therefore conducted ADT duration analysis using broad categories of ADT duration (ie, greater than or less than 12 months use) to limit the potential influence of any misclassification. Additionally, misclassification of ADT duration would likely bias the significant result we observed toward the null, as compared groups would become more similar.

In conclusion, we provide support for an association between the use of ADT in the treatment of prostate cancer and an increased risk of Alzheimer’s disease in a general population cohort

Table 3. Propensity Score-Matched Cox Regression Analysis for the Association of ADT Use With Alzheimer’s Disease

Exposure	HR (95% CI)	P
Propensity score-matched analysis		
No ADT use	Ref	Ref
ADT use	1.88 (1.10 to 3.20)	.021
Traditional multivariable-adjusted analysis		
No ADT use	Ref	Ref
ADT use	1.66 (1.05 to 2.64)	.031

NOTE. Adjusted for age; race; smoking status; anticoagulant, antiplatelet, antihypertensive, and statin therapy; and history of cardiovascular disease, diabetes, or malignancy.
Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio; Ref, reference.

Table 4. Propensity Score-Matched Cox Regression Analysis for the Association of ADT Use With Alzheimer’s Disease by Therapy Duration

Duration of ADT Use (Months)	HR (95% CI)	P	P for Trend*
No ADT use	Ref	Ref	.016
ADT users			
< 12 months ADT use	1.62 (0.82 to 3.21)	.165	
≥ 12 months ADT use	2.12 (1.11 to 4.03)	.011	

NOTE. Adjusted for age; race; smoking status; anticoagulant, antiplatelet, antihypertensive, and statin therapy; and history of cardiovascular disease, diabetes, or malignancy.
Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio.
*By category of ADT duration.

of 16,888 individuals with prostate cancer. Our study further demonstrates the utility of novel methods of analyzing electronic medical record data to generate practice-based evidence.²⁰ Future prospective studies in traditional cohorts are needed to confirm this finding.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org

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Androgen Deprivation Therapy and Future Alzheimer's Disease Risk

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Appendix

Medication names queried to identify individuals on androgen deprivation therapy: leuprolide, goserelin, triptorelin, histrelin, degarelix, flutamide, bicalutamide, nilutamide, enzalutamide, cyproterone acetate, Lupron, Zoladex, Trelstar, Vantas, Firmagon, Eulexin, Casodex, Nilandron, Xtandi, Nizoral, Androcur, Eligard, Cyprostat, Anandron, Flutamin, Cytomid, Cosudex, Calutide, and Kalumid.

