Original Article
Prostate diseases and male voiding dysfunctions

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Androgen Deprivation Therapy in Patients with Prostate Cancer is Associated with the Risk of Subsequent Alzheimer's Disease but Not with Vascular Dementia

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Purpose: We aimed to investigate the association between androgen deprivation therapy (ADT) and the risk of dementia according to subtypes of dementia in men with prostate cancer.

Materials and Methods: We performed a nationwide population-based cohort study using the nationwide claims database in Korea. A total of 195,308 men with newly diagnosed prostate cancer were identified between January 2008 and December 2017, and 132,700 men were selected for analysis after applying inclusion and exclusion criteria. The patients were divided into ADT and non-ADT groups. To adjust for imbalances in relevant comorbidities between the groups, exact matching was performed. Study events included newly developed Alzheimer's disease, vascular dementia, and overall dementia. Cox proportional hazard regression models were used.

Results: After exact matching, 44,854 men with prostate cancer were selected for the main analysis. In age-adjusted Cox regression analysis, the ADT group was significantly associated with increased risks for overall dementia (hazard ratio [HR], 1.070; 95% confidence interval [CI], 1.009–1.134; p=0.0232) and Alzheimer's disease (HR, 1.086; 95% CI, 1.018–1.160; p=0.0127), compared to the non-ADT group. No difference in vascular dementia risk was observed between the two groups (HR, 0.990; 95% CI, 0.870–1.126; p=0.8792).

Conclusions: The risk of overall dementia increased in men who received ADT. According to dementia subtypes, ADT was associated with an increased risk of Alzheimer's disease, but not with vascular dementia.

Keywords: Alzheimer disease; Androgens; Dementia; Dementia, vascular; Prostatic neoplasms

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INTRODUCTION

Androgen deprivation therapy (ADT) is commonly used to treat advanced and metastatic prostate cancer (PC). Almost half of all PC patients eventually receive ADT during the course of their treatment [1]. Although ADT can delay PC progression and improve survival, this therapy has been shown to be associated with several adverse events, including sexual dysfunction, osteoporosis, cardiovascular disease, diabetes mellitus, a decrease in muscle mass with an increase in fat mass, and cognitive dysfunction [2].

Cognitive dysfunction induced by ADT is based on the known association between age-related decline in testosterone levels and cognitive decline [3]. Testosterone levels are known to be positively associated with global cognition, memory, executive functions, and spatial performance [4]. Moreover, researchers have speculated that testosterone protects the brain against Alzheimer's disease by inhibiting the hyperphosphorylation of tau proteins and regulating the accumulation of β-amyloid, which results in the formation of neurotoxic plaques [5]. According to a recent meta-analysis, those who received ADT for PC exhibited an increased risk of developing dementia and Alzheimer's disease, compared with those who did not [6]. Indeed, the International Society of Geriatric Oncology recommends that clinicians should discuss the risk of cognitive dysfunction in older PC patients who are considered for ADT [7]. However, the association between ADT and the occurrence of dementia remains controversial, as some papulation-based observational studies have reported that there is no difference in the risk of dementia or Alzheimer's disease following ADT in PC compared with controls [8,9].

Dementia can be divided into different subtypes (*e.g.*, Alzheimer's disease, vascular dementia, and other types of dementia) [10], and the effect of ADT on cognitive dysfunction might vary according to the type of dementia. However, only a few studies have examined the association between ADT use and the occurrence of non-Alzheimer's dementia [8,11]. Therefore, we aimed to evaluate the association between ADT use and the risk of dementia after receiving ADT according to subtypes of dementia, including Alzheimer's disease and vascular dementia, using a nationwide claims database in Korea.

MATERIALS AND METHODS

1. Data source

We used data from the national health claims database of the Health Insurance Review and Assessment Service (HIRA) of Korea. The National Health Insurance is a universal health coverage system that covers over 95% of all Korean residents. The HIRA collects claims data when healthcare service providers submit a claim to HIRA for reimbursement of a service that they provide to patients. The HIRA claims data include information on 46 million patients, approximately 95% of the entire population in Korea, each year [12]. The database consists of diagnoses, procedures, prescription records, and demographic information. We identified the diagnoses using the International Classification of Disease, 10th Revision (ICD-10) codes and billing codes for prescribed medications. These codes are listed in Supplement Tables 1 and 2.

