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Original article

Risk of dementia in prostate cancer survivors: A nationwide cohort study in Korea

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ABSTRACT

Objectives: To investigate the effects of prostate cancer (PC) and various treatment modalities for PC, specifically androgen deprivation therapy (ADT), on the risk of dementia and dementia subtypes in PC survivors. *Material and methods:* A total of 51,252 patients newly diagnosed with PC from 2007 to 2013, who had no prior diagnosis of cancer or dementia, were included and matched with 209,659 non-cancer control. The screening subset was comprised of subjects who participated in a health screening program. We used

Abbreviations: AD, Alzheimer dementia; ADT, androgen deprivation therapy; BMI, body mass index; CCI, Charlson comorbidity index; KNHIS, Korean National Health Insurance Services; PC, prostate cancer; PSA, prostate specific antigen; VaD, vascular dementia.

☆ *Conflict of interest:* The authors have no conflicts of interest to disclose..

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Cox proportional hazards model to estimate the relative risk of dementia and dementia subtypes according to the primary treatment for the PC. *Results:* Compared to non-PC matched controls, PC survivors showed slightly higher risk for dementia and Alzheimer disease (AD) only in the screening cohort. While PC survivors who underwent ADT were higher risk for dementia and AD, patients who underwent surgery were lower risk for dementia and AD, compared to the non-cancer population. Compared to surgery, ADT, surgery + ADT, and active surveillance/watchful waiting showed a significantly elevated risk for dementia. *Conclusion:* PC survivors had slightly higher risk for dementia compared to non-PC controls, which might be related to the screening effects of PC. The risk for dementia was most prominent among PC patients who underwent ADT, followed by patients who underwent AS/WW, and those who underwent surgery + ADT. This finding suggests that individualized ADT strategies that consider the survival benefit and underlying dementia risk in PC survivors are necessary.

ARTICLE INFO

Keywords: Prostate cancer; Androgen deprivation therapy; Dementia; Alzheimer disease; Population-based nationwide study

Introduction

Prostate cancer (PC) is the most prevalent male cancer in the United States, and more than 3.3 million men have PC.[1] In Korea, PC is the fourth most common male cancer, and its incidence rate has increased rapidly over the past 15 years[2] due to population aging, the prostate specific antigen (PSA) screening program, and westernized diet patterns.[3]

Due to the favorable prognosis of PC, treatment-related complications are increasingly gaining attention.[4-6] In addition, given that the prevalence of PC increases with age and more than half of PC survivors are 65 years or older,[1] PC and its treatment might have a deleterious effect on cognitive function in PC patients, who are already at a high risk for dementia.

A previous Italian study suggested that the prevalence of Alzheimer dementia (AD) did not increase in PC patients,[7] and a Taiwanese study reported an insignificant increase in the prevalence of AD in PC patients compared to the general population.[8] However, another study in the United States reported that patients with PC showed higher risk for AD compared to the non-PC population.[9] Although several studies evaluated a potential link between PC treatment modalities, specifically androgen deprivation therapy (ADT), and dementia risk, the study results were inconsistent. Some studies showed that individuals who underwent ADT had an increased risk for dementia and AD in a dose-response fashion.[10,11] However, other studies also observed no significant associations between ADT and the development of AD.[8,12,13]

Assessing the effects of treat modalities for PC on dementia risk is challenging because several treatment options are currently available for PC and the modality selected depends on the extent of the disease, comorbidity, and characteristics of patients.[14] Furthermore, because most studies focused on the effect of ADT on the development of dementia, there are gaps in our knowledge regarding the effect of other treatment options for PC on the risk for dementia. Regarding the type of dementia, the risk for vascular dementia (VaD) in relation to PC treatment is also largely unknown. Therefore, the objective of the present study was to evaluate the effects of PC and treatment modalities for PC on the risk for dementia including subtypes of dementia such as AD and VaD.

Material and methods

Data sources

The present study used the Korean National Health Insurance Services (KNHIS) database. The KNHIS is a universal health coverage system that includes technically the entire Korean population (approximately 97%). The KNHIS database contains not only information regarding medical claims such as disease codes (according to the International Classification of Disease [ICD] codes), prescription, procedures, and incurred cost, but also information on beneficiaries. Furthermore, the KNHIS screening database contains information on anthropometric characteristics, health behaviors, and biochemical laboratory results collected via a biannual health screening program for all Koreans who are either 40 years or older or employed personnel regardless of age, and an annual screening for physical labor workers.[15]

The study was approved by the institutional review board of the Eulji university hospital (IRB No 2018-09-001) and all study protocols complied with the Declaration of Helsinki.

Study population

A total of 82,890 patients diagnosed with PC from January 1, 2007 to December 31, 2013 were enrolled in the present study. Among these eligible subjects, we excluded subjects aged <40 years ($n = 379$) and subjects who were diagnosed with other types of cancers ($n = 21{,}834$) or dementia ($n = 1590$) before PC diagnosis. Those who were followed-up for <1 year ($n = 6391$) were also excluded. Finally, 51,251 subjects with PC were included in the analysis.

For matched control, a 1:3 age- and sex- matching was performed and 244,335 non-cancer subjects were selected. Incident PC cases were matched to the control cases based on information regarding the year of cancer diagnosis. An exclusion criteria identical to that used for the PC group was applied to the matched control group, and the index dates of matched subjects were corresponded to the date of PC diagnosis of their matched PC group. The final number of control subjects was 209,569.

In the population that was finally included for the analysis, those who participated in the health screening program the year before PC diagnosis ($n = 30{,}953$) or the index date ($n = 109{,}742$) were selected as the "screening subset," and information on smoking status, body mass index (BMI), blood pressure, fasting glucose, and total cholesterol were available for this subpopulation. The selection scheme for the study population is presented in Figure 1.

