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# Androgen deprivation therapy and the risk of tenosynovitis in prostate cancer patients

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## Abstract

**Objectives** Androgen deprivation therapy (ADT) use in prostate cancer (PCa) patients has been reported to have an association with rheumatoid arthritis. We aimed to assess the impact of ADT on the subsequent risk of tenosynovitis.

**Methods** Using data from the National Health Insurance Research Database of Taiwan between 2001 and 2013, 3309 patients with PCa were identified. Among them, 729 ADT patients comprised the study group with 729 matched non-ADT controls. We used a 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 hazard ratios (HR) for the risk of tenosynovitis.

**Results** There were 224 (15.3%) patients with newly diagnosed tenosynovitis. Compared with non-ADT patients, ADT patients had a lower risk of subsequent tenosynovitis with an adjusted HR of 0.38 [95% confidence interval (CI) 0.28–0.51; $P < 0.001$].

**Conclusions** ADT use apparently did not increase the risk of tenosynovitis in patients with PCa. Further studies are warranted to assess the clinical significance.

**Keywords** Prostate cancer · Tenosynovitis · Androgen deprivation therapy

## Abbreviations

| | |
|---|---|
| CI | Confidence interval |
| ADT | Androgen deprivation therapy |
| PCa | Prostate cancer |
| HR | Hazard ratio |
| NHIRD | National Health Insurance Research Database |
| NHI | National Health Insurance |
| CVA | Cerebral vascular accident |
| RA | Rheumatoid arthritis |
| PSA | Prostate-specific antigen |

## Introduction

Prostate cancer (PCa) is one of the most common cancers in males worldwide and affects global public health [1]. Androgen deprivation therapy (ADT) has been a standard treatment of advanced PCa for more than 70 years [2]. There

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were approximately 500,000 patients who received ADT for PCa in the United States [3].

Some adverse effects that accompany ADT include cardiovascular disease, metabolic syndrome, and osteoporosis [4, 5]. An alteration to the immune system during ADT use was also observed [6, 7].

According to some researches, a connection seems to exist between ADT and autoimmune diseases [8, 9]. Liu et al. conducted a retrospective study with 17,168 PCa patients, which found that ADT may reduce the risk of subsequent Graves' disease, psoriasis, and uveitis [8]. Klil-Drori et al. conducted a study on ADT and autoimmune diseases, which showed that ADT was associated with a decreased incidence of ulcerative colitis [10]. Yang et al. reported a 23% increased risk of rheumatoid arthritis (RA) using the SEER database with 44,785 patients receiving ADT for PCa in the United States [9].

Yang et al. suggested androgens have a predominantly suppressive effect on the immune system that further affect RA [9]. The effects of androgen have been linked with tendon or synovium in in vitro studies [11, 12]. However, there seems to be a lack of data in the in vivo studies connecting ADT and tendinopathies.

Tendinopathies negatively impact the quality of life of patients with ADT. To date, there have been only limited investigations regarding the possible association between ADT and tendinopathies. Therefore, the aim of this large-scale, nationwide, population-based study was to investigate the association between ADT and the subsequent risk of tenosynovitis.

## Methods

### Data source and collection

All of the data used in this study were collected from the National Health Insurance Research Database (NHIRD) of Taiwan, a database that includes data from the National Health Insurance (NHI) program which is an administrative database for the medical insurance system of Taiwan [13]. We conducted this retrospective cohort study utilizing the Longitudinal Health Insurance Database 2000 (LHID2000), which is a sub-dataset of the NHIRD [12]. The LHID2000 contains the health records for one million people randomly selected from among the 23 million residents included in the NHIRD in the year 2000. The diagnoses in NHIRD and LHID2000 were used following the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM), and all the data included in the database were anonymized. 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 newly diagnosed PCa using the LHID2000 from January 2001 to December 2009 (Fig. 1). The diagnoses of PCa were confirmed by ICD-9-CM codes (ICD-9-CM: 185) [14]. ADT included the use of GnRH agonists (leuprolide, goserelin, triptorelin, and buserelin), oral antiandrogens (cyproterone acetate, bicalutamide, flutamide, and nilutamide), and estrogens (diethylstilbestrol and estramustine) [15]. The exclusion criteria of the study cohort were: PCa diagnosis before Jan 1st, 2000; patients who were younger than 50 years old at the time of diagnosis ($n = 150$); those with a history of tenosynovitis ($n = 157$); and a history of RA ($n = 32$). The study subjects were the ADT group and the control group created through matching with the study group with regard to gender, age,