2. Study population

A total of 218,203 men with PC were identified in the claims data between January 1, 2008 and December 31, 2017 from the HIRA database. To prevent the inclusion of patients receiving ongoing treatment or those previously diagnosed, we set a wash-out period. Therefore, patients diagnosed with PC before 2008 (n=22,895) were excluded. A total of 195,308 men were newly diagnosed with PC from January 1, 2008 to December 31, 2017. Patients who underwent orchiectomy (n=1,112) were excluded due to the extremely small portion of surgical ADT patients in Korea, and the effect of medical ADT on dementia was the focus of the present study. Patients with a previous history of dementia (n=9,109) were excluded. Those with a history of chemotherapy and psychotic disease before the index date or those in whom dementia occurred within 6 months from the index date were also excluded (n=52,387). A total of 132,700 men were included in the final analysis (Fig. 1). The ADT group was defined as patients who used at least one dose of gonadotropin-releasing hormone (GnRH) agonist or antagonist after PC diagnosis. We divided the study cohort into ADT (n=29,727) and non-ADT (n=102,973) groups.

3. Definition of index date, outcomes, and covariates

The index date was defined as the date of first ADT

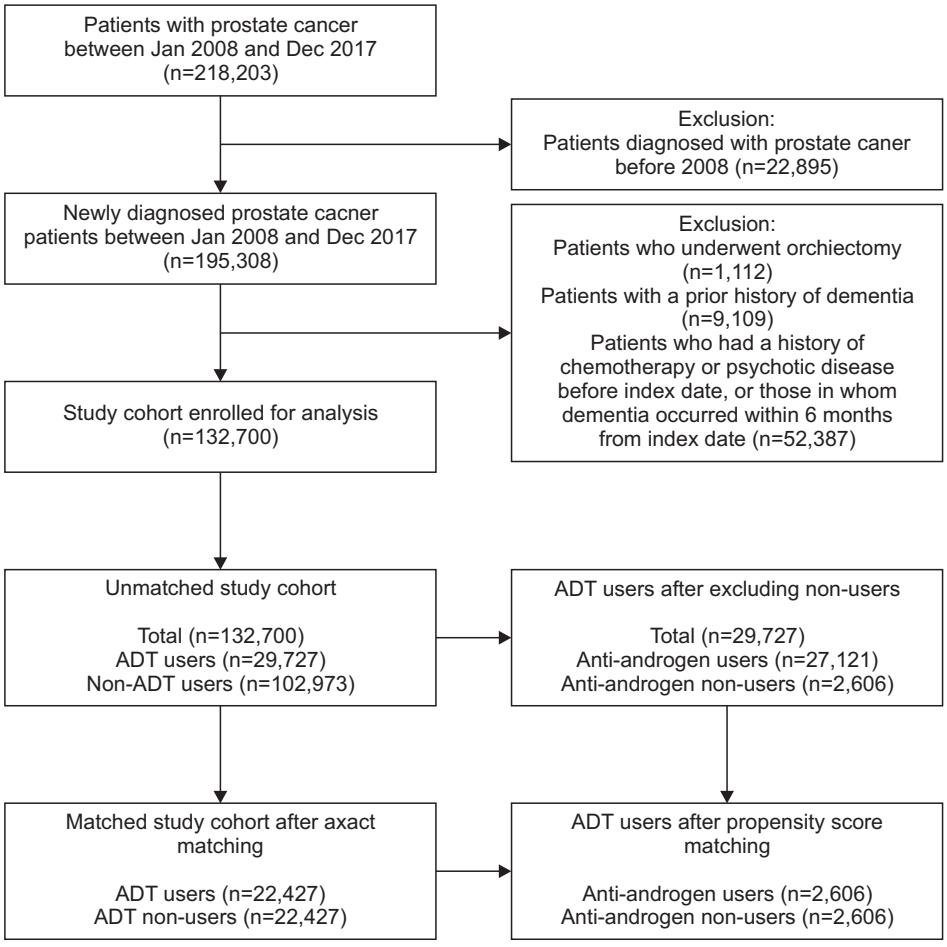

Fig. 1. Flow diagram of the study cohort. ADT: androgen deprivation therapy.

use in the ADT group and the date of PC diagnosis in the non-ADT group, and thus, the definition of index date differed between the two groups. Accordingly, as the median time from PC diagnosis to ADT in the ADT group was 24 days, we adjusted the index date of the non-ADT group by adding 24 days to the time of PC diagnosis [13]. After adjusting the index date of the non-ADT group, statistical analyses were performed. The end of follow-up was defined as the date of an event or the last valid medical record. The study outcomes were overall dementia, Alzheimer's disease, and vascular dementia. Matching covariates included age; a history of arterial fibrillation, cardiovascular disease, chronic obstructive pulmonary disease, diabetes mellitus, dyslipidemia, hypertension, peripheral vascular disease, and stroke; and the use of anticholinergics, antidepressants, antithrombotics, and benzodiazepine. These covariates were reported as risk factors for dementia in the literature. Antiandrogen use was not included as a covariate in the main analysis to avoid multicollinearity problems between ADT and antiandrogen use.

