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Original Article

Androgen deprivation therapy and the risk of subsequent keratitis

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Abstract

Objectives: The objective of the study was to determine the risk of subsequent keratitis in prostate cancer (PCa) patients treated with androgen deprivation therapy (ADT). **Materials and Methods:** Three thousand three hundred and nine patients with PCa were identified using data from Taiwan's National Health Insurance Research Database for 2001 through 2013. Among those patients, 856 treated with ADT comprised the study group, while 856 non-ADT-treated patients matched with 1:1 propensity-score-matched analysis comprised the control group. The demographic characteristics and comorbidities of all the patients were analyzed, and Cox proportional hazards regression was utilized to determine the hazard ratios (HRs) for subsequent keratitis. **Results:** A total of 157 (9.2%) patients had newly diagnosed keratitis. Compared to the non-ADT-treated patients, the ADT-treated patients had a reduced risk of subsequent keratitis, with an adjusted HR of 0.38 (95% confidence interval: 0.27–0.55; $P < 0.001$). **Conclusion:** ADT treatment apparently decreased the risk of subsequent keratitis in the investigated PCa patients, but the clinical significance of this finding should be further assessed in additional studies.

Keywords: *Androgen deprivation therapy, Keratitis, Prostate cancer*

Introduction

As one of the most commonly occurring cancers among men, prostate cancer (PCa) has substantial public health impacts worldwide [1]. For over 70 years, androgen deprivation therapy (ADT) has been utilized as a standard treatment for advanced PCa [2], with more than half a million PCa patients per year in the United States being treated with ADT in recent years [3].

ADT can be accompanied, however, by a number of adverse effects, including cardiovascular disease, osteoporosis, and metabolic syndrome [4,5]. Immune system alterations during ADT treatment have also been reported by previous studies [6,7].

The features of the male phenotype result to a large extent from a group of hormones known as androgens. The past research has shown that the meibomian gland is a target organ of these hormones, with testosterone, one of the androgens, having been shown to influence gene expression in the meibomian glands of mice [8]. This finding was corroborated by other research, indicating that patients with complete androgen insensitivity syndrome, which results in completely dysfunctional androgen receptors, have different meibomian gland secretions than people without the syndrome [9], including a possibly elevated incidence of the signs and symptoms of dry eye [10]. Such findings suggest that hormonal irregularities can affect the health of the ocular surface, although it is still not clear whether ADT causes keratitis.

Only limited research has been conducted thus far into the potential relationship between keratitis and ADT. The aim of the present nationwide, large-scale, population-based study, therefore, was to determine the relationship, if any, between ADT treatment and the risk of subsequent keratitis.

Materials and Methods

Data source and collection

The data utilized in the present study were collected from Taiwan's National Health Insurance Research Database (NHIRD), which is an administrative database for the National Health Insurance (NHI) program, the medical insurance system of Taiwan [11]. More specifically, this was a retrospective cohort study that utilized data from the Longitudinal Health Insurance Database 2000 (LHID2000), a sub-dataset of the NHIRD. The LHID2000 contains the healthcare-related records for one million people randomly selected in 2000

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from among the approximately 23 million residents of Taiwan included in the NHIRD. The diagnoses listed in the NHIRD and LHID2000 records were made according to the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM), and all the data included in both databases are anonymized. The Institutional Review Board of the Tri-Service General Hospital approved this study (approval number: TSGHIRB NO B-104-21).

Study population

Using the LHID2000 data from January 2001 to December 2009, we identified the patients who were newly diagnosed with PCa during that time [Figure 1]. The PCa diagnoses of the patients were confirmed base on the ICD-9-CM code used (that is, ICD-9-CM: 185) [12]. Furthermore, patients were identified as having received ADT if they were treated with GnRH agonists (that is, buserelin, goserelin, leuprolide, and triptorelin), oral antiandrogens (that is, bicalutamide, cyproterone acetate, flutamide, and nilutamide), and/or estrogens (that is, diethylstilbestrol and estramustine) [12]. The exclusion criteria for the study were as follows: a diagnosis of PCa prior to January 1, 2000 (n = 452), being below the age of 50 years when diagnosed with PCa (n = 150); having a prior history of keratitis (n = 58); and a lack of complete medical records (n = 31). The subjects included in the study included those patients treated with ADT (that is, the ADT group) and a control group consisting of patients not treated with ADT that was created by matching such patients with those in the ADT group in a 1-to-1 manner with respect to age, gender, insured region, and urbanization.