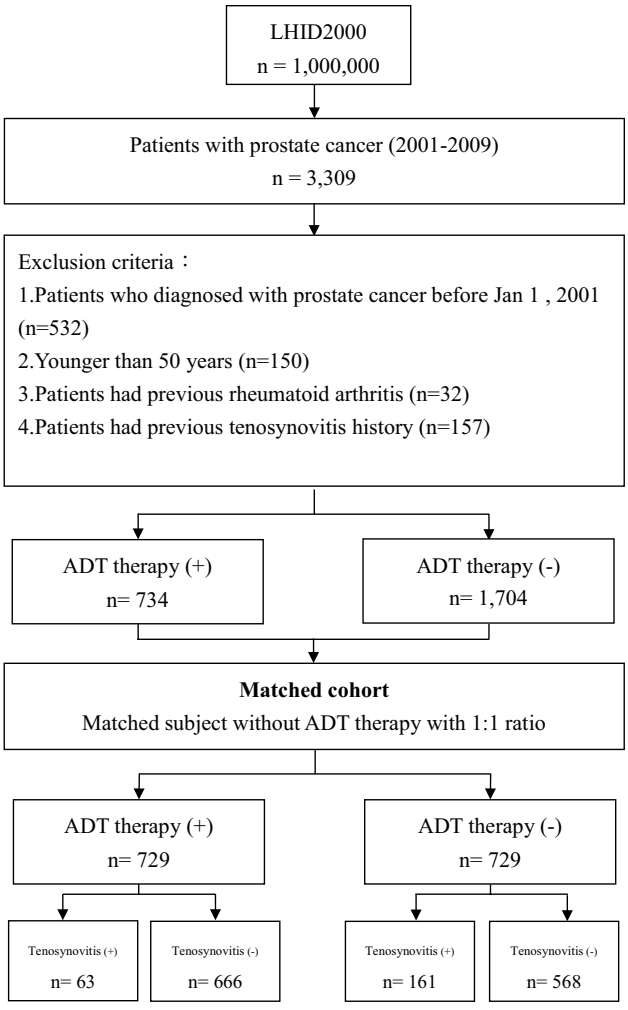


**Fig. 1** Study flowchart of cohort selection. ADT, androgen deprivation therapy

insured region, and urbanization at a ratio of one study group patient to one control group patient.

In the study group, each patient's first date of filling a prescription of ADT was assigned as the index date and considered as the starting point for the investigation of that patient, whereas for the control group, the year of the index date was matched to the year in which the control subjects had utilized a medical service.

### Study outcomes

The study examined patients newly diagnosed with tenosynovitis (ICD-9-CM: 727.0) who were required to have at least two outpatient visits to or one inpatient hospitalization for tenosynovitis by orthopedists, rehabilitation physicians, or rheumatologists. The outcome was the incidence of newly diagnosed tenosynovitis in both ADT and non-ADT patients.

There were 1458 subjects in this study, with 729 patients in the study group and 729 patients in the control group. Each subject was tracked for a 4-year period starting with their index date. The incidence of tenosynovitis was confirmed only after a patient had begun receiving ADT and after more than 30 days had passed since the index date. In this study, censoring was defined as death, the date of incidence of tenosynovitis, or the end of the follow-up period on December 31st, 2013, whichever came first.