4. Statistical analysis

Exact matching was performed to correct for imbalances in comorbidities between the groups. To decrease the risk of confounding variables [14], the patients were matched using the following criteria: 1) age (±0 years); 2) comorbidities (exact match: presence and absence); and 3) medications (exact match: use and no use). The gmatch macro of SAS® (http://people.duke.edu/~hammill/software/gmatch.sas) was used for the analysis. Statistical analyses were performed in both unmatched and matched cohorts. Pearson's chi-square test, Fisher's exact test, and independent two-sample t-test were used to investigate differences in characteristics between the ADT and non-ADT groups. Kaplan–Meier curves were generated to examine the cumulative incidence of outcomes based on ADT use and the duration of ADT. The log-rank test was conducted to evaluate differences among the groups. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using unadjusted and age-adjusted Cox proportional hazards regression models to calculate the effect

of ADT on the incidence of dementia. In addition, we analyzed whether the cumulative dose of ADT was related to the occurrence of dementia. The duration of ADT was defined as the sum of the action periods of each ADT preparation. The duration of ADT was divided into <1 year, 1–2 years, 2–3 years, and >3 years. Time-varying Cox regression analyses were performed for each of the matched datasets as sensitivity analyses. A p-value of <0.05 was considered significant for all analyses. All analyses in this study were conducted using SAS ver. 9.4 (SAS System for Windows; SAS Institute Inc., Cary, NC, USA) or R ver. 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

5. Study ethics

This study was approved by the Institutional Review Board of Gangnam Severance Hospital (No. 3-2018-0308) and was performed in accordance with the principles of the Declaration of Helsinki. The patient-identifying information was not accessible from the HIRA database.

RESULTS

After exact matching, each of the study groups (ADT and non-ADT) comprised 22,427 patients. The mean age of the patients in each group was 71.16±7.38 years. The follow-up durations were 3.58±2.14 years in the ADT group and 3.68±2.26 years in the non-ADT group (Table 1).

In age-adjusted Cox regression analysis, age was associated with an increased risk of overall dementia (HR, 1.122; 95% CI, 1.117–1.127; p<0.0001), Alzheimer's disease (HR, 1.130; 95% CI, 1.124–1.136; p<0.0001), and vascular dementia (HR, 1.089; 95% CI, 1.079–1.100; p<0.0001) (Table 2-4). Notably, ADT was also found to be significantly associated with increased risks of overall dementia (HR, 1.070; 95% CI, 1.009–1.134; p=0.0232) and Alzheimer's disease (HR, 1.086; 95% CI, 1.018–1.160; p=0.0127), compared with no ADT. However, no difference was observed in vascular dementia between the ADT and non-ADT groups (HR, 0.990; 95% CI, 0.870–1.126; p=0.8792) (Table 2-4). The risk of overall dementia and Alzheimer's disease was affected by the duration