Outcomes

Subjects were considered to have new onset dementia if antidementia medications (rivastigmine, galantamine, memantine, and donepezil hydrochloride) were prescribed ≥2 times and the codes for dementia (ICD codes: F00-03, G23.1, G 30, G31, or F10.7) were assigned for incurred medical cost claims submitted to the KNHIS before December 31, 2015.[16] The subtypes of dementia were AD (ICD-10 F00 or G30), VaD (ICD-10 F01), and other dementia (ICD-10 F02, F03, G23.1, or G31, or F10.7). According to the Korean National Health Insurance Reimbursement Criteria, evidence of cognitive dysfunction is required before antidementia medications can be prescribed. Thus, every physician must document one of the following evidence regarding cognitive decline: (1) Mini-Mental State Examination score ≤ 26 and (2) either a Global Deterioration Scale score ≥3 or a Clinical Dementia Rating scale ≥1. The study population was followed-up from baseline to the date of any dementia incidence, death, or until December 31, 2017, whichever occurred first.

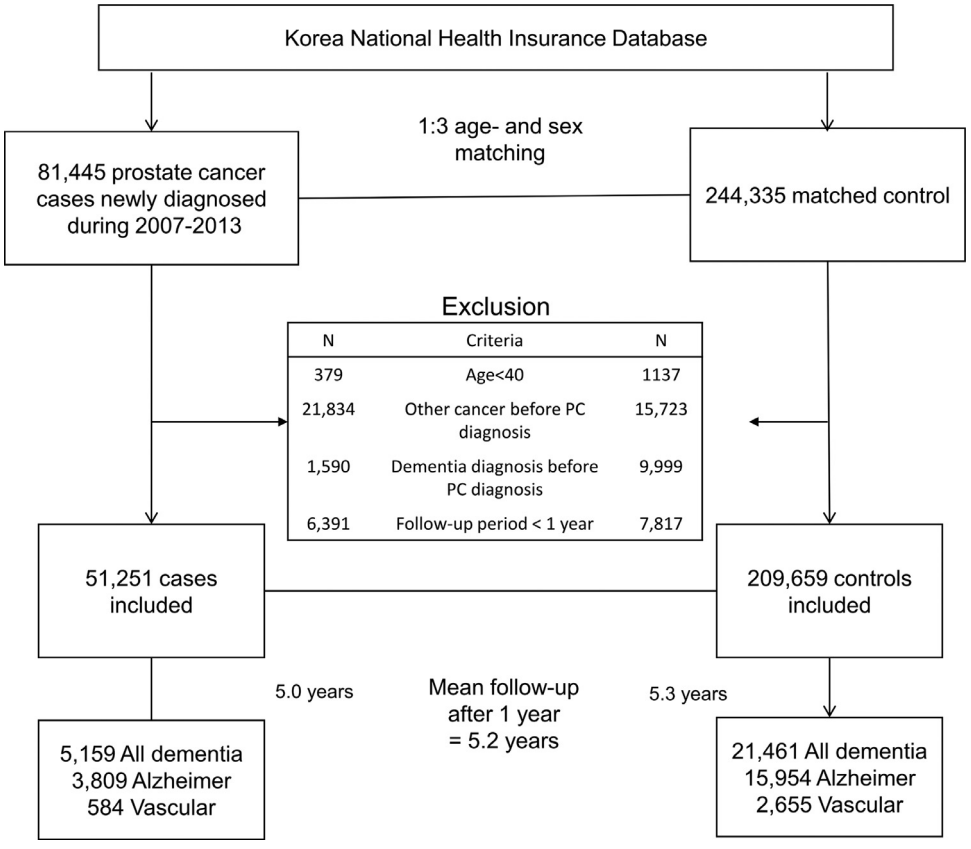

Fig. 1. Flow diagram of study participants.

Covariates

We categorized income levels into 4 groups based on the insurance premium quartiles, and the Medicaid group was merged with the lowest income. Residential areas were categorized as either a metropolitan, city, or rural area. We diagnosed hypertension (I10/I15 & antihypertensive medication), diabetes (E11-E14 & antidiabetes medication), and dyslipidemia (E78 & lipid lowering medication) using the ICD 10 code and/or if relevant medication was prescribed. The use of statin and aspirin was determined using prescription data. Information regarding comorbidities were collected using the Charlson comorbidity index (CCI).[17] Information on BMI, systolic and diastolic blood pressure, smoking status, and laboratory results, including fasting glucose and total cholesterol, were only obtained from the screening subset. The BMI was calculated as weight/height squared (kg/m^2) and categorized into 5 groups based on the obesity criteria for the Asian population.[18] Smoking status was categorized as nonsmokers, past smokers, and current.

Statistical analysis

Basic characteristics of the study population were compared using the *t*test for continuous variables and the chi-square test for categorical variables. The incidence probability was assessed

using the Kaplan-Meier analysis. We used the Cox proportional hazard model to compare the incidence of dementia and to estimate the effect of different PC treatment modalities on incident dementia. In addition to the crude model, age was adjusted in model 2. Model 3 was additionally adjusted for income, CCI, diabetes mellitus, hypertension, and dyslipidemia. Aspirin and statin use were also adjusted for model 4 and smoking status, BMI, blood glucose, systolic blood pressure, and total cholesterol were adjusted for model 5. Patients were divided into 6 treatment groups: (1) AS/WW, (defined as patients who did not undergo active treatment after PC diagnosis), (2) surgery, (3) surgery + ADT, (4) radiotherapy (RT) + ADT, (5) ADT only, and (6) RT only groups.

All statistical analyses were conducted using SAS 9.3 (Cary, NC), and 2-sided *P* values <0.05 were considered statistically significant.