### Covariates

Covariates including age at diagnosis, alcohol abuse, obesity, tobacco use disorder, and comorbidities were analyzed for both groups. The comorbidities in this study were diabetes mellitus (ICD-9-CM: 250), hypertension (ICD-9-CM: 401–405), hyperlipidemia (ICD-9-CM: 272.4), coronary heart disease (ICD-9-CM: 410–414), cerebral vascular accident (ICD-9-CM: 430–438), and chronic obstructive pulmonary disease (COPD) (ICD-9-CM: 491, 492, 496). The patients with PCa were classified into the following five age groups: 50–59 years, 60–69 years, 70–79 years, and ≥ 80 years. The patients were also categorized by income into four groups based on their monthly income levels in New Taiwan Dollars (NTD): those with an income of less than NTD 20,000; those with an income of NTD 20,000 to NTD 39,999; those with an income of NTD 40,000 to NTD 59,999; and those with an income of ≥ NTD 60,000. The patients were also categorized into four categories from highest to lowest based on their level of urbanization. The patients were also categorized according to their place of residence in Taiwan based on the following four regions: northern region, central region, southern region, and other regions (eastern and outlying islands).

### Statistical analysis

All statistical analyses were performed using the SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA), and data management was performed using Microsoft® SQL Server® 2008 software. The Chi square test was used for descriptive analyses concerning the distribution of demographic characteristics, income, geography, level of urbanization, and comorbidities between the scabies and non-scabies patients.

We used Cox proportional hazards regression models to estimate the effects of risk factors on the hazard ratios (HRs) accompanying 95% confidence intervals (CIs). All the models were adjusted for the covariates (age, income, geography, urbanization, and comorbidities). The level of statistical significance was set at a two-sided $P < 0.05$.

## Results

There were 3309 patients with PCa selected from the NHIRD from 2001 to 2009. After meeting all inclusion and exclusion criteria, there were 734 ADT patients and 1704 non-ADT patients. We used 1:1 propensity score matching, 729 patients were in the ADT group and 729 other patients were selected for the non-ADT group (Fig. 1). The mean follow-up period was $3.8 \pm 0.7$ years. The demographic characteristics of study subjects are shown in Table 1. Most of the patients belonged to the older than 70 years cohort, lower income group, and were residents of northern Taiwan. Compared to the non-ADT group, there were no differences in age and income. Furthermore, the ADT group had more tobacco use, and more COPD.

Table 2 shows the incidence of tenosynovitis among 1458 patients during the 4-year follow-up period. A total of 224 (0.87%) patients were newly diagnosed with tenosynovitis; 63 (8.6%) in the ADT group and 161 (22.1%) in the non-ADT group. The incidence rates of tenosynovitis between the ADT and non-ADT groups were significantly different. There was a crude HR with 0.36 (95% CI 0.27–0.48) by Cox regression analysis in ADT group compared with non-ADT group. The Kaplan–Meier curves showed patients with ADT had significantly lower risks of developing tenosynovitis than those without ADT (Fig. 2, $P < 0.001$).

After adjusting for age, income, urbanization, and comorbidities by Cox regression analysis, the adjusted HR of tenosynovitis was 0.38 (95% CI 0.28–0.51) in ADT patients. Hypertension (aHR 0.67; 95% CI 0.50–0.90) and CVA (aHR 0.51; 95% CI 0.34–0.76) also had a decreased risk of tenosynovitis (Table 3).

