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ORIGINAL ARTICLE

Digoxin lowers the incidence of prostate cancer: A nationwide population-based study

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Abstract

Background: In vitro studies have confirmed that cardiac glycosides can induce apoptosis in both hormone-dependent and -independent prostate cancer (PCa) cell lines. The aim of this study was to investigate the incidence of PCa among patients treated with and without digoxin using a nationwide population-based database in Taiwan.

Methods: We retrieved data of men aged 30 years or older who were newly diagnosed with heart failure between January 1998 and December 2003 from the National Health Insurance program database in Taiwan. We divided the patients into digoxin users and non-digoxin users. Kaplan-Meier curves and Cox proportional hazard analysis were used to examine the risk of subsequent PCa between the digoxin and non-digoxin groups.

Results: The mean ± SD follow-up (years) periods in the digoxin and non-digoxin groups were 8.6 ± 1.78 and 8.3 ± 1.75, respectively. The cumulative incidence of PCa during the follow-up period was 3.5% (147/4233) in the non-digoxin group compared with 3.0% (65/2154) in the digoxin group. The log-rank test revealed that the digoxin group had a similar incidence of PCa to the non-digoxin group ($p = 0.18$). After adjusting for age, benign prostatic hyperplasia, and comorbidities, Cox proportional hazard regression analysis showed that digoxin was associated with a significantly decreased risk of developing PCa (hazard ratio, 0.74; 95% CI, 0.548-0.993; $p = 0.045$). Moreover, logistic regression analysis showed that the risk of PCa decreased with a longer duration of digoxin use during the study period compared to those who had never used digoxin ($p = 0.043$).

Conclusion: The cardiac glycoside digoxin had significant effects on reducing the incidence of PCa in a time-dependent manner. Our findings may imply the potential application of cardiac glycosides in the prevention and management of PCa.

Keywords: Digoxin; Heart failure; Prostate cancer

1. INTRODUCTION

Prostate cancer (PCa) has long been the most common male cancer in Europe and North America.[1,2] Although the incidence of PCa in Asia is relatively lower, it has rapidly increased over the last two decades, including in Taiwan.[1] PCa is an androgen-dependent tumor, and deprivation of androgens may suppress its development and even reduce its severity. Clinically localized PCa is mainly treated with surgery or radiation therapy and minimally invasive alternative treatments. Even though these treatment modalities can result in good cancer control compared to other solid malignancies, these treatments also cause considerable side effect and reduce the quality of life in many patients. Moreover, the tumor will eventually progress to a status refractory to androgen-deprivation in one third of cases, known as castration-resistant prostate cancer (CRPC), which is the lethal form of PCa. Despite the development of newer life-prolonging agents such as chemotherapy and hormonal therapy, the prognosis of CRPC remains poor. Therefore, newer agents, and especially those with a good tolerance profile are urgently needed to treat and prevent CRPC.

In our previous study, we demonstrated that cardiac glycosides such as digoxin, a widely used drug for patients with advanced heart failure, can suppress cell growth or even cause apoptosis in both androgen-dependent and -independent PCa cell lines.[3] The mechanism may be through Na+/K+ ATPase modulation changing the intracellular concentration of calcium, thereby inducing apoptosis. This action was not related to androgens, and the tumoricidal effects of the cardiac glycosides were both time- and dose-dependent. These findings suggested the potential therapeutic use of cardiac glycosides for PCa.

Cardiac glycosides have also been shown to inhibit PCa growth in vitro[3,4] and in vivo[5] by other investigators, although no randomized control trials have yet been conducted. Therefore, observational population studies to validate the preclinical studies are critical for the further development of cardiac glycosides as novel PCa treatment. However, previous observational studies have reported conflicting results,[6,7] and no previous study has been conducted in an Asian population.

In this study, we investigated the effects of digoxin on the incidence of PCa using a proprietary secondary database of patients

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enrolled in the National Health Insurance (NHI) program in Taiwan. The purpose of this study was to test the hypothesis that using cardiac glycosides can lower the incidence of PCa.