Results

Baseline characteristics of the study subjects

The mean ages of the PC and control groups were 68.5 (standard deviation [SD] 8.4) and 67.8 (SD 9.0), respectively. Subjects with PC had higher income levels and were likely to live in urban areas. There was a higher prevalence of hypertension (51.0% vs 41.9%), diabetes (18.2% vs 16.0%), and dyslipidemia (23.2% vs 15.1%) among subjects with PC, and they also had higher CCI scores (1.7 ± 1.8 vs 1.4±1.7) compared to control subjects. The proportion of aspirin (6.3% vs 5.0%) and statin (22.7% vs 16.7%) use was higher in PC group compared to non-cancer control. In the screening subset, subjects with PC showed a lower current smoking rate (21.2% vs 27.0%) and tended to be more obese than control subjects (Table 1).

Comparison of dementia risk between PC patients and control subjects

The mean follow-up time for the total population after a 1-year time lag was 5.2 years (5.0 years for PC subjects and 5.3 years for matched control subjects). The maximum follow-up period after PC diagnosis was 11 years. A total of 26,590 patients developed dementia; 19,763 (74.3%) patients developed AD and 3239 (12.2%) patients developed VaD.

The risk for all dementia was not different between the PC and control groups, while the risk for VaD was slightly lower in the PC group (adjusted hazard ratio [aHR] 0.89, 95% CI 0.82-0.98). However, in the screening subset, the PC group was at a slightly higher risk for all types of dementia (aHR 1.07, 95% CI 1.03, 1.12) and AD (aHR 1.08 95% CI 1.03-1.13) (Table 2).

Dementia risk in PC survivors compared to matched controls according to treatment modalities

Survivors who underwent only surgery had lower risk for all dementia (aHR 0.80, 95% 0.75-0.85), AD (aHR 0.81, 95% CI 0.75-0.87), and VaD (aHR 0.75, 95% CI 0.63-0.89). However, subjects who underwent ADT had increased risk for all cause dementia (aHR 1.13 95% CI 1.09-1.18) and AD (aHR 1.12 95% CI 1.07-1.18). The risk for dementia was not significantly different in the other groups (surgery + ADT, RT, and RT + ADT). Analyses of the screening subset revealed similar results (Table 3).

Dementia risk in PC survivors compared to the surgery group according to treatment modalities

The incidence of dementia, AD, and VaD was higher in the ADT group compared to the surgery group. Subjects in either the AS/WW or surgery + ADT group were more likely to develop all types of dementia and AD than subjects in the surgery only group (Fig 2).

Table 1
Baseline characteristics of study participants.

	All population			Screening cohort		
	Prostate cancer population	Matched controls		Prostate cancer population	Matched controls	*P*
N	51,251	209,659		30,953	109,742	
Age, mean ± SD	68.5 ± 8.4	67.8 ± 9.0	<0.001	67.9 ± 8.0	67.2 ± 8.5	<0.001
Income level			<0.001			<0.001
Rank 1-5 (lowest)	11,479 (22.4)	56,983 (27.2)		6352 (20.5)	26,417 (24.1)	
Rank 6-10	8,937 (17.4)	40,869 (19.5)		5,712 (18.5)	22,457 (20.5)	
Rank 11-15	12,153 (23.7)	50,113 (23.9)		7,619 (24.6)	27,414 (25.0)	
Rank 16-20 (highest)	18,682 (36.5)	61,694 (29.4)		11,270 (36.4)	33,454 (30.5)	
Place of residence, urban	23,909 (46.7)	93,005 (44.4)	<0.001	13,984 (45.2)	47,612 (43.4)	<0.001
Hypertension	26,131 (51.0)	87,789 (41.9)	<0.001	15,528 (50.2)	47,081 (42.9)	<0.001
Diabetes mellitus	9345 (18.2)	33,502 (16.0)	<0.001	5260 (17.0)	17,230 (15.7)	<0.001
Dyslipidemia	11,880 (23.2)	31,729 (15.1)	<0.001	7150 (23.1)	17,686 (16.1)	<0.001
Charlson Comorbidity Index, mean ± SD	1.7 ± 1.8	1.4 ± 1.7	<0.001	1.6 ± 1.7	1.4 ± 1.6	<0.001
Duration of dementia, mean ± SD	5.0 ± 2.5	5.3 ± 2.3	<0.001	5.0 ± 2.3	5.3 ± 2.2	<0.001
Use of aspirin	3024 (6.3)	10,050 (5.0)	<0.001	2385 (7.7)	7357 (6.7)	<0.001
Use of statin	10,945 (22.7)	33,370 (16.7)	<0.001	7550 (24.4)	21,921 (20.0)	<0.001
Smoking status						<0.001
Nonsmoker				14,739 (47.6)	48,845 (44.5)	
Ex-smoker				9642 (31.2)	31,317 (28.5)	
Current-smoker				6572 (21.2)	29,580 (27.0)	
Body mass index						<0.001
<18.5				836 (2.7)	3748 (3.4)	
18.5-23				10,509 (34.0)	39,949 (36.4)	
23-25				8939 (28.9)	30,422 (27.7)	
25-30				10,054 (32.5)	33,488 (30.5)	
≥30				615 (2.0)	2135 (2.0)	
Systolic blood pressure, mean ± SD				128.7 ± 15.4	129.53 ± 15.9	<0.001
Diastolic blood pressure, mean ± SD				78.1 ± 9.9	78.7 ± 10.1	<0.001
Fasting glucose, mean ± SD				103.6 ± 25.5	104.4 ± 27.6	<0.001
Total cholesterol, mean ± SD				189.3 ± 36.2	190.1 ± 36.6	0.0003

Compared to the surgery group, the AS/WW group had higher risk for all dementia (aHR 1.27, 95% CI 1.15-1.39) and AD (aHR 1.29, 95% CI 1.16-1.44). The surgery + ADT group was also at a higher risk for all dementia (aHR 1.19, 95% CI 1.07-1.34) and AD (1.16, 95% CI 1.01-1.32) than the surgery only group. The RT + ADT group showed an increased risk for all dementia (aHR 1.36, 95% CI 1.12-1.65) and VaD (aHR 1.77, 95% CI 1.08-2.91). The ADT only group showed higher risk for AD (aHR 1.52, 95% CI 1.41-1.65), and VaD (aHR 1.39, 95% CI 1.11-1.75). Analyses involving the screening cohort generally revealed similar results (Table 4).