**Table 1** Demographic characteristics associated with the prostate cancer patients who received androgen deprivation therapy (ADT) and the control group

| Characteristics | ADT patients, *n* (%) | Non-ADT patients, *n* (%) | *P* value |
|---|---|---|---|
| No. of cases | 729 | 729 | |
| Gender | | | |
| Male | 729 (100.0%) | 729 (100.0%) | |
| Age | | | 0.771 |
| 50–59 | 28 (3.8%) | 31 (4.3%) | |
| 60–69 | 139 (19.1%) | 150 (20.6%) | |
| 70–79 | 343 (47.1%) | 332 (45.5%) | |
| ≥ 80 | 219 (30.0%) | 216 (29.6%) | |
| Insured region | | | 0.999 |
| Northern Taiwan | 369 (50.6%) | 470 (64.5%) | |
| Middle Taiwan | 115 (15.8%) | 94 (12.9%) | |
| Southern Taiwan | 215 (29.5%) | 149 (20.4%) | |
| Other (eastern Taiwan and outlying islands) | 30 (4.1%) | 16 (2.2%) | |
| Urbanization | | | < 0.05* |
| 1 (highest) | 330 (45.3%) | 359 (49.2%) | |
| 2 | 137 (18.8%) | 175 (24.0%) | |
| 3 | 176 (24.1%) | 133 (18.2%) | |
| 4 (lowest) | 86 (11.8%) | 62 (8.5%) | |
| Insured amount of NTD[a] | | | 0.571 |
| < 20,000 | 655 (89.8%) | 638 (87.5%) | |
| 20,000–39,999 | 30 (4.1%) | 36 (4.9%) | |
| 40,000–59,999 | 23 (3.2%) | 28 (3.8%) | |
| ≥ 60,000 | 21 (2.9%) | 27 (3.7%) | |
| Comorbidity disease | | | |
| Diabetes mellitus | 220 (30.2%) | 189 (25.9%) | 0.07 |
| Hypertension | 461 (63.2%) | 442 (60.6%) | 0.305 |
| Hyperlipidemia | 175 (24.0%) | 195 (26.7%) | 0.229 |
| Coronary heart disease | 251 (34.4%) | 241 (33.1%) | 0.580 |
| Cerebral vascular accident | 203 (27.8%) | 176 (24.1%) | 0.107 |
| COPD | 275 (37.7%) | 233 (32.0%) | < 0.05* |
| Alcoholism | 4 (0.5%) | 2 (0.3%) | 0.413 |
| Obesity | 61 (1.2%) | 112 (0.6%) | < 0.001* |
| Tobacco use disorder | 240 (32.9%) | 197 (27.0%) | < 0.05* |

ADT, androgen deprivation therapy; COPD, chronic obstructive pulmonary disease

*$P < 0.05$

[a]NTD refers to New Taiwan dollars, of which 1 US dollar = 30 TWD

**Table 2** Prostate cancer patients with and without ADT therapy as predictors of tenosynovitis identified by Cox regression

| | No. of cases | |
|---|---|---|
| | ADT patients $n = 729$ | Non-ADT patients $n = 729$ |
| With tenosynovitis | 63 (8.6%) | 161 (22.1%) |
| Without tenosynovitis | 666 (91.4%) | 568 (77.9%) |
| Crude HR | 0.36 (0.27 to 0.48)** | |

ADT, androgen deprivation therapy

**$P < 0.001$ for comparison between patients with two groups

## Discussion

This nationwide cohort study is the first study, which we know of, to investigate the association between ADT and the risk of tenosynovitis. We enrolled 3309 patients with PCa in a propensity score matched analysis with adjustment for age and comorbidities. We excluded patients who had history of RA. The study result revealed that ADT use did not increase the risk of tenosynovitis compared to the non-ADT group with a 4-year follow-up period.

Tenosynovitis is defined as the inflammation of a tendon and its synovial sheath. Tenosynovitis may be due to

