

No increased risk of psoriasis in patients receiving androgen deprivation therapy for prostate cancer: a 17-year population-based study

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Objective: Androgen deprivation therapy (ADT) use in prostate cancer (PCa) patients has been reported to exacerbate the course of psoriasis. We aimed to assess the impact of ADT on the subsequent risk of psoriasis.

Methods: We utilized data from the National Health Insurance Research Database of Taiwan between 1996 and 2013. In total, 17,168 patients with PCa were identified; 5,141 ADT patients comprised the study group with 5,141 matched non-ADT controls. We used 1:1 propensity score-matched analysis. The demographic characteristics and comorbidities of the patients were analyzed; Cox proportional hazards regression was used to calculate the HRs for the risk of psoriasis.

Results: Eighty-nine (0.87%) patients with newly diagnosed psoriasis were identified. Compared with non-ADT patients, ADT patients had similar risk of subsequent psoriasis with an HR of 0.95 (95% CI 0.63–1.45; $P=0.816$). However, a higher risk of psoriasis was observed in angiotensin-converting enzyme inhibitors patients (adjusted HR 2.14, 95% CI 1.09–4.20; $P<0.05$).

Conclusion: ADT use did not increase risk of psoriasis in patients with PCa. Further studies are warranted to assess the clinical significance.

Keywords: prostate cancer, psoriasis, androgen deprivation therapy

Introduction

Prostate cancer (PCa) is one of the most prevalent cancers worldwide and is the cancer with the highest incidence in males in the USA, especially in elderly individuals.¹ In 2017, there was estimated to be 161,360 new cases of PCa in the USA, with 26,730 deaths. Androgen deprivation therapy (ADT) is a core component of a combined modality of advanced PCa treatment. Around 500,000 PCa patients have received ADT in the USA in 2000.² However, long-term deprivation of androgen may cause some systemic adverse effects, such as metabolic complications and cardiovascular disease.³⁻⁷ Alterations to the immune system in patients with ADT were also noted.^{8,9} Increased risk of rheumatoid arthritis in patients with ADT has also been observed.¹⁰ The possible role of ADT as a risk factor of systemic diseases remains an important health concern.

Psoriasis is an immune-mediated disorder with a prevalence rate ranging from 0.1% to 2.9% around the world.^{11,12} Psoriasis is characterized by the hyperproliferation of keratinocytes and immune-mediated inflammation, which are crucial in the pathophysiology.¹³ The peak incidence of psoriasis is in elderly people; the incidences of psoriasis increased after 30 years of age with a peak in patients aged over 70 years.¹¹ Psoriasis may be triggered by a number of exogenous or endogenous factors, such as

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stress, infection, or drugs.^{14,15} The impact of hormone therapy on psoriasis remains largely unclear.

It has previously been reported that a 57-year-old patient developed exacerbation of psoriasis after ADT use in Poland.¹⁶ Klil-Drori et al conducted a study on ADT and autoimmune diseases, which showed that ADT was not associated with psoriasis; however, they did not provide further explanation.¹⁷ To date, there have been only limited investigations regarding the possible association between ADT and psoriasis. A link between ADT and psoriasis may exist and needs to elucidate. Therefore, the aim of this large-scale, nationwide, population-based study was to investigate the association between ADT and the subsequent risk of psoriasis.

Methods

Data source and collection

We conducted a large cohort study using data from National Health Insurance Research Database (NHIRD) of Taiwan. The NHIRD is a database that includes data from the National Health Insurance (NHI) program. The NHI program is the unique medical insurance system of Taiwan, which covers 99.5% of Taiwan's 23 million residents.¹⁸ For this study, we used the Registry for Catastrophic Illness Patient Database (RCIPD), a subdatabase of the NHIRD. In Taiwan, patients diagnosed with PCa, or other major diseases, are entitled to a waiver for medical payment after receiving a catastrophic illness certification. All data in the NHIRD and RCIPD are anonymous and encrypted for research purposes.