Discussion

This study directly evaluated the association between PC treatment modalities and the incidence of dementia among PC patients. We showed that the PC group that underwent health screening was at a slightly higher risk for all dementia and AD. In addition, we found that the risk for dementia varied according to treatment modalities. Patients who underwent only surgery were at the lowest risk for dementia. The risk for dementia among patients in the AS/WW group was similar to that of control group. PC patients who underwent ADT showed

Table 2
Risk of dementia in prostate cancer patients compared to matched controls.

	N	Event	Person-year	IR (per 1000)	Model 1	Model 2	Model 3	Model 4	Model 5
All participants									
Overall dementia									
Control	209,659	21,461	1,112,023	19.3	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	
Case	51,251	5129	254,168.6	20.2	1.05 (1.02, 1.09)	1.03 (1.00, 1.06)	1.00 (0.97, 1.03)	1.00 (0.97, 1.03)	
Alzheimer's dementia									
Control	209,659	15,954	1,112,023	14.3	1 (Ref.)	1 (Ref.)	1 (Ref.)	1(Ref.)	
Case	51,251	3809	254,168.6	15.0	1.05 (1.02, 1.09)	1.03 (1.00, 1.07)	1.00 (0.97, 1.04)	1.00 (0.97, 1.04)	
Vascular dementia									
Control	209,659	2655	1,112,023	2.4	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	
Case	51,251	584	254,168.6	2.3	0.97 (0.88, 1.06)	0.94 (0.86, 1.03)	0.88 (0.81, 0.97)	0.89 (0.82, 0.98)	
Screening cohort									
Overall dementia									
Control	109,742	9566	583,381.7	16.4	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Case	30,953	2818	154,159.5	18.3	1.12 (1.08, 1.17)	1.08 (1.03, 1.13)	1.06 (1.01, 1.10)	1.06 (1.02, 1.11)	1.07 (1.03, 1.12)
Alzheimer's dementia									
Control	109,742	7169	583,381.7	12.3	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Case	30,953	2114	154,159.5	13.7	1.13 (1.07, 1.18)	1.08 (1.03, 1.13)	1.06 (1.01, 1.12)	1.07 (1.02, 1.12)	1.08 (1.03, 1.13)
Vascular dementia									
Control	109,742	1169	583,381.7	2.0	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Case	30,953	309	154,159.5	2.0	1.01 (0.89, 1.14)	0.97 (0.85, 1.10)	0.93 (0.82, 1.05)	0.93 (0.82, 1.06)	0.96 (0.84, 1.08)

IR: incidence rate.
Model 1: Crude model.
Model 2: adjusted for age.
Model 3: adjusted for age, income, Charlson comorbidity index, diabetes mellitus, hypertension, and dyslipidemia.
Model 4: adjusted for age, income, Charlson comorbidity index, diabetes mellitus, hypertension, dyslipidemia, aspirin use, and statin use.
Model 5: adjusted for age, income, Charlson comorbidity index, diabetes mellitus, hypertension, dyslipidemia, aspirin use, statin use, smoking status, BMI, blood glucose, systolic blood pressure, and total cholesterol.

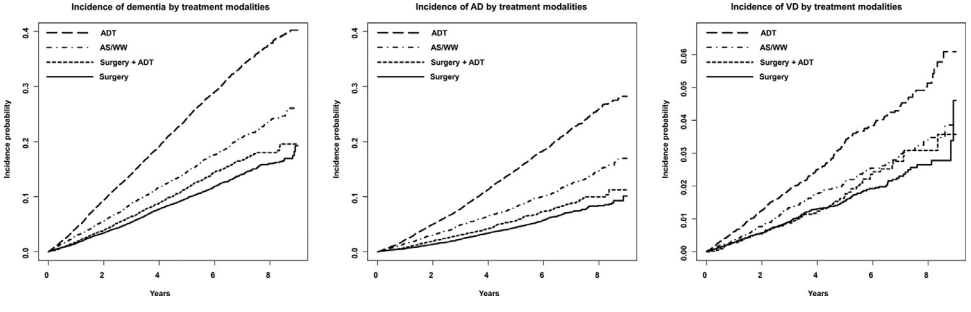

Fig. 2. Incidence of dementia in prostate cancer patients according to treatment modalities.

higher risk for dementia than the control group. A major strength of this study is its large sample size and representativeness. Additionally, we compared the risk for dementia according to various treatment modalities and extensively adjusted for sociodemographic and cardiovascular risk factors.

When the analysis was confined to the screening subset, we found that PC patients showed higher risk for dementia and AD compared to the general population. In Korea, PSA screening

Table 3
Risk of dementia in prostate cancer patients by treatment modality compared to matched controls.