2. METHODS

2.1. Data source

The Department of Health in Taiwan launched the NHI program on March 1, 1995. By the end of 1996, more than 96% of the Taiwanese population was receiving nearly all forms of healthcare services under the program. From the inception of the program, the Bureau of NHI prospectively collected patient data, including registration files and original claims for reimbursement. Medical charts and claims are validated by the Bureau to ensure that diagnosis coding is accurate. For research purposes, the National Health Insurance Research Database (NHIRD) is derived from these data and is maintained by the National Health Research Institutes. The official longitudinal dataset Longitudinal Health Insurance Database 2005 (LHID 2005) contains a random sample of one million beneficiaries in the year 2005. This dataset represents all beneficiaries, and there are no statistically significant differences between the LHID 2005 and all enrollees according to reports from the National Health Research Institutes. In the NHIRD, diagnoses are coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). We used the LHID 2005 in this study, and all personal identifiers were encrypted. In addition, this study was approved by the Ethics Committee of Taipei Veterans General Hospital (Institutional Review Board 2016-02-002CC).

2.2. Study population

Figure 1 provides a summary of the recruitment process. We enrolled male subjects who had been newly diagnosed with heart failure between 1998 and 2003. The inclusion criteria were male patients aged ≥ 30 years in 1998 who had been diagnosed with heart failure (ICD-9-CM code 428). The exclusion criteria were the presence of heart failure or PCa (ICD-9-CM code 185) or the use of digoxin prior to inclusion in the study. The study endpoint was developing PCa or the last visit before December 31, 2009. The date and diagnosis of PCa were confirmed according to either the issuance of a catastrophic illness certificate for cancer (most cases), the date of prostatectomy or orchiectomy, or the use of gonadotropin-releasing hormone agonists or anti-androgens.

The patients who fulfilled the eligibility criteria were further stratified into two groups based on the use of digoxin between January 1, 1998, and December 31, 2003, as the digoxin group and the non-digoxin group. Outpatient claims data were reviewed to identify the date and duration of digoxin prescriptions. The digoxin group was defined as those who used digoxin and diagnosed with PCa after the use of digoxin. The non-digoxin group was defined as those who did not use digoxin or those who were diagnosed with PCa before the use of digoxin. We hypothesized the time of exposure to digoxin should be adequate to affect the development of PCa. Therefore, patients who were diagnosed with PCa within 6 months after the first dose of digoxin (digoxin exposure less than 6 months) were excluded. We also excluded patients diagnosed with PCa before the development of heart failure.

The following important confounding factors were considered in multivariate analysis: benign prostatic hyperplasia (ICD-9-CM code 600.0), hypertension (ICD-9-CM codes 400-405), diabetes mellitus (ICD-9-CM code 250), cirrhosis (ICD-9-CM codes 571.2 and 571.5-571.6), chronic obstructive pulmonary disease (ICD-9-CM code 493.2), chronic kidney disease (ICD-9-CM codes 580-587), and hyperthyroidism (ICD-9-CM code 242).

2.3. Statistical analysis

The chi-square test and independent *t* test were used to test differences between the digoxin and non-digoxin groups in discrete and continuous variables, respectively. Kaplan-Meier estimates of the cumulative risk of PCa were plotted after being stratified by digoxin use. The PCa hazard ratios (HRs) of the digoxin and non-digoxin groups were analyzed using a Cox proportional hazards model, adjusted by age, and comorbidities. A logistic