Pathological information or imaging findings of PCa are needed for registration into the RCIPD.¹⁹ We used the ICD, 9th revision, Clinical Modification (ICD-9-CM) for diagnoses in NHIRD and RCIPD. This study was approved by the Institutional Review Board of the Tri-Service General Hospital (approval number: TSGHIRB NO B-104-21).

Study population

We selected patients with PCa using the RCIPD data between January 1996 and December 2013. The diagnoses of PCa were confirmed by both ICD-9-CM codes (ICD-9-CM: 185)²⁰ and inclusion in the RCIPD. In addition, all patients with PCa who were followed-up for at least 180 days after the initial diagnoses of PCa were then enrolled in this study (Figure 1). The exclusion criteria of this study included PCa diagnosis before 1 January 1997 (n=684); patients who were younger than 40 years at the time of diagnosis (n=144); patients who received a bilateral orchiectomy (n=1,065); history of

psoriasis (n=286); and less than 180 days follow-up after the initial diagnoses of PCa (n=1,306). The selected patients in the study population were then divided into two groups: ADT patients and non-ADT patients.

Study outcomes and covariates

The use of ADT includes the use of GnRH agonists (leuprolide, goserelin, triptorelin, and buserelin), oral antiandrogens (cyproterone acetate, bicalutamide, and flutamide), and estrogens (diethylstilbestrol). Patients newly diagnosed with psoriasis (ICD-9-CM: 696, 696.1, 696.8) by dermatologists or rheumatologists were identified in the NHIRD. The outcome was the incidence of newly diagnosed psoriasis in both ADT and non-ADT patients. The exact incidence of psoriasis among ADT patients was determined by only including those who received a psoriasis diagnosis after the initiation of ADT and at least 180 days after the PCa diagnosis. Meanwhile, the incidence of psoriasis among non-ADT patients was identified by only including those who received a psoriasis diagnosis at least 180 days after the PCa diagnosis and after the median time to ADT use in this study. Censoring was defined as death on the dates of diagnosis of psoriasis or until the end of the follow-up period on the 31 December 2013, whichever came first.

Covariates including age at diagnosis, alcohol abuse (ICD-9-CM: 303, 305), tobacco-use disorder (ICD-9-CM: 305.1, 649.01, V15.82), obesity (ICD-9-CM: 278), comorbidities, and related medication were according to ICD-9-CM codes and analyzed for both groups. The patients with PCa were classified into the following five age groups: <50 years, 50–60 years, 60–70 years, 70–80 years, and >80 years. Comorbidities that have been reported to be related to psoriasis in the previous literature, including streptococcal infection (ICD-9-CM: 034.0, 038.0, 041.0, 320.2, 482.3, V02.51, V02.52) and HIV disease (ICD-9-CM: 042) were recorded. Related medications including lithium, antihypertensive medications (beta-blockers), antimalarial medications (plaquenil, quinacrine, chloroquine), NSAIDs, and angiotensin-converting enzyme inhibitors (ACEI) were recorded.

Statistical analyses

The baseline characteristics of the patients were first analyzed using descriptive statistics. The two groups (ADT and non-ADT patients) were compared using the chi-squared test for categorical variables. The Kaplan–Meier (KM) curve was used to estimate the cumulative incidences of psoriasis for the two groups and the difference between the ADT