Table 1. Demographic characteristics of the study cohort

Variable	Before matching			After exact matching		
	ADT (n=29,727)	Non-ADT (n=102,973)	p-value	ADT (n=22,427)	Non-ADT (n=22,427)	p-value
Age (y)	72.72±7.87	64.11±10.16	<0.0001	71.16±7.38	71.16±7.38	>0.9999
Follow-up (y)	3.24±2.07	3.50±2.28	<0.0001	3.58±2.14	3.68±2.26	<0.0001
ADT (y)						
No		102,973 (100)			22,427 (100)	
<1	8,118 (27.31)			6,125 (27.31)		
1–2	7,765 (26.12)			5,608 (25.01)		
2–3	5,265 (17.71)			3,955 (17.63)		
≥3	8,579 (28.86)			6,739 (30.05)		
Atrial fibrillation	875 (2.94)	1,822 (1.77)	<0.0001	172 (0.77)	172 (0.77)	>0.9999
Cardiovascular disease	7,517 (25.29)	21,626 (21.00)	<0.0001	4,633 (20.66)	4,633 (20.66)	>0.9999
COPD	4,388 (14.76)	9,906 (9.62)	<0.0001	2,335 (10.41)	2,335 (10.41)	>0.9999
Diabetes mellitus	10,726 (36.08)	32,201 (31.27)	<0.0001	7,566 (33.74)	7,566 (33.74)	>0.9999
Dyslipidemia	11,679 (39.29)	40,961 (39.78)	<0.0001	8,314 (37.07)	8,314 (37.07)	>0.9999
Hypertension	12,156 (40.89)	32,509 (31.57)	<0.0001	8,224 (36.67)	8,224 (36.67)	>0.9999
Peripheral artery disease	2,387 (8.03)	6,894 (6.69)	<0.0001	985 (4.39)	985 (4.39)	>0.9999
Stroke	3,807 (12.81)	8,941 (8.68)	<0.0001	1,838 (8.20)	1,838 (8.20)	>0.9999
Anti-cholinergic	16,616 (55.90)	47,368 (46.00)	<0.0001	12,692 (56.59)	12,692 (56.59)	>0.9999
Anti-depressant	14,365 (48.32)	46,806 (45.45)	<0.0001	11,050 (49.27)	11,050 (49.27)	>0.9999
Anti-thrombotic	19,247 (64.75)	58,269 (56.59)	<0.0001	13,861 (61.80)	13,861 (61.80)	>0.9999
Benzodiazepine	24,008 (80.76)	82,178 (79.81)	0.0003	18,647 (83.15)	18,647 (83.15)	>0.9999

Values are presented as mean±standard deviation or number (%).
ADT: androgen deprivation therapy, COPD: chronic obstructive pulmonary disease.

Table 2. Age-adjusted Cox regression analysis of the risk of overall dementia in the matched study cohort

Variable	Unadjusted analysis		Age adjusted analysis			
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.122 (1.117–1.127)	<0.0001	1.122 (1.117–1.127)	<0.0001	1.122 (1.117–1.128)	<0.0001
ADT use						
No	Ref.		Ref.			
Yes	1.083 (1.022–1.148)	0.0007	1.070 (1.009–1.134)	0.0232		
Duration of ADT (y)						
No	Ref.				Ref.	
<1	0.962 (0.868–1.067)	0.4652			1.123 (1.013–1.246)	0.0279
1–2	1.354 (1.223–1.498)	<0.0001			1.324 (1.197–1.466)	<0.0001
2–3	1.083 (0.970–1.209)	0.1544			1.085 (0.972–1.211)	0.1473
≥3	1.046 (0.971–1.127)	0.2332			0.963 (0.894–1.038)	0.3255

ADT: androgen deprivation therapy, HR: hazard ratio, CI: confidence interval.

Table 3. Age-adjusted Cox regression analysis of the risk of Alzheimer's disease in the matched study cohort

Variable	Unadjusted analysis		Age adjusted analysis			
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.130 (1.124–1.136)	<0.0001	1.130 (1.124–1.136)	<0.0001	1.130 (1.124–1.136)	<0.0001
ADT use						
No	Ref.		Ref.			
Yes	1.098 (1.028–1.172)	0.0051	1.086 (1.018–1.160)	0.0127		
Duration of ADT (y)						
No	Ref.				Ref.	
<1	0.930 (0.826–1.047)	0.2289			1.102 (0.979–1.241)	0.1072
1–2	1.369 (1.220–1.535)	<0.0001			1.343 (1.198–1.507)	<0.0001
2–3	1.159 (1.026–1.308)	0.0175			1.166 (1.033–1.317)	0.0133
≥3	1.063 (0.979–1.155)	0.1453			0.978 (0.900–1.062)	0.5890

ADT: androgen deprivation therapy, HR: hazard ratio, CI: confidence interval.

Table 4. Age-adjusted Cox regression analysis of the risk of vascular dementia in the matched study cohort

Variable	Unadjusted analysis		Age adjusted analysis			
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.089 (1.079–1.100)	<0.0001	1.089 (1.079–1.100)	<0.0001	1.090 (1.079–1.101)	<0.0001
ADT use						
No	Ref.		Ref.			
Yes	1.000 (0.879–1.138)	>0.9999	0.990 (0.870–1.126)	0.8792		
Duration of ADT (y)						
No	Ref.				Ref.	
<1	0.974 (0.777–1.219)	0.8152			1.100 (0.878–1.379)	0.4065
1–2	1.216 (0.964–1.533)	0.0983			1.190 (0.944–1.500)	0.1416
2–3	0.891 (0.686–1.157)	0.3875			0.888 (0.684–1.154)	0.3740
≥3	0.977 (0.829–1.152)	0.7848			0.918 (0.778–1.082)	0.3080

ADT: androgen deprivation therapy, HR: hazard ratio, CI: confidence interval.

of ADT (Table 2, 3); however, the risks were not increased linearly. On the other hand, the duration of ADT did not affect the risk of vascular dementia (Table 4). In the sensitivity analyses of each of the matched datasets, time-varying Cox regression analyses confirmed the statistical findings reported above (data not

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shown).