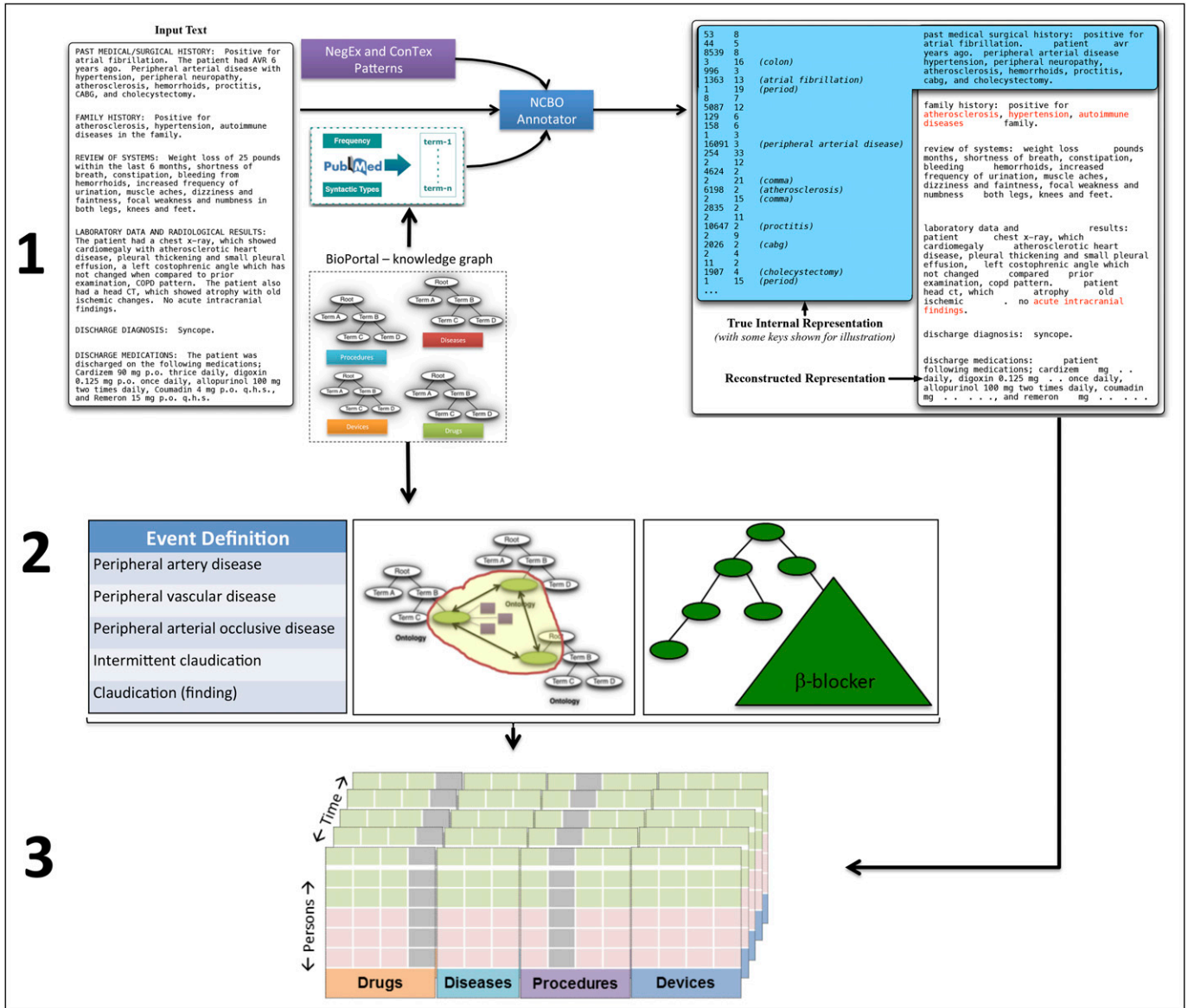


Fig A1. Three steps of the text processing workflow: (1) A custom dictionary derived from BioPortal ontologies and supplemented with trigger terms from NegEx and ConText is used to index (recognize) disease and drug term mentions in narratives as well as recognize contextual cues such as negation or family history. Patient and temporal meta-data are also indexed in this step. The output of this step is indexed positive present mentions of drugs and conditions. (2) Specification of the definition for events (indications and outcomes) and drugs of interest along with normalization schemes for grouping and aggregating terms by synonymy or class. (3) Using the temporal information, the aggregated event and drug mentions, and contextual filters to create a patient-feature matrix and construct patient cohorts for further statistical analysis. Using the temporal information is crucial; for example, a case in which mentions of a drug temporally follows an outcome is used differently in the downstream analysis than a case where a drug precedes the outcome. NCBO, National Center for Biomedical Ontology.

Table A1. The Concepts and Terms Defining Prostate Cancer and Alzheimer's Disease in Clinical Text Analysis