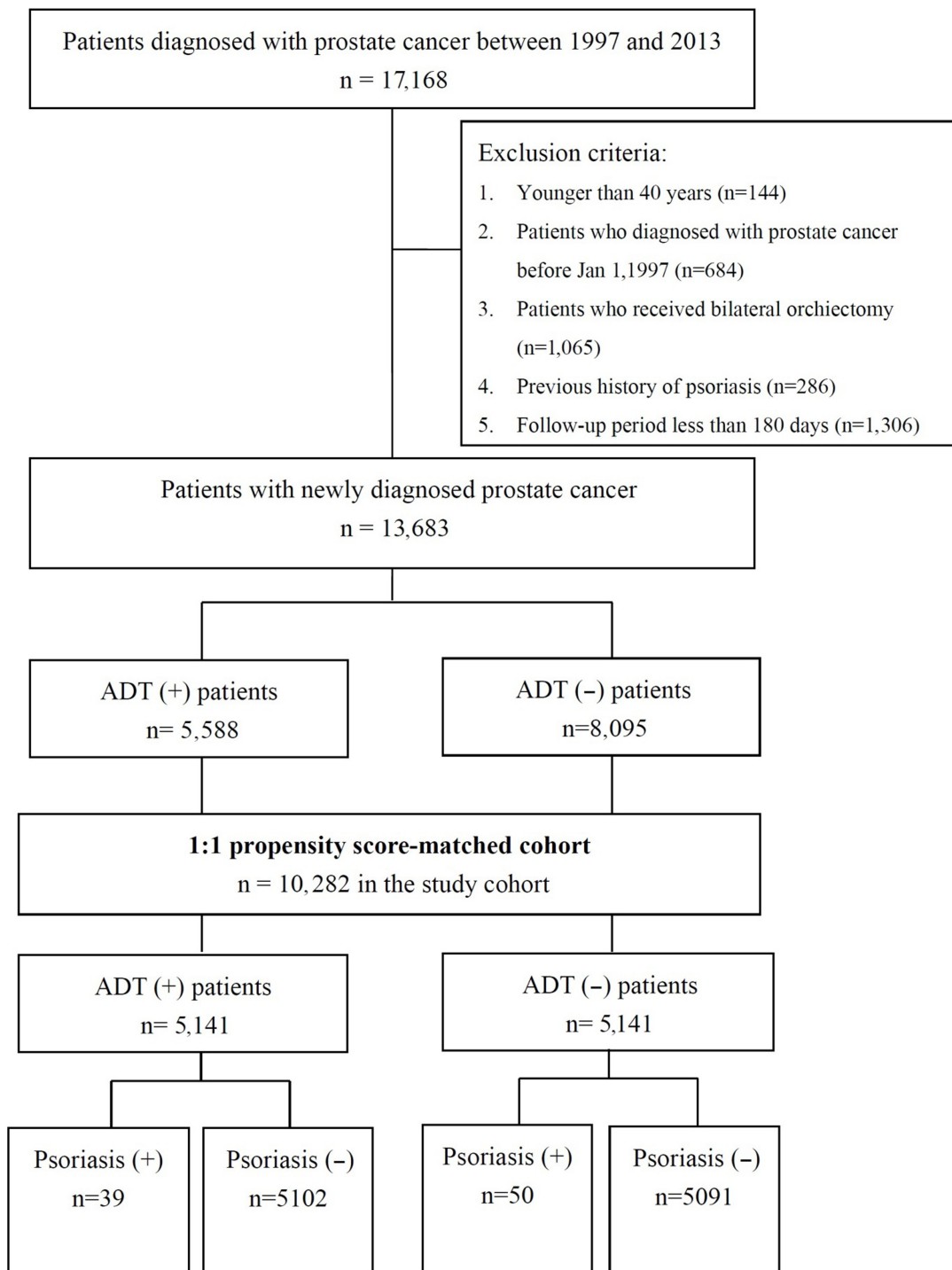


Figure 1 Study flowchart of cohort selection.
Abbreviation: ADT, androgen deprivation therapy.

group and non-ADT group was calculated with a log-rank test. HRs were calculated using propensity score-matched and multivariable-adjusted Cox proportional hazards models to test the association between ADT and psoriasis.

The proportional hazard assumption was tested using Schoenfeld residuals and a log-minus-log graph. The SPSS,

version 22.0 for Windows (IBM, Armonk, NY, USA), and the SAS, version 9.2 (SAS Institute, Cary, NC, USA), were used to perform all statistical analyses. The STATA, version 11.2 (StataCorp, College Station, TX, USA), was used to produce KM curve plots with number at risk. Comparison results with a $P < 0.05$ were considered statistically significant.