	N	Event	Duration	IR (per 1000)	Model 1	Model 2	Model 3	Model 4	Model 5
All participants									
Overall dementia									
Control	209,659	21,461	1,112,023	19.3	1 (Ref.)	1(Ref.)	1 (Ref.)	1 (Ref.)	
AS/WW	7547	796	40,582.5	19.6	0.99 (0.92, 1.06)	1.01 (0.94, 1.08)	0.96 (0.89, 1.03)	0.96 (0.90, 1.03)	
Surgery	18,288	1019	98,889.1	10.3	0.54 (0.50, 0.57)	0.81 (0.76, 0.86)	0.79 (0.74, 0.84)	0.80 (0.75, 0.85)	
	5865	425	31,374.9	13.5	0.71 (0.64, 0.78)	0.96 (0.87, 1.05)	0.94 (0.85, 1.04)	0.95 (0.86, 1.05)	
Surgery + ADT									
RT	457	32	1667.6	19.2	1.09 (0.77, 1.54)	0.91 (0.64, 1.29)	0.86 (0.61, 1.22)	0.85 (0.60, 1.21)	
RT + ADT	1385	114	5253.2	21.7	1.22 (1.02, 1.47)	1.07 (0.90, 1.28)	1.04 (0.87, 1.25)	1.05 (0.87, 1.26)	
ADT	17,709	2743	76,401.4	35.9	1.89 (1.82, 1.97)	1.17 (1.13, 1.22)	1.13 (1.08, 1.18)	1.13 (1.09, 1.18)	
Alzheimer's dementia									
Control	209,659	15,954	1,112,023	14.3	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	
AS/WW	7547	612	40,582.5	15.1	1.02 (0.94, 1.10)	1.04 (0.96, 1.12)	0.99 (0.91, 1.08)	0.99 (0.92, 1.08)	
Surgery	18,288	749	98,889.1	7.6	0.53 (0.49, 0.57)	0.82 (0.76, 0.88)	0.81 (0.75, 0.87)	0.81 (0.75, 0.87)	
	5,865	304	31,374.9	9.7	0.68 (0.61, 0.76)	0.94 (0.84, 1.05)	0.93 (0.83, 1.04)	0.94 (0.84, 1.05)	
Surgery + ADT									
RT	457	27	1667.6	16.2	1.27 (0.87, 1.85)	1.06 (0.73, 1.55)	1.01 (0.69, 1.48)	1.00 (0.69, 1.46)	
RT + ADT	1385	75	5253.2	14.3	1.11 (0.88, 1.39)	0.97 (0.77, 1.22)	0.95 (0.76, 1.19)	0.96 (0.76, 1.20)	
ADT	17,709	2042	76401.4	26.7	1.90 (1.82, 1.99)	1.16 (1.11, 1.22)	1.12 (1.07, 1.18)	1.12 (1.07, 1.18)	
Vascular dementia									
Control	209,659	2655	1,112,023	2.4	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	
AS/WW	7547	91	40,582.5	2.2	0.92 (0.75,1.13)	0.93 (0.76,1.15)	0.85 (0.69,1.05)	0.86 (0.70,1.06)	
Surgery	18,288	135	98,889.1	1.4	0.58 (0.48, 0.68)	0.78 (0.65, 0.92)	0.73(0.62, 0.87)	0.75 (0.63, 0.89)	
	5865	60	31,374.9	1.9	0.80 (0.62, 1.04)	1.00 (0.77, 1.29)	0.95 (0.73, 1.23)	0.97 (0.75, 1.25)	
Surgery + ADT									
RT	457	1	1667.6	0.6	0.27 (0.04, 1.92)	0.23 (0.03, 1.62)	0.20 (0.03, 1.4)	0.20 (0.03, 1.41)	
RT + ADT	1385	18	5253.2	3.4	1.54 (0.97, 2.45)	1.34 (0.85, 2.14)	1.24 (0.78, 1.98)	1.26 (0.79, 2.01)	
ADT	17,709	279	76,401.4	3.7	1.55 (1.37, 1.75)	1.03 (0.91, 1.17)	0.97 (0.86, 1.10)	0.97 (0.86, 1.10)	
Screening cohort									
Overall dementia									
Control	109,742	9566	583,381.7	16.4	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
AS/WW	3976	389	21,466.7	18.1	1.07 (0.96, 1.18)	1.02 (0.92, 1.13)	0.99 (0.89, 1.10)	0.99 (0.90, 1.10)	1.00 (0.91, 1.11)
Surgery	12,235	644	64,679.6	10.0	0.61 (0.57, 0.66)	0.88 (0.81, 0.95)	0.87 (0.80, 0.94)	0.87 (0.81, 0.95)	0.89 (0.82, 0.97)
	3998	278	21,103.5	13.2	0.81 (0.72, 0.91)	1.06 (0.94, 1.20)	1.04 (0.92, 1.17)	1.05 (0.93, 1.19)	1.07 (0.95, 1.21)
Surgery + ADT									
RT	314	22	1149.7	19.1	1.31 (0.87, 2.00)	1.05 (0.69, 1.59)	0.99 (0.65, 1.51)	0.98 (0.65, 1.49)	0.99 (0.65, 1.51)
RT + ADT	965	72	3702.0	19.4	1.33 (1.05, 1.67)	1.13 (0.90, 1.43)	1.10 (0.88, 1.39)	1.11 (0.88, 1.39)	1.13 (0.89, 1.42)
ADT	9465	1413	42,058	33.6	2.08 (1.97, 2.20)	1.23 (1.16, 1.30)	1.20 (1.14, 1.27)	1.20 (1.14, 1.27)	1.21 (1.14, 1.28)

(*continued on next page*)

Table 3 (*continued*)