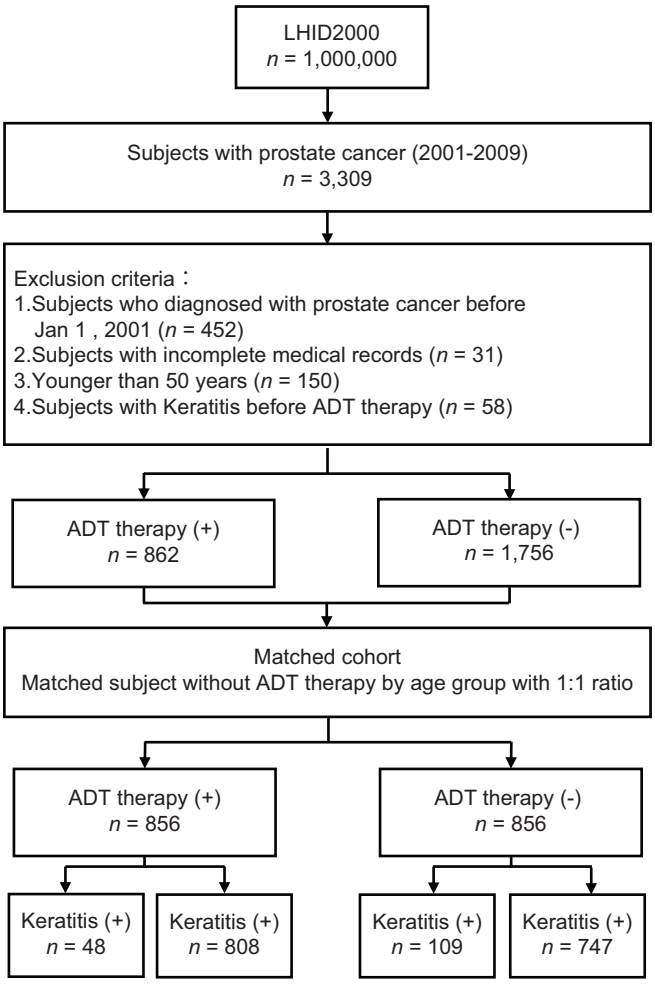

Figure 1: Flowchart of the study cohort selection. ADT: Androgen deprivation therapy

For the ADT group, the date on which each patient first filled an ADT prescription was defined as the index date for that patient, while for the control group, the index date year was assigned in a matched manner according to a year, in which each of the control subjects had used a medical service.

Study outcomes

The main study outcome was a new diagnosis of keratitis (ICD-9-CM: 370) for which an ophthalmologist or ophthalmologists required the given patient to make at least two outpatient visits or to undergo one inpatient hospitalization. The incidence rates of such newly diagnosed cases of keratitis in both the ADT-treated and non-ADT-treated patients were determined.

A total of 1712 patients were ultimately included in this study, with 856 of those patient comprising the ADT-treated study group and another 856 patients comprising the non-ADT-treated control group. Each patient was tracked for a period of 4 years beginning from his or her index date. The incidence of keratitis was confirmed only after a given patient had started to receive ADT treatment and at least 30 days had passed since the patient's index date. Censoring was defined in this study according to whichever of the following came first: the date of death, the date of the incidence of keratitis, or the end of the overall follow-up period on December 31, 2013.

Covariates

Covariates were analyzed for both the groups, with the covariates being considered included the patient's age at diagnosis, alcohol abuse status, obesity status, tobacco use disorder status, and various comorbidities. The comorbidities considered were cerebral vascular accident (ICD-9-CM: 430–438), chronic obstructive pulmonary disease (COPD) (ICD-9-CM: 491, 492, 496), coronary heart disease (ICD-9-CM: 410–414), diabetes mellitus (ICD-9-CM: 250), hyperlipidemia (ICD-9-CM: 272.4), and hypertension (ICD-9-CM: 401-405). All of the patients were classified into one of the following five age groups: 50–59 years, 60–69 years, 70–79 years, and ≥80 years. The patients were likewise categorized into one of the following four income groups based on their monthly income in New Taiwan Dollars (NTD): those receiving less than NTD 20,000 per month; those receiving NTD 20,000 to NTD 39,999 per month; those receiving NTD 40,000 to NTD 59,999 per month; and those receiving ≥ NTD 60,000 per month. Finally, the patients were further categorized into one of the four urbanization categories ranging from the highest to lowest levels of urbanization according to their level of urbanization and into one of the following four regions of Taiwan according to the locations of their residence: Northern, Central, Southern, and other (Eastern and outlying islands).