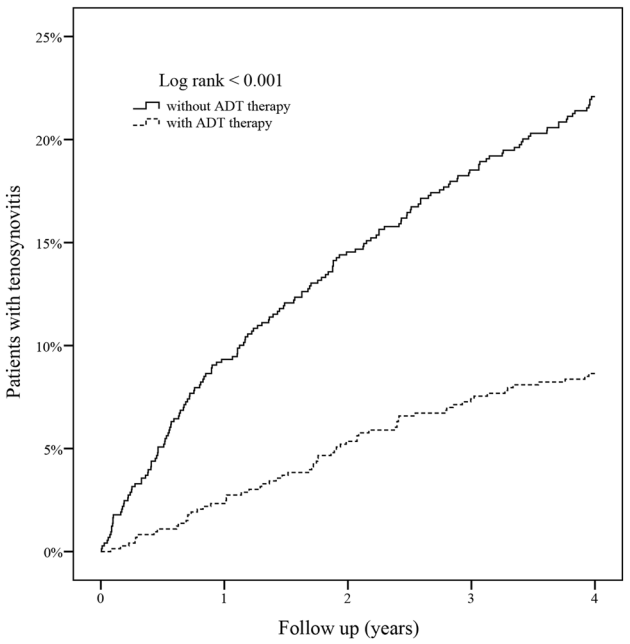


**Fig. 2** Kaplan–Meier curves according to androgen deprivation therapy use for the cumulative probability of remaining tenosynovitis free in the propensity score matched cohort. ADT, androgen deprivation therapy

tendon overuse or systemic diseases (i.e., RA), or infection [16, 17]. Tenosynovitis is common in middle-aged people. In this study, there was no difference in age in both ADT and non-ADT groups. In addition, the ADT group was slightly older than the non-ADT group, so they may be prone to reducing their activity or overusing their tendons. Patients with CVA with decreased risk of tenosynovitis as noted in this study may be so due to poor activity or little movement in their daily lives.

There were several studies reporting that androgen may be associated with tendinopathies. Dehghan et al. conducted an animal study with rats which revealed that testosterone reduced the expression of relaxin/insulin-like family peptide receptor 1 and 2 in the patellar tendon and lateral collateral ligament of the knee [18]. The relaxin may affect mesenchymal tissue such as tendons, acting on collagen content. Marqueti et al. reported that androgens reduced matrix metallopeptidase 2 (MMP2) expression in tendons that cause poor tissue remodeling [19]. Parssinen et al. reported that anabolic androgenic steroids reduce insulin-like growth factor-1 (IGF-1) mRNA levels in certain tendons that further decreased collagen synthesis and tendon healing [20]. ADT reduced the testosterone level and may reverse these negative effects on the tendons.

There are several existing risk factors of tenosynovitis such as female, being older than 40 years, repetitive movement of joints, history of inflammatory arthritis, and pregnancy. The fluctuating hormone level may induce inflammation. It has been reported the use of ADT for PCa decreased several inflammatory cytokines [21, 22]. In our study, majority of the ADT patients were older than 70 years who had decreased their daily movement with age which may decrease the risk of tenosynovitis. In addition,