	N	Event	Duration	IR (per 1000)	Model 1	Model 2	Model 3	Model 4	Model 5
Alzheimer's dementia									
Control	109,742	7169	58,3381.7	12.3	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
AS/WW	3976	307	21,466.7	14.3	1.11 (0.99, 1.25)	1.07 (0.95, 1.20)	1.04 (0.92, 1.16)	1.04 (0.92, 1.16)	1.05 (0.93, 1.17)
Surgery	12,235	478	64,679.6	7.4	0.61 (0.55, 0.67)	0.88 (0.81, 0.97)	0.88 (0.80, 0.96)	0.88 (0.80, 0.97)	0.90 (0.82, 0.98)
	3998	201	21,103.5	9.5	0.78 (0.68, 0.90)	1.03 (0.90, 1.19)	1.02 (0.89, 1.18)	1.03 (0.90, 1.19)	1.045 (0.91, 1.21)
Surgery + ADT									
RT	314	18	1149.72	15.7	1.48 (0.93, 2.35)	1.17 (0.74, 1.87)	1.12 (0.70, 1.78)	1.11 (0.70, 1.76)	1.12 (0.70, 1.78)
RT + ADT	965	46	3702.04	12.4	1.16 (0.87, 1.55)	0.99 (0.74, 1.32)	0.97 (0.73, 1.30)	0.97 (0.73, 1.30)	0.99 (0.74, 1.32)
ADT	9465	1064	42,058	25.3	2.10 (1.97, 2.24)	1.22 (1.15, 1.30)	1.20 (1.12, 1.28)	1.20 (1.12, 1.28)	1.21 (1.13, 1.29)
Vascular dementia									
Control	109,742	1169	583,381.7	2.0	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
AS/WW	3976	41	21,466.7	1.9	0.93 (0.68, 1.27)	0.91 (0.66, 1.24)	0.85 (0.62, 1.16)	0.86 (0.63, 1.17)	0.87 (0.64, 1.19)
Surgery	12,235	81	64,679.6	1.3	0.63 (0.50, 0.79)	0.84 (0.67, 1.06)	0.81 (0.64, 1.02)	0.82 (0.66, 1.04)	0.86 (0.69, 1.08)
	3998	36	21,103.5	1.7	0.86 (0.61, 1.19)	1.06 (0.76, 1.47)	1.01 (0.73, 1.41)	1.03 (0.74, 1.44)	1.07 (0.77, 1.49)
Surgery + ADT									
RT	314	0	1149.7	0	N/A	N/A	N/A	N/A	N/A
RT + ADT	965	8	3702.0	2.2	1.15 (0.57, 2.31)	0.99 (0.49, 1.98)	0.93 (0.46, 1.86)	0.93 (0.46, 1.86)	0.95 (0.47, 1.90)
ADT	9465	143	42,058	3.4	1.71 (1.44, 2.04)	1.07 (0.90, 1.28)	1.03 (0.87, 1.23)	1.03 (0.87, 1.23)	1.04 (0.87, 1.24)

IR: incidence rate, N/A: not applicable.
Model 1: Crude model.
Model 2: adjusted for age.
Model 3: adjusted for age, income, Charlson comorbidity index, diabetes mellitus, hypertension, and dyslipidemia.
Model 4: adjusted for age, income, Charlson comorbidity index, diabetes mellitus, hypertension, dyslipidemia, aspirin use, and statin use.
Model 5: adjusted for age, income, Charlson comorbidity index, diabetes mellitus, hypertension, dyslipidemia, smoking status, BMI, blood glucose, aspirin use, statin use, systolic blood pressure, and total cholesterol.

is not included in the government-funded screening program, but is included in private health screening programs. Therefore, PC patients are more likely to be people who participate in the PSA screening programs, have a high socioeconomic status, choose healthy lifestyles, and practice preventive treatment.[19] This screening effect could partially be responsible for the discrepancies in the risk for dementia.

PC survivors who underwent only surgery had a lower risk for dementia and AD compared to the matched control population. Surgery is a popular option for men with localized PC or for those whose PC is in the locoregional stage. Therefore, this group is more likely to participate in preventive health care and to seek healthier lifestyle patterns than the general population.[19] In the screening cohort, participation in a private screening program could have acted as an unmeasured confounding factor. This explains the observed positive effects of surgery as a PC treatment modality on the risk for dementia.

Patients who underwent ADT were more likely to develop dementia and AD compared to the surgery group and general population, consistent with the results of previous studies.[10,11,20-22] Similarly, a review in 2000 on the possible effect of ADT on neuro-cognition suggested that ADT could lead to cognitive decline and, therefore, caution should be exercised when administering ADT.[23] In contrast, several studies that involved neurocognitive testing showed a negative association between ADT and cognitive decline[21,24,25]. The discrepancy in dementia outcomes in these studies could be due to the enrolment of predominantly well-educated white people with

Table 4
Risk of dementia in prostate cancer patients by treatment modality compared to surgery group.