Statistical analysis

The statistical software SPSS, version 19.0 (SPSS Inc., Chicago, IL, USA), was used to perform all the statistical analyses, while the Microsoft® SQL Server® 2008 software was used to perform the data management. Descriptive analyses of the distributions of demographic characteristics, comorbidities, geography, income levels, and urbanization levels of the scabies and non-scabies patients were conducted using the Chi-squared test.

The effects of various risk factors on the hazard ratios (HRs) were estimated, along with accompanying 95% confidence intervals (CIs), using Cox proportional hazards regression models. All of these models were adjusted for the aforementioned covariates (that is age, comorbidities, income level, geography, and urbanization level). The level of statistical significance was set at $P < 0.05$, two tailed.

Results

A total of 3309 patients who received a PCa diagnosis from 2001 to 2009 were identified in the LHID2000 data. After applying the aforementioned inclusion criteria and exclusion criteria, a total of 862 ADT-treated patients and 1756 non-ADT-treated patients remained. We then applied 1:1 propensity score matching to those remaining patients such that 856 of the 862 ADT-treated patients were included in the ADT group and 856 of the 1756 non-ADT-treated patients were included in the non-ADT group [Figure 1]. The mean follow-up period for the patients in both the groups was 3.8 ± 0.7 years. The demographic characteristics of the patients in the two groups are shown in Table 1. The majority of patients were more than 70 years old, in the lowest income group, and resided in Northern Taiwan. There were no statistically significant differences in age or income between the ADT group and the non-ADT group. However, the ADT group had higher rates of diabetes, hypertension, hyperlipidemia, cardiovascular disease, cerebral vascular accident (CVA), and tobacco use.

The overall incidence of newly diagnosed keratitis among the 1712 patients in the two groups over the 4-year follow-up period was 9.2%, with 157 patients being diagnosed overall, including 48 (5.6%) in the ADT group and 109 (12.8%) in the non-ADT group [Table 2]. Therefore, the two groups differed significantly in their respective incidence rates of keratitis. According to the Cox regression analysis, the crude HR for the ADT group in comparison with the non-ADT group was 0.42 (95% CI 0.29-0.59). Furthermore, Kaplan–Meier curves indicated that the patients who received ADT treatment had a significantly reduced likelihood of developing keratitis in comparison to those not treated with ADT [Figure 2, $P < 0.001$].

After making adjustments for age, income level, urbanization level, and comorbidities through a Cox regression analysis, we further found that the adjusted HR of keratitis for the ADT group patients was 0.38 (95% CI: 0.27–0.55) [Table 3].

Discussion

To the best of our knowledge, this nationwide cohort study is the first to investigate the relationship between treatment with ADT and the risk of subsequent keratitis. A total of 3309 patients with PCa were subjected to a propensity score-matched analysis adjusted for age and comorbidities. The results indicated that the patients treated with ADT had a reduced risk of keratitis relative to those not treated with ADT during the 4-year follow-up period.

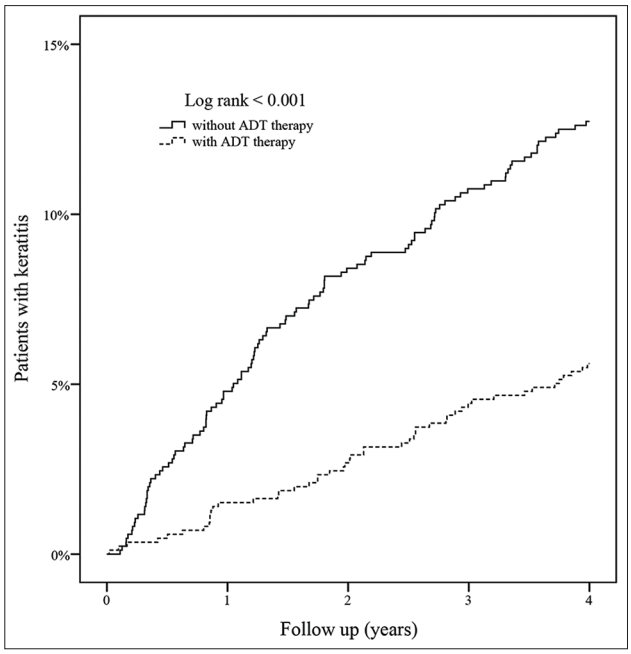

Figure 2: Kaplan–Meier curves indicating the cumulative rates of keratitis in patients treated with ADT and patients not treated with ADT and in the propensity score-matched cohort. ADT: Androgen deprivation therapy