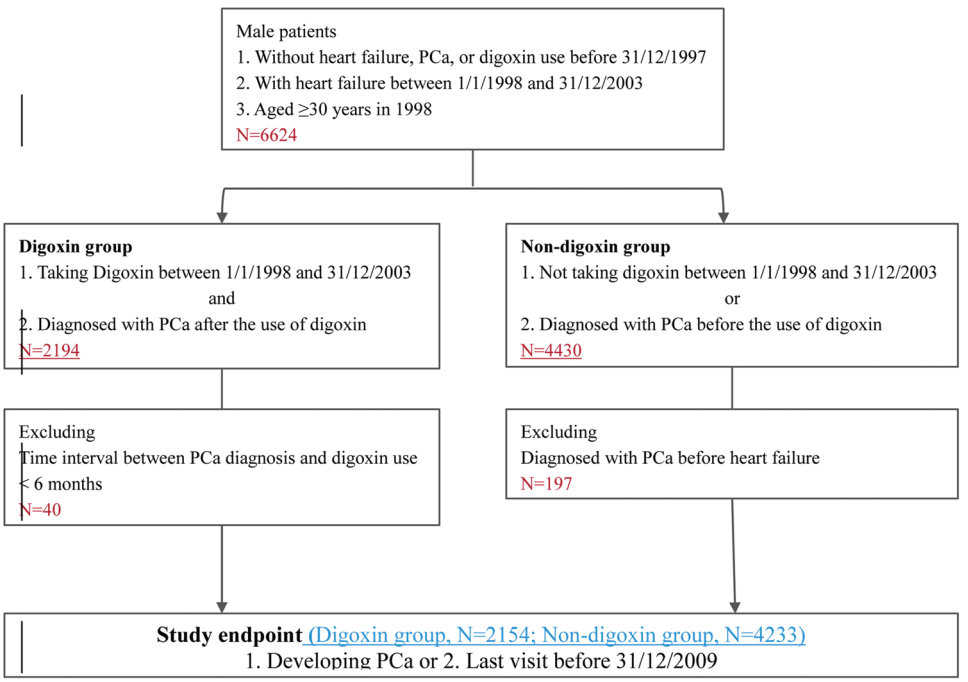

Fig. 1 Flowchart of the patient recruitment. PCa = prostate cancer.

regression model was used to assess time-dependent effects of digoxin. Data were analyzed using PASW Statistics software version 19 (SPSS Inc., Chicago, IL, USA). A p value < 0.05 (two-tailed) was considered to be statistically significant.

3. RESULTS

The demographic and clinical characteristics of both groups are shown in Table 1. There were 2154 patients in the digoxin group and 4233 patients in the non-digoxin group. The mean ± SD follow-up (years) periods in the digoxin and non-digoxin groups were 8.6 ± 1.78 and 8.3 ± 1.75, respectively. The digoxin group were significantly older than the non-digoxin group (64.5 vs 62.1 years; p < 0.001). The prevalence rates of cirrhosis, chronic obstructive pulmonary disease, chronic kidney disease, and hypertension were significantly higher in the digoxin group compared with the non-digoxin group.

The cumulative incidence of PCa during the follow-up period was 3.5% (147/4233) in the non-digoxin group compared with 3.0% (65/2154) in the digoxin group. The Kaplan-Meier curves and estimates of the cumulative incidence of PCa are shown in Figure 2. The log-rank test revealed that the digoxin group had a similar incidence of PCa to the non-digoxin group (p = 0.18).

The HRs for PCa between the digoxin and non-digoxin group are presented in Table 2. After adjusting for benign prostatic hyperplasia, hypertension, diabetes mellitus, cirrhosis, chronic obstructive pulmonary disease, chronic kidney disease, and hyperthyroidism, the results of Cox proportional hazard regression analysis showed that digoxin was associated with a significantly decreased risk of developing PCa (HR, 0.74; 95% CI, 0.548-0.993; p = 0.045).

Furthermore, we used a logistic regression model to examine the dose-dependent effect of digoxin, and the results showed that the risk of PCa decreased with a longer duration of digoxin use during the study period compared to those who had never used digoxin (p = 0.043).

4. DISCUSSION

In this nationwide population-based observational study, we found that the use of digoxin was associated with a lower risk of developing PCa in patients with heart failure. Furthermore, the difference was bigger with a longer exposure to digoxin. That is, a longer duration of digoxin use was associated with a lower risk of developing PCa.