	N	Event	Person -year	IR (per 1000)	Model 1	Model 2	Model 3	Model 4	Model 5
All participants									
Overall dementia									
Surgery	18,288	1019	98,889.1	10.3	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	
AS/WW	7547	796	40,582.5	19.6	1.85 (1.69, 2.03)	1.31 (1.19, 1.44)	1.27 (1.16, 1.40)	1.27 (1.15, 1.39)	
	5865	425	31,374.9	13.5	1.31 (1.17, 1.47)	1.20 (1.07, 1.34)	1.19 (1.07, 1.34)	1.19 (1.07, 1.34)	
Surgery + ADT									
RT	457	32	1667.6	192	2.02 (1.42, 2.87)	1.18 (0.83, 1.67)	1.13 (0.79, 1.61)	1.11 (0.78, 1.58)	
	1385	114	5253.2	21.7	2.27 (1.87, 2.76)	1.38 (1.13, 1.68)	1.36 (1.12, 1.65)	1.36 (1.12, 1.65)	
RT + ADT									
ADT	17,709	2743	76,401.4	35.9	3.53 (3.28, 3.79)	1.57 (1.45, 1.70)	1.53 (1.42, 1.66)	1.52 (1.41, 1.65)	
Alzheimer's dementia									
Surgery	18,288	749	98,889.1	7.6	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	
AS/WW	7547	612	40,582.5	15.1	1.92 (1.72, 2.14)	1.34 (1.20, 1.49)	1.30 (1.16, 1.45)	1.29 (1.16, 1.44)	
	5865	304	31,374.9	9.7	1.28 (1.12, 1.46)	1.16 (1.01, 1.32)	1.16 (1.01, 1.32)	1.16 (1.01, 1.32)	
Surgery + ADT									
RT	457	27	1667.6	16.2	2.38 (1.62, 3.49)	1.36 (0.92, 1.99)	1.31 (0.90, 1.92)	1.29 (0.88, 1.89)	
	1385	75	5253.2	14.3	2.08 (1.64, 2.64)	1.24 (0.98, 1.57)	1.22 (0.96, 1.56)	1.22 (0.96, 1.55)	
RT + ADT									
ADT	17,709	2042	76,401.4	26.7	3.58 (3.30, 3.90)	1.54 (1.41, 1.69)	1.51 (1.37, 1.65)	1.50 (1.36, 1.64)	
Vascular dementia									
Surgery	18,288	135	98,889.1	1.4	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	
AS/WW	7547	91	40,582.5	2.2	1.60 (1.22, 2.09)	1.25 (0.96, 1.65)	1.22 (0.93, 1.60)	1.20 (0.92, 1.58)	
	5865	60	31,374.9	1.9	1.40 (1.03, 1.90)	1.30 (0.96, 1.76)	1.30 (0.96, 1.76)	1.30 (0.96, 1.76)	
Surgery + ADT									
RT	457	1	1667.6	0.6	0.48 (0.067, 3.40)	0.31 (0.04, 2.22)	0.30 (0.04, 2.11)	0.28 (0.04, 20)	
	1385	18	5253.2	3.4	2.69 (1.64, 4.41)	1.83 (1.11, 3.00)	1.79 (1.09, 2.9)	1.77 (1.08, 2.91)	
RT + ADT									
ADT	17,709	279	76,401.4	3.7	2.69 (2.19, 3.31)	1.45 (1.15, 1.82)	1.42 (1.13, 1.79)	1.39 (1.11, 1.75)	
Screening cohort									
Overall dementia									
Surgery	12,235	644	64,679.6	10.0	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
AS/WW	3976	389	21,466.7	18.1	1.76 (1.55, 2.00)	1.24 (1.09, 1.41)	1.22 (1.07, 1.38)	1.21 (1.06, 1.38)	1.20 (1.05, 1.36)
	3998	278	21,103.5	13.1	1.32 (1.15, 1.52)	1.21 (1.05, 1.39)	1.21 (1.05, 1.39)	1.21 (1.05, 1.39)	1.21 (1.05, 1.39)
Surgery + ADT									
RT	314	22	1149.7	19.1	2.08 (1.36, 3.18)	1.21 (0.79, 1.86)	1.16 (0.76, 1.78)	1.14 (0.75, 1.75)	1.14 (0.74, 1.75)
	965	72	3702.0	19.4	2.10 (1.64, 2.68)	1.31 (1.02, 1.67)	1.28 (1.00, 1.64)	1.27 (1.00, 1.63)	1.27 (0.99, 1.62)
RT + ADT									
ADT	9465	1413	42,058	33.6	3.40 (3.09, 3.73)	1.52 (1.37, 1.68)	1.50 (1.35, 1.66)	1.49 (1.34, 1.65)	1.46 (1.32, 1.62)
Alzheimer's dementia									
Surgery	12,235	478	64,679.6	7.4	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
AS/WW	3976	307	21,466.7	14.3	1.86 (1.61, 2.15)	1.29 (1.12, 1.50)	1.27 (1.09, 1.47)	1.26 (1.09, 1.46)	1.25 (1.08, 1.45)
	3998	201	21,103.5	9.5	1.29 (1.09, 1.52)	1.18 (1.00, 1.39)	1.18 (1.00, 1.39)	1.18 (1.00, 1.39)	1.18 (1.00, 1.39)
Surgery + ADT									
RT	314	18	1149.7	15.7	2.34 (1.46, 3.75)	1.35 (0.84, 2.17)	1.29 (0.81, 2.07)	1.28 (0.80, 2.05)	1.28 (0.80, 2.05)

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Table 4 (*continued*)

	N	Event	Person -year	IR (per 1000)	Model 1	Model 2	Model 3	Model 4	Model 5
	965	46	3702.0	12.4	1.85 (1.33, 2.50)	1.14 (0.84, 1.54)	1.12 (0.82, 1.52)	1.11 (0.82, 1.51)	1.11 (0.82, 1.50)
RT + ADT									
ADT	9465	1064	42,058	25.3	3.45 (3.10, 3.84)	1.51 (1.34, 1.70)	1.49 (1.33, 1.68)	1.49 (1.32, 1.67)	1.46 (1.30, 1.65)
Vascular dementia									
Surgery	12,235	81	64,679.6	1.3	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
AS/WW	3976	41	21,466.7	1.9	1.49 (1.02, 2.18)	1.14 (0.78, 1.67)	1.12 (0.77, 1.65)	1.11 (0.75, 1.62)	1.06 (0.72, 1.56)
	3998	36	21,103.5	1.7	1.36 (0.92, 2.01)	1.26 (0.85, 1.87)	1.26 (0.85, 1.86)	1.25 (0.85, 1.86)	1.23 (0.83, 1.82)
Surgery + ADT									
RT	314	0	1149.7	0	N/A	N/A	N/A	N/A	N/A
	965	8	3702.0	2.2	1.78 (0.86, 3.69)	1.20 (0.58, 2.49)	1.17 (0.56, 2.44)	1.14 (0.55, 2.38)	1.11 (0.53, 2.30)
RT + ADT									
ADT	9465	143	42,058	3.4	2.71 (2.06, 3.56)	1.39 (1.03, 1.88)	1.38 (1.02, 1.86)	1.34 (0.99, 1.82)	1.26 (0.93, 1.71)