Several studies have reported that androgen deficiency may be associated with ocular disease, as ADT effectively reduces exposure of the meibomian gland to active androgens. Therefore, since the ocular tissue is targeted by androgen hormones [13]; contains both 5a-reductase mRNA and androgen receptor proteins [14]; and reacts to androgen hormones with increased lipid synthesis, production, and release [15,16], it would be reasonable to hypothesize that an androgen deficiency would result in meibomian gland dysfunction. Androgens have previously been found to regulate the development, differentiation, and lipid elaboration of non-ocular sebaceous glands, and the meibomian gland itself is a large sebaceous gland [17,18]. In non-ocular sebaceous glands, a reduction in the level of androgens results in a marked decline in gland activity and lipid output [17,19].

The ADT group and the non-ADT group in this study did not differ significantly in terms of age, although the non-ADT group patients were slightly younger, on average, that the ADT group patients. A total of 157 (9.2%) of the patients in both groups received a new diagnosis of keratitis, including 48 patients (5.6%) in the ADT group and 109 patients (12.8%) in the non-ADT group. After making adjustments for age, income level, urbanization level, and comorbidities through Cox regression analysis, we found that the adjusted HR of keratitis was 0.38 (95% CI: 0.27–0.55) in the ADT group patients. Meanwhile, Krenzer *et al*. conducted a study with 21 patients, 15 with ADT and 6 controls, in which the

Table 1: Demographic characteristics of the patients who received androgen deprivation therapy for prostate cancer and the control group patients

Characteristics	ADT patients, *n* (%)	Non-ADT patients, *n* (%)	*P*
Number of cases	856	856	
Gender			
Male	856 (100.0)	856 (100.0)	
Age			0.95
50-59	35 (4.1)	34 (4.0)	
60-69	167 (19.5)	176 (20.6)	
70-79	407 (47.5)	398 (46.5)	
≥80	247 (28.9)	248 (29.0)	
Insured region			0.999
Northern Taiwan	444 (51.9)	548 (64)	
Central Taiwan	131 (15.3)	105 (12.3)	
Southern Taiwan	245 (28.6)	188 (22.0)	
Other (Eastern Taiwan and outlying islands)	36 (4.2)	15 (1.8)	
Urbanization			<0.05*
1 (highest)	391 (45.7)	422 (49.3)	
2	168 (19.6)	196 (22.9)	
3	200 (23.4)	156 (18.2)	
4 (lowest)	97 (11.3)	82 (9.6)	
Insured amount NTD[a]			0.203
<20,000	767 (89.6)	747 (87.3)	
20,000-39,999	36 (4.2)	36 (4.2)	
40,000-59,999	27 (3.2)	30 (3.5)	
≥60,000	26 (3.0)	43 (5.0)	
Comorbidity disease			
Diabetes mellitus	270 (31.5)	154 (18.0)	<0.001*
Hypertension	558 (65.2)	371 (43.3)	<0.001*
Hyperlipidemia	222 (25.9)	153 (17.9)	<0.001*
Coronary heart disease	316 (36.9)	221 (25.8)	<0.001*
Cerebral vascular accident	243 (28.4)	177 (20.7)	<0.001*
COPD	328 (38.3)	211 (24.6)	<0.001*
Alcoholism	6 (0.7)	3 (0.4)	0.316
Obesity	1 (0.1)	4 (0.5)	0.179
Tobacco use disorder	288 (33.6)	180 (21.0)	<0.001*

[a]NTD for which the exchange rate is 1 US dollar: 31 NTD, *P<0.05. ADT: Androgen deprivation therapy, COPD: Chronic obstructive pulmonary disease, NTD: New Taiwan dollars

Table 2: Prostate cancer patients with and without androgen deprivation therapy as predictors of keratitis identified by Cox regression

	Number of cases	
	ADT patients (*n*=856), *n* (%)	Non-ADT patients (*n*=856)
With keratitis	48 (5.6)	109 (12.7)
Without keratitis	808 (94.4)	747 (87.3)
Crude HR	0.42 (0.29-0.59)**	

**P<0.001 for comparison between patients in the two groups.
ADT: Androgen deprivation therapy

ADT patients showed no increase in keratitis compared with the control group [20].