Results

In total, 17,168 patients with PCa were identified in this study. Of these, 13,683 PCa patients met all inclusion and exclusion criteria. There were 5,588 (32.5%) ADT patients and 8,095 non-ADT patients (Figure 1). The median time from PCa diagnosis to ADT use was 14.6 days. After 1:1 propensity score matching, 5,141 patients were selected in the ADT group and another 5,141 patients were identified as the non-ADT group. The demographic characteristics of the full cohort and the 1:1 propensity score-matched cohort are demonstrated in Table 1. ADT patients were significantly older (74.15 ± 8.34 vs 68.51 ± 10.45 years), had more tobacco-use disorder, and more NSAID medication use. There were no differences in age, comorbidities, and medication use in the propensity score-matched cohort.

Overall, 89 (0.87%) patients were newly diagnosed with psoriasis during a median follow-up of 3.29 years (IQR: 2.42–5.68 years): 39 (0.76%) in the ADT group and 50 (0.97%) in the non-ADT group (Figure 1). Cox proportional hazard regression showed that the crude HR was 0.95 (95% CI 0.66–1.45, $P=0.825$) for ADT use in patients with PCa compared with non-ADT patients (Table 2). After adjusting for age, comorbidities, and medication use, the adjusted HR of psoriasis was 0.95 (95% CI 0.63–1.45;

$P=0.816$) in ADT patients. Tobacco-use disorder, NSAID, and ACEI use significantly increased the crude HR of psoriasis, but after adjustment, only ACEI use was found to be a significant risk factor for psoriasis (adjusted HR 2.14, 95% CI 1.09–4.20; $P<0.05$).

The KM curve showed a similar risk of psoriasis in both the ADT and non-ADT patients (Figure 2). We did further analysis on age as a factor and no statistically significant difference was found between the two groups (Table 3). Furthermore, the duration of ADT use was also analyzed, and we found no obvious differences with statistical significance.

Discussion

We performed a large-scale cohort study to fully investigate the association between ADT and the risk of psoriasis. We enrolled 10,282 patients newly diagnosed with PCa in a propensity score-matched analysis with multivariable regression models adjusted for age, comorbidities, and medication use. Patients with ADT use had no increased risk of psoriasis compared with non-ADT patients. Long-term deprivation of androgen may have impact on systemic diseases; our study revealed that ADT use did not increase risk of psoriasis in patients with PCa.

Table 1 Demographic characteristics of prostate cancer patients according to use of ADT

Variables no (%)	Full cohort		P-value	1:1 propensity score-matched cohort		P-value
	ADT patients	Non-ADT patients		ADT patients	Non-ADT patients	
Total	5,588 (100)	8,095 (100)		5,141 (100)	5,141 (100)	
Age at diagnosis (years)			<0.001*			0.974
<50	34 (0.61)	342 (4.22)		34 (0.66)	33 (0.64)	
50–60	279 (4.99)	1,428 (17.64)		279 (5.43)	277 (5.39)	
60–70	1,297 (23.21)	2,609 (32.23)		1,295 (25.19)	1,315 (25.58)	
70–80	2,571 (46.01)	2,566 (31.70)		2,398 (46.64)	2,366 (46.02)	
≥80	1,407 (25.18)	1,150 (14.21)		1,135 (22.08)	1,150 (22.37)	
Mean age	74.15±8.34	68.51±10.45	<0.001*	73.58±8.39	73.51±8.30	0.698
Comorbidity						
Alcohol abuse	15 (0.19)	15 (0.19)	0.702	10 (0.19)	10 (0.19)	>0.999
Tobacco-use disorder	870 (15.57)	1,024 (12.65)	<0.001*	758 (14.74)	756 (14.71)	0.955
Obesity	13 (0.23)	15 (0.19)	0.546	12 (0.23)	10 (0.19)	0.669
HIV disease	0 (0.00)	1 (0.01)	0.406	0 (0.00)	0 (0.00)	>0.999
Streptococcal infections	15 (0.27)	10 (0.12)	0.051	14 (0.27)	7 (0.14)	0.126
Medication use						
Lithium	7 (0.13)	5 (0.06)	0.217	5 (0.10)	3 (0.06)	0.479
Antihypertensive drugs	542 (9.70)	712 (8.80)	0.071	468 (9.10)	446 (8.68)	0.445
NSAIDs	834 (14.92)	976 (12.06)	<0.001*	719 (13.99)	677 (13.17)	0.226
Antimalarial drugs	17 (0.30)	23 (0.28)	0.830	15 (0.29)	13 (0.25)	0.705
Angiotensin-converting enzyme inhibitors	282 (5.05)	369 (4.56)	0.187	242 (4.71)	257 (5.00)	0.491