In the ADT group (n=29,727), antiandrogen was prescribed in most patients (n=27,121, 91.2%). The ADT group was divided into antiandrogen users and non-users. After a 1:1 propensity score matching based on age and duration of ADT, the antiandrogen user and non-user groups comprised 2,606 patients each (Supplement Table 3). In the matched cohort, age-adjusted Cox regression analysis revealed no significant difference in the risks for overall dementia, Alzheimer's disease, and vascular dementia between the antiandrogen users and non-users (Supplement Table 4).

DISCUSSION

In this study, we observed an association between ADT and the subsequent risk of overall dementia in this large population-based cohort study. Moreover, we noted that the effect of ADT on the risk of dementia differed according to the subtype of dementia: ADT increased the risk of incident Alzheimer's disease, but not the risk of vascular dementia (Fig. 2).

A randomized clinical trial by Green et al [15] first reported that pharmacological androgen suppression may decrease cognitive function, including memory, attention, and executive function. However, a previous prospective study found no association between androgen suppression and cognitive function [16]. Since then, several large observational studies published over the last decade have shown conflicting results. Some studies have found an association between ADT use and an increased risk of overall dementia or Alzheimer's disease [17,18]. On the contrary, others have reported that ADT was not associated with the risk of overall dementia or Alzheimer's disease [8,9]. Despite these controversies, a recent meta-analysis demonstrated that the risks of overall dementia and Alzheimer's disease are increased in ADT users [6]. However, most researchers have set study endpoints of either overall dementia with Alzheimer's disease or Alzheimer's disease only. Therefore, it remains unclear whether the risk of overall dementia increases due to an increased risk of Alzheimer's disease or due to an increased risk of non-Alzheimer's dementia. In the present study, we investigated the association between ADT and dementia by classifying individuals into overall dementia, Alzheimer's disease, and vascular dementia, considering vascular dementia representative of non-Alzheimer's dementia. Our results showed that ADT is associated with subsequent Alzheimer's disease, but not with vascular dementia, suggesting that the increased risk of overall dementia following ADT is due to an increased risk of Alzheimer's disease.

Several possible biological explanations may account for the increased risk of Alzheimer's disease after ADT. The first explanation is the relationship between testosterone levels and dementia. Carcaillon et al [19] performed a population-based study to investigate low testosterone levels and risk of dementia in older men, and their results showed that low levels of testosterone were associated with Alzheimer's disease. Testosterone is an endogenous neuroprotective factor that can affect an individual's susceptibility to Alzheimer's disease through increased neuronal resilience against Alzheimer's disease-related insults and reduced β-amyloid accumulation [5]. Indeed, plasma levels of β-amyloid have been found to be higher in men who received ADT as treatment for PC [20]. In addition, a

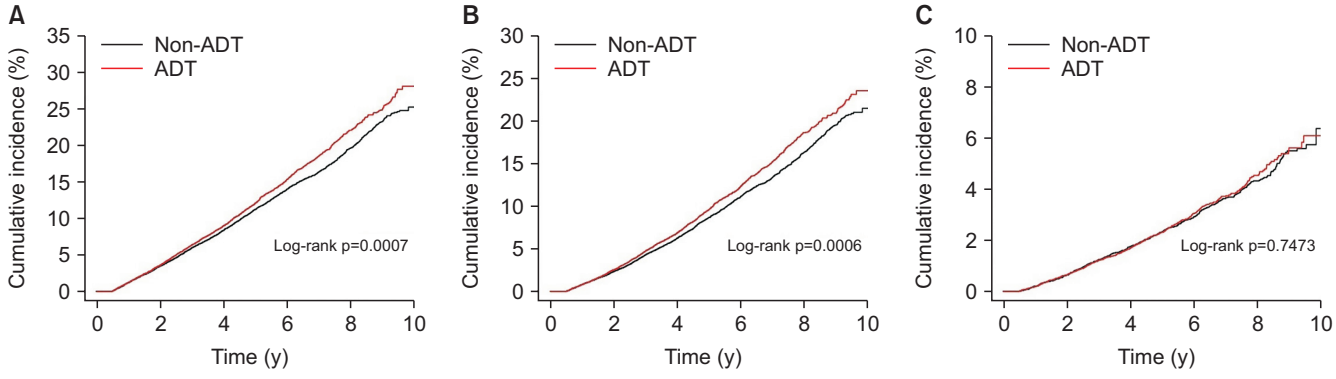

Fig. 2. Cumulative incidence of dementia in the matched cohort. (A) Overall dementia following ADT, (B) Alzheimer's disease following ADT, and (C) vascular dementia following ADT. ADT: androgen deprivation therapy.