The outcomes observed in our study may be related to inflammation. Studies conducted recently reported decreased levels of several inflammatory cytokines, including interleukin (IL)-1β, IL-2, tumor necrosis factor (TNF)-α, and interferon-γ, in PCa patients after ADT treatment [21,22]. The reduced levels of these cytokines following ADT treatment may contribute, in turn, to reduced incidences of inflammation-related conditions such as keratitis. However, according to the research by Sutherland *et al*., both humans and mice experiencing suppressed androgen levels exhibit thymic regeneration accompanied by increased levels of circulating T-cells that may, in turn, cause an enhanced immune response [2,23]. The number of genes that sex hormone levels are reported to influence in ocular tissues is extensive and includes those responsible for a variety of inflammatory mediators, including IL-1, IL-6, TNF-α, and vascular endothelial growth factor [24-26]. However, the exact relations between hormones and these mediators have yet to be fully illuminated. Further studies are thus needed to identify the mechanism underlying the association between ADT and inflammatory responses.

The strength of the present study was that it was a large cohort study that utilized data from a longitudinal nationwide database. However, the study did also have some limitations. First, the results of any laboratory tests, such as those for prostate specific antigen (PSA) levels, C-reactive

Table 3: Independent predictors of keratitis identified by Cox regression analysis

	Crude HR (95%CI)	Adjusted HR (95%CI)
Prostate cancer		
Non-ADT	1	1
ADT	0.42 (0.29-0.59)**	0.38 (0.27-0.55)**
Age		
50-59	1	1
60-69	1.06 (0.49-2.25)	0.91 (0.41-2.02)
70-79	0.76 (0.37-1.58)	0.54 (0.24-1.22)
≥80	0.64 (0.30-1.38)	0.43 (0.18-1.01)
Insured region		
Northern Taiwan	1	1
Central Taiwan	0.81 (0.49-1.35)	0.81 (0.48-1.37)
Southern Taiwan	1.05 (0.73-1.51)	1.03 (0.69-1.56)
Other (Eastern Taiwan and outlying islands)	1.09 (0.44-2.67)	1.21 (0.47-3.08)
Urbanization		
1 (highest)	1	1
2	1.17 (0.78-1.76)	1.16 (0.77-1.74)
3	1.06 (0.70-1.61)	1.15 (0.75-1.79)
4 (lowest)	1.35 (0.82-2.22)	1.37 (0.78-2.40)
Insured amount NTD[a]		
<20,000	1	1
20,000-39,999	0.92 (0.41-2.08)	0.76 (0.32-1.81)
40,000-59,999	0.94 (0.39-2.30)	0.7 (0.27-1.82)
≥60,000	1.1 (0.51-2.35)	0.8 (0.36-1.80)
Comorbidity disease		
Diabetes mellitus	0.84 (0.57-1.22)	0.82 (0.54-1.25)
Hypertension	1.02 (0.74-1.39)	1.12 (0.75-1.68)
Hyperlipidemia	1.18 (0.82-1.69)	1.16 (0.77-1.75)
Coronary heart disease	1.15 (0.83-1.60)	1.21 (0.81-1.79)
Cerebral vascular accident	1.12 (0.79-1.59)	1.12 (0.75-1.66)
COPD	1.17 (0.84-1.63)	1.18 (0.62-2.24)
Alcoholism	NA	NA
Obesity	2.36 (0.33-16.89)	1.84 (0.25-13.6)
Tobacco use disorder	1.17 (0.83-1.64)	1.16 (0.60-2.24)

**P<0.001, [a]NTD for which the exchange rate is 1 US dollar: 31 NTD. NTD: New Taiwan dollars, ADT: Androgen deprivation therapy, HR: Hazard ratio, COPD: Chronic obstructive pulmonary disease, CI: Confidence interval, NA: Not applicable

protein levels, or infectious parameters, are not included in the NHIRD because it is an administrative database. As such, the degree of keratitis for any given patient could not be defined. Relatedly, the Gleason's scores and clinical stages of PCa, which are indicators of the severity of PCa, are also not available in the NHIRD, nor do the NHIRD data include the timing and type of ADT, which can be of assistance for subsequent risk analyses of PCa. Moreover, data regarding various risk factors for PCa, such as body mass index, dietary habits, and family history, are also not included in the NHIRD data. Finally, this study was a retrospective study. As such, additional prospective studies would be of value in further investigating the relation between ADT treatment and keratitis.

Conclusion

In conclusion, the results of this nationwide, large-scale, population-based study revealed that the risk of keratitis in PCa patients was decreased by treatment with ADT. This finding could serve as a reference for physicians in terms of understanding the advantages and disadvantages of ADT treatment. That said, additional studies could help to further clarify the relationship between ADT and keratitis.

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Conflicts of interest

There are no conflicts of interest.

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