Note: * $P<0.05$.

Abbreviation: ADT, androgen deprivation therapy.

Table 2 Independent risk factors of psoriasis among androgen deprivation therapy identified by Cox regression analysis

Psoriasis (n=89)	Crude HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
ADT use	0.95 (0.63–1.45)	0.825	0.95 (0.63–1.45)	0.816
Age	1.02 (0.99–1.04)	0.235	1.01 (0.98–1.04)	0.424
Comorbidity				
Alcohol abuse	NA	NA	NA	NA
Tobacco-use disorder	1.79 (1.07–3.01)	0.027*	1.62 (0.96–2.76)	0.073
Obesity	4.97 (0.70–35.70)	0.110	3.73 (0.51–27.52)	0.196
HIV disease	NA	NA	NA	NA
Streptococcal infections	NA	NA	NA	NA
Medication use				
Lithium	NA	NA	NA	NA
Antihypertensive drugs	1.54 (0.84–2.84)	0.161	1.31 (0.71–2.44)	0.392
NSAIDs	1.68 (1.01–2.78)	0.045*	1.54 (0.92–2.57)	0.100
Antimalarial drugs	NA	NA	NA	NA
Angiotensin-converting enzyme inhibitors	2.48 (1.28–4.78)	0.006*	2.14 (1.09–4.20)	0.026*

Note: * $p < 0.05$.

Abbreviations: ADT, androgen deprivation therapy; NA, not applicable.

Several diseases are associated with psoriasis, including cardiovascular disease, dyslipidemia, impaired glucose tolerance, depressive disorder, and inflammatory bowel disorders.²¹ An increased risk of cardiovascular disease in patients with ADT has been previously reported.^{3,4} Reduced testosterone levels following ADT has been proved to decrease insulin sensitivity and increase body fat.^{4,22} In addition, ADT use is indicated to carry a higher risk of anemia and depressive disorders.^{23,24} Increased risk of rheumatoid arthritis has been observed in patients with ADT.¹⁰ Thus, ADT may play a role in the pathogenesis of autoimmune diseases. We hypothesized that ADT may change the risk of psoriasis. However, no statistically significant differences of subsequent psoriasis were found in current study.

Ziółkowska et al reported on exacerbation of psoriasis after ADT treatment in a 57-year-old patient with PCa in

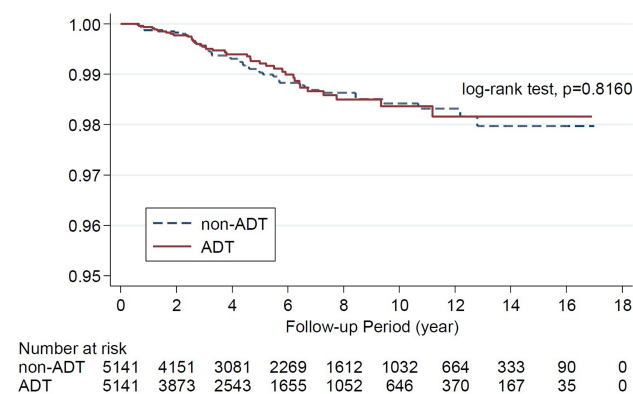


Figure 2 Kaplan–Meier curves according to ADT use for the cumulative probability of remaining psoriasis free in the propensity score-matched cohort.