recent animal study demonstrated that chemical castration elicited deterioration of memory function in the hippocampus [21]. The second explanation is that ADT may affect the functional activity and structure of the brain. In one study, although ADT did not affect the results of cognitive function tests, ADT users showed decreased brain activation during cognitive control, in addition to decreased functional brain connectivity involved in cognitive control, compared with non-users [22]. Also, ADT users showed decreased gray matter volume, whereas non-users did not [23].

ADT is associated with an increase in the risk of cardiovascular diseases [24]. Thus, it can be postulated that ADT might increase the risk of vascular dementia. However, the present study showed that ADT was not associated with the risk of vascular dementia. To the best of our knowledge, only one study on this issue has been conducted and demonstrated that there is no significant association between ADT and vascular dementia [8]. Meanwhile, a few longitudinal studies have examined the relationship between low testosterone levels and incident dementia. In their results, low testosterone might have been associated with an increased risk of Alzheimer's disease; however, vascular dementia was not associated with testosterone levels [19]. In a recent study, ADT use reduced the risk of ischemic cardiovascular diseases and cerebrovascular diseases [25]. However, due to the lack of research results, it is difficult to draw conclusions about this topic. Hence, further studies are warranted to confirm the association between ADT and vascular dementia.

It is controversial whether longer ADT periods increase the risk of dementia or Alzheimer's disease [6]. In the present study, the duration of ADT affected the risks of overall dementia and Alzheimer's disease. However, such effect was not dose-dependent. There was no statistically significant difference in the risk of overall dementia among men who received ADT for more than 2 years, compared to those who did not, and there was no statistically significant difference in the risk of Alzheimer's disease in men who received ADT for more than 3 years, compared to those without ADT. This lack of a dose-dependent relationship could be due to immortal time bias and unmeasured or unadjusted confounders, which are common limitations of observational studies. While an analysis design was applied to solve the immortal time bias in this study, it was not possible to completely homogenize each group divided according to ADT duration. In the future, large-scale research or development of research techniques will be needed to overcome these limitations.

To the best of our knowledge, two previous studies analyzed the association between ADT and non-Alzheimer's dementia. Deka et al [8] demonstrated that ADT does not increase the risk for overall dementia, Alzheimer's disease, and vascular dementia. However, they focused on evaluating radiotherapy-treated PC patients registered with the US Department of Veterans Affairs. Robinson et al [11] reported that the risk of Alzheimer's disease was similar between the GnRH agonist and PC free-male groups, while the risks of overall dementia and non-Alzheimer's dementia were higher in the GnRH agonist group than in the PC free-male group [11]. This study was a population-based study using Prostate Cancer Database Sweden data, which included 97% of all Swedish men with PC. They compared PC patients on watchful waiting or ADT with PC-free men. In Sweden, non-Alzheimer's dementia mainly consists of unspecified dementias. Differences in research design or population characteristics may account for the differences in these results. Hence, more research is needed to generalize these results.

The present study has several strengths. First, we analyzed a large nationwide database that included nearly all Korean men diagnosed with PC for over 10 years. A large sample size is an essential factor in a retrospective cohort study [26]. According to a recent systematic review by Sari Motlagh et al [6], all large cohort studies with more than 100,000 participants found an association between ADT use and an increased risk of dementia or Alzheimer's disease. However, some cohort studies with a smaller sample size reported that ADT was not associated with the occurrence of dementia or Alzheimer's disease [6]. Second, in the present study, the index date of the non-ADT group was adjusted, and time-dependent Cox regression (time-varying Cox regression) was performed as a sensitivity analysis. Since a time-dependent covariate in the model determines whether the classifying event has occurred during the estimation process, it is known to be the most appropriate method with which to resolve an immortal-time bias [27,28]. A time-dependent Cox regression model has the advantage of using all study follow-up data; therefore, this method is known to increase the statistical power using all data. Kim et al [29] performed a meta-analysis and a meta-regression analysis

and reported that a method for controlling immortal time bias could affect the outcomes and be related to discrepancies in results. However, only a few previous studies have reported the presence of an immortal time bias [8,9]. Third, we endeavored to reduce confounding bias by strict restriction of the study cohort and by performing exact matching using various covariates known to be closely associated with dementia risk.