AS/WW: active surveillance/watchful waiting; IR: incidence rate, N/A: not applicable.
Model 1: Crude model.
Model 2: adjusted for age.
Model 3: adjusted for age, income, Charlson comorbidity index, diabetes mellitus, hypertension, and dyslipidemia.
Model 4: adjusted for age, income, Charlson comorbidity index, diabetes mellitus, hypertension, dyslipidemia, aspirin use, and statin use.
Model 5: adjusted for age, income, Charlson comorbidity index, diabetes mellitus, hypertension, dyslipidemia, smoking status, BMI, blood glucose, aspirin use, statin use, systolic blood pressure, and total cholesterol.

good cognitive reserve, the small sample size, and the short follow-up period. This might have decreased the power of the study, which might have made it impossible to detect a significant difference.

Several plausible mechanisms have been suggested for the effects of ADT on the risk for dementia and AD. First, a decrease in the serum testosterone level could contribute to the cognitive degeneration. Androgen plays an important role in the regeneration of axons and the growth of neurons,[26] and a previous study demonstrated that withdrawal of androgen was associated with decreased spine synapse density on pyramidal neurons in the area of the hippocampus that plays a key role in learning and memory.[27] Furthermore, depletion of serum androgen caused the accumulation of beta amyloid proteins in the brain leading to detrimental effects on neuronal cells.[28] Another explanation for the deleterious effect of ADT on cognitive function among PC patients is that ADT could change the brain structure by decreasing the gray matter volume of the dorsolateral prefrontal, frontopolar, and primary motor cortices, which can affect the performance of tasks involving working memory.[29] Finally, patients who underwent ADT showed reduced task-related activation of the right parietal-occipital area during functional magnetic resonance imaging. This might be associated with the decreased cognitive abilities observed among PC survivors who undergo ADT.[30]

In contrast to AD, we showed that the risk for VaD was slightly lower among PC subjects compared to controls. It is possible that the difference in the proportions of statin users between the PC subjects and non-cancer controls might be related to the observed lower risk for VaD among PC subjects. However, PC patients who underwent only ADT and those who underwent RT + ADT showed higher risk for VaD than patients who underwent surgery, probably because of screening bias. Most of the previous studies did not directly measure the risk for VaD in relation to ADT.[8,10-12,20,21] Additionally, only 1 Swedish study reported that the GnRH agonist was associated with a 24% higher risk for non-Alzheimer dementia.[31] To our knowledge, the present study is the first study to directly investigate the association between ADT and VaD.

Interestingly, the surgery + ADT group had higher risk for all cause dementia than the surgical treatment only group in the screening subset. Based on the treatment guidelines, PC with nodal involvement is treated with adjuvant ADT after surgical treatment because of survival ben-

efits.[32,33] However, in addition to the high incidence of overall dementia and AD observed in our study, ADT is associated with an increased risk for other morbidities such as coronary arterial disease,[34] heart failure,[35] atrial fibrillation,[35] stroke,[36] and osteoporotic fracture.[37,38] The RT + ADT group was at a higher risk for dementia than the surgery only group, further supporting the effect of ADT on the risk for dementia. Thus, urologists should consider the risk and benefit of ADT for each individual in order to optimize its use.

Our study reports clinical implications for the management of PC survivors. Because ADT is likely to increase the risk for dementia, urologists should consider the risk factors for dementia in patients when deciding to administer adjuvant or salvage ADT. Furthermore, preventive measurements for AD and VaD, such as regular tests for cognitive function,[39] lifestyle intervention,[40,41] and cardiovascular risk factor management, including the use of antihypertensives[42] or statins,[43] should be an essential part of salvage or adjuvant ADT for PC patients.

The present study has some limitations. First, because we used administrative data, detailed clinical information regarding the PC state and the recurrence of the cancer were not included in the analysis. Thus, our evaluation of the influence of PC severity on the risk of dementia was limited. Second, because we diagnosed dementia using the disease code and claim data for reimbursement, concerns regarding diagnostic inaccuracy for dementia might be raised. Furthermore, patients with early-stage dementia were likely to be misclassified as normal subjects due to the subtle clinical symptoms of early-stage dementia. However, because strict criteria are used for the diagnosis of dementia and for the prescription of antidementia medications under the Korean National Health Insurance system, the reliability of dementia diagnosis is reasonably high.[44] Third, because the present study is not a prospective cohort study on dementia, some important information such as the genetic polymorphism, domain of cognitive function, and education and literacy levels were not assessable. Finally, we did not diagnose dementia using a formal cognitive test during the regular follow-up period. Therefore, we could not identify the cognitive domains that were mainly affected by PC treatment modalities.

In conclusion, PC patients were at a slightly higher risk for dementia than the general population, and this was largely due to the screening effects. ADT use was not only associated with AD, but also VaD. Our study suggests that the risk for dementia should be considered to identify the optimal PC treatment strategy for each patient.

CRediT authorship contribution statement

Jihun Kang: Conceptualization, Investigation, Methodology, Visualization, Writing - original draft. **Dong Wook Shin:** Conceptualization, Investigation, Methodology, Resources, Supervision, Visualization, Writing - review & editing. **Kyungdo Han:** Data curation, Formal analysis, Software. **Sang Hyun Park:** Data curation, Formal analysis, Software. **Won Gu Lee:** Supervision, Validation. **Jung Eun Yoo:** Supervision, Validation, Writing - review & editing. **Seung-Hyo Woo:** Supervision, Validation. **Jinsung Park:** Conceptualization, Investigation, Methodology, Resources, Supervision, Writing - review & editing.

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