Cardiac glycosides have been shown to be cytotoxic in a range of cancer cell lines,[8,9] among which PCa is one of the most studied types of cancer. Many studies have investigated the anti-cancer mechanism of cardiac glycosides. Our group and others have found that cardiac glycosides induce cell apoptosis in both androgen-dependent and -independent PCa cell lines, possibly by altering the influx of intracellular calcium.[3,4] Other potential mechanisms include Na^+/K^+ ATPase pump inhibition,[10] inhibition of mitogen-activated protein kinase and p53 synthesis,[11] inhibition of hypoxia-inducible factor 1, alpha subunit,[12] and more recently, activation of anti-cancer immunity.[13,14]

Platz et al[7] used a laboratory-epidemiology two-staged approach to screen available nonchemotherapy formulae and discovered that cardiac glycosides had a potent inhibitory effect on PCa. They also used a cohort database and found that using cardiac glycosides was negatively associated with the incidence rates of overall and the lethal form of PCa. In their prospective cohort study, the authors analyzed the effects of the use of digoxin after adjusting for many covariates including body mass index, ethnicity, family history, smoking, physical activity, and daily intake. However, there were still some limitation to their study. First, the use of digoxin before cohort inclusion was not recorded. Second, the density of transrectal ultrasound-guided prostate biopsy was not addressed, and the protective effect of digoxin may have been a result of the underuse of transrectal ultrasound-guided prostate biopsy. Third, the number of patients treated with digoxin was relatively small.

Kaapu et al[15] conducted a retrospective cohort study and found no association between the overall risk of PCa and the use of digoxin (HR, 1.01; 95% CI, 0.87-1.16). Similar results were obtained for high-grade (Gleason 7-10) and metastatic PCa. Nevertheless, the risk estimates for high-grade PCa tended to decrease with the duration of digoxin use (p for trend = 0.052), suggesting that long-term usage of the drug may reduce the risk (HR, 0.71; 95% CI, 0.49-1.03).

Flahavan et al[16] performed a retrospective cohort study to examine associations between digoxin exposure and mortality in men with PCa. They reported that digoxin exposure was associated with a nonsignificant decrease in PCa mortality.

Some important confounding factors should be considered in this study, including age, cardiac and related factors, and those related to prostate hyperplasia. The incidence of PCa strongly increases with age. Based on US Surveillance from 2000 to 2008, the incidence rate of PCa is 9.2/100,000 for men aged 40-44 years. That rate increases sharply to 984.8/100,000 in men aged 70-74 years.[17] Associations between hypertension/other underlying cardiac issues and metabolic syndrome have been reported. In this study, the incidence rates of comorbid conditions such as obesity, hypertension, hyperlipidemia, and diabetes were higher in the digoxin group. The relationship between metabolic syndrome and PCa is well known, and therefore it is possible that a cohort of regular digoxin users are prone to a higher risk of PCa, as shown in our results. Patients with a diagnosis of heart failure are more likely to have PCa than those without a diagnosis of heart failure (unpublished data). The large-scale epidemiological study to assess the risk of a man developing PCa following the diagnosis of benign prostatic hyperplasia was reported by Ørsted et al[18] and revealed that benign prostatic hyperplasia was associated with a 2- to -3-fold increased risk of the development of PCa along with a 2- to 8-fold increased risk of mortality. In this study, we also found that the diagnosis of benign prostatic hyperplasia was a risk factor for the development of PCa.

The present study is the largest cohort study to examine the effect of digoxin in reducing the risk of developing PCa in Asian patients with heart failure. Furthermore, we adjusted for several confounding factors which may have masked the effect of digoxin to explore the independent role of digoxin on PCa. Nevertheless, there are several limitations to this study. First, the NHIRD only includes data on Taiwanese patients, and

Table 1

Demographic and clinical characteristics of study subjects

Characteristic	Digoxin (n = 2154)	Non-digoxin (n = 4233)	p
Age, y (SD)	64.5 (12.06)	62.1 (12.68)	< 0.001
Follow-up, y (SD)	8.6 (1.78)	8.3 (1.75)	< 0.001
Comorbidities, n (%)			
BPH	927 (43)	1711 (40.4)	0.066
Diabetes mellitus	1105 (51.3)	2129 (50.3)	0.448
Cirrhosis	248 (11.5)	391 (9.2)	0.004
COPD	1587 (73.7)	2801 (66.2)	< 0.001
CKD	1016 (47.2)	1711 (40.4)	< 0.001
Hypertension	1969 (91.4)	3722 (87.9)	< 0.001
Hyperthyroidism	82 (3.8)	160 (3.8)	0.957

BPH = benign prostatic hyperplasia; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease.