Despite these advantages, our study has a few limitations. First, cognitive reserve, lifestyle, and psychosocial factors, such as education, occupational attainment, physical activity, smoking, and alcohol consumption, are known risk factors for dementia [30]. However, the claims data that we utilized only included diagnostic and prescribing billing codes. Cancer stage and pathologic features were not contained in the claims data. Therefore, these factors could not be controlled for in the present study. Second, ICD codes and prescribing billing codes were used to select patients and match confounders in the present study. However, since this may include falsely diagnosed patients, our results may not reflect reality. While a case definition can be used to solve this problem, it is necessary to confirm that it reflects real world practice. However, studies on the incidences and case definitions of dementia have not been conducted in Korea. In the future, validation of a case definition of dementia that can reflect actual patients with dementia in Korea is needed. If so, future research will be able to exclude falsely diagnosed dementia and derive research results that reflect the real world. These are essential limitations of a claims data-based study. In the near future, prospectively designed clinical trials are needed to elucidate the association between ADT and the risk of dementia and all subtypes thereof.

CONCLUSIONS

The present study demonstrated that the risk of overall dementia is higher in PC patients who have undergone ADT. ADT was associated with an increased risk of Alzheimer's disease, but not with vascular dementia, suggesting that the subsequent risk of dementia following ADT is mainly due to Alzheimer's disease. Thus, if ADT is offered, clinicians should consider the risk factors for dementia in PC patients, avoid unnecessary prolonged use of ADT, and closely monitor the occurrence of potential adverse events, including dementia.

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Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: JWK, KSC. Data curation: HSL, JYP. Formal analysis: HSL, JYP. Funding acquisition: DKK, KSC. Investigation: JWK, HKA, JSH, DL. Methodology: JWK, DKK, HSL. Project administration: JWK, DKK, KSC. Supervision: KSC. Validation: HKA, DKK, JSH, DL. Visualization: JWK, JYP. Writing – original draft: JWK. Writing – review & editing: JWK, KSC.

Supplementary Materials

Supplementary materials can be found *via* https://doi.org/10.5534/wjmh.210019.

Data Sharing Statement

The data required to reproduce these findings can not be shared at this time due to legal and ethical reasons.

REFERENCES

1. Meng MV, Grossfeld GD, Sadetsky N, Mehta SS, Lubeck DP, Carroll PR. Contemporary patterns of androgen deprivation therapy use for newly diagnosed prostate cancer. Urology 2002;60(3 Suppl 1):7-11; discussion 11-2.
2. Smith MR. Side effects of androgen deprivation therapy [Internet]. Waltham (MA): UpToDate [cited 2020 Oct 30]. Available from: https://www.uptodate.com/contents/side-effects-of-androgen-deprivation-therapy.
3. Hsu B, Cumming RG, Waite LM, Blyth FM, Naganathan V, Le Couteur DG, et al. Longitudinal relationships between reproductive hormones and cognitive decline in older men: the Concord Health and Ageing in Men Project. J Clin Endocrinol Metab 2015;100:2223-30.
4. Holland J, Bandelow S, Hogervorst E. Testosterone levels and cognition in elderly men: a review. Maturitas 2011;69:322-37.
5. Pike CJ, Carroll JC, Rosario ER, Barron AM. Protective ac-