Abbreviation: ADT, androgen deprivation therapy.

Poland.¹⁶ They supposed that alterations in the sex hormones may have triggered psoriasis.¹⁶ However, the underlying pathophysiologic mechanisms and the influences of ADT are complicated. In a study from the United Kingdom Clinical Practice Research Datalink, a decreased risk of ulcerative colitis was found in patients with ADT.²⁵ Psoriasis has been reported to be associated with ulcerative colitis.²⁶ Therefore, a possible link between ADT and psoriasis may exist but the complex interactions between ADT and autoimmune diseases are not fully understood. In addition, the typical characteristic of psoriasis is localized hyperproliferation of keratinocytes. T cell-mediated hyperproliferation (Th-1, Th-17, and Th-22 cells) and the overexpression of pro-inflammatory cytokines play important roles in the pathophysiology of psoriasis.¹³ Inflammatory cytokines are markedly elevated, and cytokine interactions have been reported to activate STAT1, STAT3, and NF- κ B in patients with psoriasis.²⁷ In addition, IL-6 and IL-17 have the ability to regulate keratinocyte proliferation in psoriatic lesions via STAT and NF- κ B pathway,²⁷ and androgen receptor-dependent, T cell-mediated immunomodulatory

Table 3 The risk of psoriasis and ADT by age

Age (years)	Adjusted HR (95% CI)	
	ADT patients	Non-ADT patients
<50	NA	1 (ref.)
50–60	NA	1 (ref.)
60–70	1.17 (0.52–2.61)	1 (ref.)
70–80	0.78 (0.42–1.46)	1 (ref.)
≥ 80	1.99 (0.77–5.17)	1 (ref.)

Abbreviations: ADT, androgen deprivation therapy; NA, not applicable; ref, reference.

activities were observed in patients with ADT.²⁸ ADT use reduced the Th-1 and Th-17 cell levels and also decreased the IL-6 level.²⁹ Therefore, there is evidence to suggest that the use of ADT in PCa patients may reduce the incidence of psoriasis.

Psoriasis is a complex disease, which can be provoked or exacerbated by many endogenous or exogenous factors. Drug exposure is an important triggering factor including lithium, antihypertensive drugs, NSAIDs, antimalarial drugs, and ACEIs.³⁰ This study demonstrated that antihypertensive drugs, NSAIDs, antimalarial drugs, and ACEIs resulted in an increased risk of psoriasis; however, only ACEIs use was identified as a significant independent risk factor for psoriasis (adjusted HR 2.14, 95% CI 1.09–4.20). ACEI-provoked psoriasis has been observed in previous reports.^{31,32} The peak age of psoriasis was 70 years and over in Taiwan.^{11,12,33}

The strengths of our study lie in the large population-based database, and more than 10,000 PCa patients enrolled in our analysis. In addition, the NHIRD covers ~99% of the 23 million residents of Taiwan, making the analysis broadly representative. However, this study is subject to several limitations. First, details of the laboratory tests are not available in the NHIRD, and so further comparison of laboratory data could not be performed. The levels of sex hormones and inflammatory markers were not investigated. Second, the definite influences of ADT on psoriasis could not be identified directly, even with our cohort design study. Furthermore, the immune system may be altered in PCa patients; therefore, it is valuable to compare the impact of ADT in patients without PCa.^{34,35} However, it is difficult to compare the effects of androgen deviation in non-PCa patients. Third, although the diagnoses were defined using the ICD-9 coding system, the diagnosis of PCa was validated by RCPID, which was confirmed by specialists after reviewing pathological information or imaging findings. Finally, this is a retrospective study, so further prospective studies are needed to fully evaluate the relationship between ADT use and the risk of psoriasis.

In conclusion, this large-scale nationwide population-based study found that ADT use in patients with PCa does not increase the risk of psoriasis. This finding could provide helpful information for physicians in assessing the risks and benefits of ADT use. Further studies are required to have a better understanding of the relationship between ADT and psoriasis.

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Disclosure

The authors report no conflicts of interest in this work.

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