**Table 3** Independent predictors of tenosynovitis identified by Cox regression analysis

| | Crude HR (95% CI) | Adjusted HR (95% CI) |
|---|---|---|
| Prostate cancer | | |
| Non-ADT | 1 | 1 |
| ADT | 0.36 (0.27–0.48)** | 0.38 (0.28–0.51)** |
| Age | | |
| 50–59 | 1 | 1 |
| 60–69 | 1.05 (0.55–2.00) | 1.12 (0.57–2.19) |
| 70–79 | 0.94 (0.51–1.74) | 1.21 (0.61–2.40) |
| ≥ 80 | 0.46 (0.23–0.89)* | 0.53 (0.25–1.10) |
| Insured region | | |
| Northern Taiwan | 1 | 1 |
| Middle Taiwan | 0.55 (0.35–0.89)† | 0.63 (0.39–1.02) |
| Southern Taiwan | 0.88 (0.64–1.21) | 1.15 (0.81–1.63) |
| Other (eastern Taiwan and outlying islands) | 1.33 (0.70–2.52) | 1.77 (0.90–3.47) |
| Urbanization | | |
| 1 (highest) | 1 | 1 |
| 2 | 0.64 (0.46–0.91)* | 0.63 (0.45–0.89)* |
| 3 | 0.87 (0.62–1.22) | 0.83 (0.58–1.19) |
| 4 (lowest) | 0.60 (0.35–1.05) | 0.54 (0.30–1.01) |
| Insured amount of NTD[a] | | |
| < 20,000 | 1 | 1 |
| 20,000–39,999 | 1.45 (0.84–2.49) | 1.07 (0.59–1.92) |
| 40,000–59,999 | 1.04 (0.51–2.11) | 0.78 (0.37–1.63) |
| ≥ 60,000 | 1.29 (0.66–2.52) | 0.91 (0.45–1.82) |
| Comorbidity disease | | |
| Diabetes mellitus | 0.65 (0.47–0.89)* | 0.76 (0.54–1.07) |
| Hypertension | 0.57 (0.44–0.74)** | 0.67 (0.50–0.90)* |
| Hyperlipidemia | 1.06 (0.79–1.42) | 1.18 (0.85–1.62) |
| Coronary heart disease | 0.83 (0.63–1.11) | 1.03 (0.76–1.40) |
| Cerebral vascular accident | 0.41 (0.28–0.60)** | 0.51 (0.34–0.76)* |
| COPD | 0.62 (0.46–0.84)* | 0.95 (0.59–1.54) |
| Alcoholism | 0.05 (0–326.19) | NA |
| Obesity | 0.05 (0–754.30) | NA |
| Tobacco use disorder | 0.59 (0.43–0.81)* | 0.77 (0.46–1.30) |

ADT, androgen deprivation therapy; HR, hazard ratio; COPD, chronic obstructive pulmonary disease; CI, confidence interval; NA, not applicable

*$P < 0.05$, **$P < 0.001$

[a]NTD refers to New Taiwan dollars, of which 1 US dollar = 30 TWD

we excluded patients who had a previous history of RA to ensure the accuracy of study outcome, i.e., tenosynovitis.

Yang et al. reported a 23% increased risk of rheumatoid arthritis (RA) in 44,785 patients who received ADT for PCa from 1994 to 2006 [9]. They claimed that androgen-mediated thymic regeneration may increase the risk of RA. RA is an autoimmune-related chronic inflammatory disorder in joints. The aim of our study is to observe the association between ADT and tenosynovitis except RA. We observed that ADT did not increase the risk of tenosynovitis. The possible mechanism may be related to some inflammatory response. Recent studies have also found that several inflammatory cytokines decrease after ADT use in PCa patients, including IL-1β, IL-2, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ [21, 22]. Reduction of these inflammatory cytokines after ADT use may contribute to the suppression of inflammation such as tenosynovitis. However, Sutherland et al. reported that mice and men receiving androgen suppression experience thymic regeneration with an increase in circulating T cells which may elevate immune response [23]. Further studies are warranted to find the mechanism between ADT and inflammation response.

The strength of our study is a large cohort study utilizing a longitudinal nationwide database. However, our study had some limitations. First, details of the laboratory tests are not available in the NHIRD, such as PSA, C-reactive protein (CRP) levels, or infectious parameters as the NHIRD is an administrative database. Therefore, it is unable to define the degree of tenosynovitis. Other confounding factors such as body weight, body mass index, occupation of heavy work, habits of daily life, history of repetitive strain injury are not available in the NHIRD and these unmeasured confounders may be risk factors of tenosynovitis. Second, the clinical stage and Gleason's scores of PCa, which help to define severity of PCa, are also not included in the NHIRD. Moreover, risk factors of prostate cancer, such as family history, body mass index, and dietary habits, are not available in the NHIRD. Finally, this is a retrospective study and a retrospective analysis in such a study design may not be able to clearly figure out this issue. Further prospective studies are warranted to further investigate the relationship between ADT and tenosynovitis.

In conclusion, this large-scale nationwide population-based study found that ADT use in patients with PCa does not increase the risk of tenosynovitis. This finding could provide information for physicians in understanding the benefits and drawbacks of ADT use. Further studies are warranted to fully discover the relationship between ADT and tenosynovitis.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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