tions of sex steroid hormones in Alzheimer's disease. Front Neuroendocrinol 2009;30:239-58.
6. Sari Motlagh R, Quhal F, Mori K, Miura N, Aydh A, Laukhtina E, et al. The risk of new onset dementia and/or Alzheimer disease among patients with prostate cancer treated with androgen deprivation therapy: a systematic review and meta-analysis. J Urol 2021;205:60-7.
7. Boyle HJ, Alibhai S, Decoster L, Efstathiou E, Fizazi K, Mottet N, et al. Updated recommendations of the International Society of Geriatric Oncology on prostate cancer management in older patients. Eur J Cancer 2019;116:116-36.
8. Deka R, Simpson DR, Bryant AK, Nalawade V, McKay R, Murphy JD, et al. Association of androgen deprivation therapy with dementia in men with prostate cancer who receive definitive radiation therapy. JAMA Oncol 2018;4:1616-7.
9. Khosrow-Khavar F, Rej S, Yin H, Aprikian A, Azoulay L. Androgen deprivation therapy and the risk of dementia in patients with prostate cancer. J Clin Oncol 2017;35:201-7.
10. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. Lancet 2017;390:2673-734.
11. Robinson D, Garmo H, Van Hemelrijck M, Damber JE, Bratt O, Holmberg L, et al. Androgen deprivation therapy for prostate cancer and risk of dementia. BJU Int 2019;124:87-92.
12. Kim L, Kim JA, Kim S. A guide for the utilization of Health Insurance Review and Assessment Service national patient samples. Epidemiol Health 2014;36:e2014008.
13. Jepsen P, Johnsen SP, Gillman MW, Sørensen HT. Interpretation of observational studies. Heart 2004;90:956-60.
14. Cochran WG. Matching in analytical studies. Am J Public Health Nations Health 1953;43(6 Pt 1):684-91.
15. Green HJ, Pakenham KI, Headley BC, Yaxley J, Nicol DL, Mactaggart PN, et al. Altered cognitive function in men treated for prostate cancer with luteinizing hormone-releasing hormone analogues and cyproterone acetate: a randomized controlled trial. BJU Int 2002;90:427-32.
16. Alibhai SM, Breunis H, Timilshina N, Marzouk S, Stewart D, Tannock I, et al. Impact of androgen-deprivation therapy on cognitive function in men with nonmetastatic prostate cancer. J Clin Oncol 2010;28:5030-7.
17. Baik SH, Kury FSP, McDonald CJ. Risk of Alzheimer's disease among senior medicare beneficiaries treated with androgen deprivation therapy for prostate cancer. J Clin Oncol 2017;35:3401-9.
18. Jayadevappa R, Chhatre S, Malkowicz SB, Parikh RB, Guzzo T, Wein AJ. Association between androgen deprivation therapy use and diagnosis of dementia in men with prostate cancer. JAMA Netw Open 2019;2:e196562.
19. Carcaillon L, Brailly-Tabard S, Ancelin ML, Tzourio C, Foubert-Samier A, Dartigues JF, et al. Low testosterone and the risk of dementia in elderly men: impact of age and education. Alzheimers Dement 2014;10(5 Suppl):S306-14.
20. Almeida OP, Waterreus A, Spry N, Flicker L, Martins RN. One year follow-up study of the association between chemical castration, sex hormones, beta-amyloid, memory and depression in men. Psychoneuroendocrinology 2004;29:1071-81.
21. Shin MS, Kim TW, Park SS, Ko IG, Kim CJ, Kim M, et al. Long-term surgical and chemical castration deteriorates memory function through downregulation of PKA/CREB/BDNF and c-Raf/MEK/ERK pathways in hippocampus. Int Neurourol J 2019;23:116-24.
22. Chao HH, Uchio E, Zhang S, Hu S, Bednarski SR, Luo X, et al. Effects of androgen deprivation on brain function in prostate cancer patients - a prospective observational cohort analysis. BMC Cancer 2012;12:371.
23. Chao HH, Hu S, Ide JS, Uchio E, Zhang S, Rose M, et al. Effects of androgen deprivation on cerebral morphometry in prostate cancer patients--an exploratory study. PLoS One 2013;8:e72032.
24. Keating NL, O'Malley A, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. J Natl Cancer Inst 2012;104:1518-23.
25. Kim DK, Lee HS, Park JY, Kim JW, Ha JS, Kim JH, et al. Does androgen-deprivation therapy increase the risk of ischemic cardiovascular and cerebrovascular diseases in patients with prostate cancer? A nationwide population-based cohort study. J Cancer Res Clin Oncol 2021;147:1217-26.
26. Levin KA. Study design IV. Cohort studies. Evid Based Dent 2006;7:51-2.
27. Mi X, Hammill BG, Curtis LH, Lai EC, Setoguchi S. Use of the landmark method to address immortal person-time bias in comparative effectiveness research: a simulation study. Stat Med 2016;35:4824-36.
28. Cho IS, Chae YR, Kim JH, Yoo HR, Jang SY, Kim GR, et al. Statistical methods for elimination of guarantee-time bias in cohort studies: a simulation study. BMC Med Res Methodol 2017;17:126.
29. Kim JH, Lee B, Han DH, Chung KJ, Jeong IG, Chung BI. Discrepancies on the association between androgen deprivation therapy for prostate cancer and subsequent dementia: meta-analysis and meta-regression. Oncotarget 2017;8:73087-97.
30. Sosa-Ortiz AL, Acosta-Castillo I, Prince MJ. Epidemiology of dementias and Alzheimer's disease. Arch Med Res 2012;43:600-8.