String	Drug/Event	Concept Unique Identifier
Alzheimer dementia	Alzheimer's disease	C0002395
Alzheimer disease	Alzheimer's disease	C0002395
Alzheimer disease 1	Alzheimer's disease	C2931257
Alzheimer disease 10	Alzheimer's disease	C1864828
Alzheimer disease 11	Alzheimer's disease	C1853360
Alzheimer disease 12	Alzheimer's disease	C1970209
Alzheimer disease 3	Alzheimer's disease	C1843013
Alzheimer disease 4	Alzheimer's disease	C1847200
Alzheimer disease 8	Alzheimer's disease	C1846735
Alzheimer disease type 1 β	Alzheimer's disease	C2931257
Alzheimer disease type 3	Alzheimer's disease	C1843013
Alzheimer disease type 4	Alzheimer's disease	C1847200
Alzheimer disease, early onset	Alzheimer's disease	C0750901
Alzheimer disease, late onset	Alzheimer's disease	C0494463
Alzheimer type dementia	Alzheimer's disease	C0002395
Alzheimer's dementia	Alzheimer's disease	C0002395
Alzheimer's disease	Alzheimer's disease	C0002395
Alzheimer's disease with early onset	Alzheimer's disease	C0750901
Alzheimer's disease with late onset	Alzheimer's disease	C0494463
Alzheimers dis	Alzheimer's disease	C0002395
Dementia Alzheimer's type	Alzheimer's disease	C0002395
Dementia in Alzheimer's disease	Alzheimer's disease	C0002395
Dementia in Alzheimer's disease with early onset	Alzheimer's disease	C0750901
Dementia in Alzheimer's disease with late onset	Alzheimer's disease	C0494463
Dementia, Alzheimer type	Alzheimer's disease	C0002395
Disease, Alzheimer	Alzheimer's disease	C0002395
Disease, Alzheimer's	Alzheimer's disease	C0002395
Early onset Alzheimer disease	Alzheimer's disease	C0750901
Late onset Alzheimer disease	Alzheimer's disease	C0494463
Senile dementia, Alzheimer type	Alzheimer's disease	C0002395
Adenocarcinoma of prostate	Prostate cancer	C0007112
Adenocarcinoma of the prostate	Prostate cancer	C0007112
CA - cancer of prostate	Prostate cancer	C0376358
CA prostate	Prostate cancer	C0376358
Cancer of prostate	Prostate cancer	C0376358
Cancer of the prostate	Prostate cancer	C0376358
Cancer, prostate	Prostate cancer	C0376358
Cancer, prostatic	Prostate cancer	C0376358
Cancers, prostate	Prostate cancer	C0376358
Carcinoma of prostate	Prostate cancer	C0600139
Carcinoma of the prostate	Prostate cancer	C0600139
Carcinoma prostate	Prostate cancer	C0600139
Carcinoma prostatic	Prostate cancer	C0600139
Ductal adenocarcinoma of the prostate	Prostate cancer	C0349672
Embryonal rhabdomyosarcoma of the prostate	Prostate cancer	C1335508
Endometrioid carcinoma of the prostate	Prostate cancer	C0349672
Hormone refractory prostate cancer	Prostate cancer	C1328504
Hormone-refractory prostate cancer	Prostate cancer	C1328504
Leiomyosarcoma of prostate	Prostate cancer	C1335511
Leiomyosarcoma of the prostate	Prostate cancer	C1335511
Malignant neoplasm of prostate	Prostate cancer	C0376358
Malignant neoplasm of the prostate	Prostate cancer	C0376358
Metastatic prostate cancer	Prostate cancer	C0936223
Metastatic prostate carcinoma	Prostate cancer	C0936223
Neuroendocrine tumor of the prostate	Prostate cancer	C1335515
pN0 prostate cancer	Prostate cancer	C1709722
pN1 prostate cancer	Prostate cancer	C1709723
Prostate adenocarcinoma	Prostate cancer	C0007112
Prostate cancer	Prostate cancer	C0376358
Prostate cancer metastatic	Prostate cancer	C0936223
Prostate cancer recurrent	Prostate cancer	C0278838
Prostate cancer stage I	Prostate cancer	C0278834
Prostate cancer stage II	Prostate cancer	C0278835
Prostate cancer stage IV	Prostate cancer	C0278837
Prostate cancers	Prostate cancer	C0376358

(continued on following page)

Androgen Deprivation Therapy and Alzheimer's Disease

Table A1. The Concepts and Terms Defining Prostate Cancer and Alzheimer's Disease in Clinical Text Analysis (continued)

String	Drug/Event	Concept Unique Identifier
Prostate carcinoma	Prostate cancer	C0600139
Prostate carcinoma metastatic	Prostate cancer	C0936223
Prostate ductal adenocarcinoma	Prostate cancer	C0349672
Prostate embryonal rhabdomyosarcoma	Prostate cancer	C1335508
Prostate rhabdomyosarcoma	Prostate cancer	C1335518
Prostate sarcoma	Prostate cancer	C0238393
Prostatic cancer	Prostate cancer	C0376358
Prostatic cancer metastatic	Prostate cancer	C0936223
Prostatic cancers	Prostate cancer	C0376358
Prostatic carcinoma	Prostate cancer	C0600139
pT2 prostate cancer	Prostate cancer	C1709725
pT2a prostate cancer	Prostate cancer	C1709726
pT2b prostate cancer	Prostate cancer	C1709727
pT2c carcinoma of prostate	Prostate cancer	C1709728
pT2c prostate cancer	Prostate cancer	C1709728
pT3 prostate cancer	Prostate cancer	C1709729
pT3b prostate cancer	Prostate cancer	C1709731
Recurrent cancer of the prostate	Prostate cancer	C0278838
Recurrent prostate cancer	Prostate cancer	C0278838
Recurrent prostate carcinoma	Prostate cancer	C0278838
Rhabdomyosarcoma of prostate	Prostate cancer	C1335518
Rhabdomyosarcoma of the prostate	Prostate cancer	C1335518
Sarcoma of prostate	Prostate cancer	C0238393
Sarcoma of the prostate	Prostate cancer	C0238393
Small cell carcinoma of the prostate	Prostate cancer	C1300585
Stage I prostate cancer	Prostate cancer	C0278834
Stage II prostate cancer	Prostate cancer	C0278835
Stage III prostate cancer	Prostate cancer	C0278836
Stage IV prostate cancer	Prostate cancer	C0278837

Table A2. Variable ICD-9 Diagnostic Codes

Term	ICD-9 Code	CPT Code	Notes
Prostate cancer	185		
Radical prostatectomy	60.5	55810-55815, 55840-55845	
Alzheimer's disease	331.0		
Cardiovascular disease	443.9, 440.2, 428, 413, 414 (excluding 414.1x), 412, 411, 410		410 and 412 (myocardial infarction) included only if before prostate cancer diagnosis
Diabetes	250; 357.2; 362.0-362.0x; 366.41		
Stroke	430, 431, 432, 433, 434, 436		
Frontotemporal dementia	331.1		
Lewy body dementia	331.82		
Malignancy	140-172; 174; 175; 179-184; 186-209.3		

Abbreviations: CPT, Current Procedural Terminology; ICD-9, International Classification of Diseases-9th revision.

Table A3. Gleason Score Distribution in Available Patients (n = 4,373)

Gleason Score	No.	%
3	1	0.0
4	31	0.7
5	103	2.4
6	2,413	55.2
7	1,248	28.5
8	374	8.6
9	184	4.2
10	19	0.4

Table A4. Traditional Multivariable Cox Regression for the Association of Androgen Deprivation Therapy With Negative Controls

Outcome	HR (95% CI)	P	No.*
Anaphylaxis	0.21 (0.03 to 1.52)	.120	32
Rhabdomyolysis	1.27 (0.27 to 5.90)	.764	14
Tuberculosis	1.30 (0.75 to 2.25)	.346	101
Allergic rhinitis	1.27 (0.90 to 1.80)	.178	290
Abdominal aortic aneurysm	0.92 (0.57 to 1.48)	.729	178

NOTE. Adjusted for age; race; smoking status; anticoagulant, antiplatelet, antihypertensive, and statin therapy; and history of cardiovascular disease, diabetes, or malignancy

Abbreviation: HR, hazard ratio.

*Number of relevant failure events.