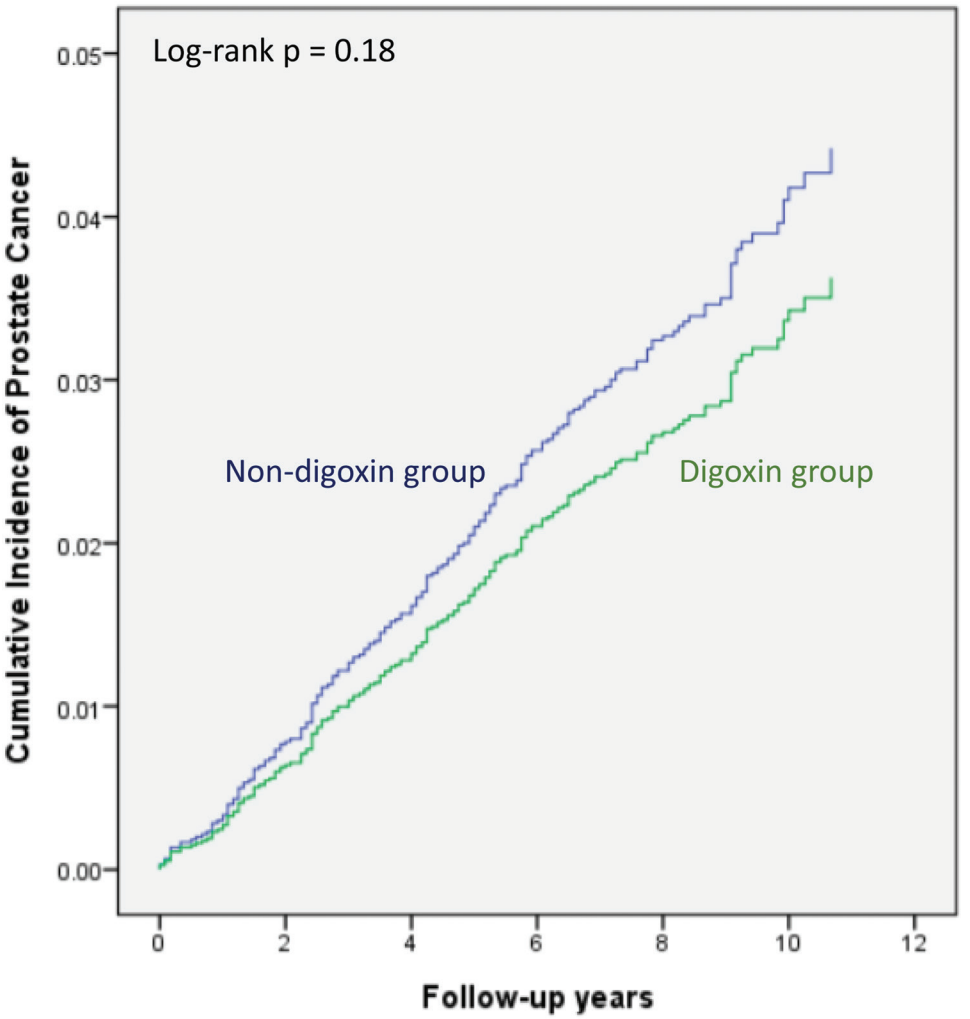

Fig. 2 Cumulative incidence of prostate cancer.

Table 2

Risk factors for prostate cancer in study subjects

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age	1.05 (1.038-1.066)	< 0.001	1.04 (1.022-1.053)	< 0.001
Digoxin	0.82 (0.608-1.098)	0.180	0.74 (0.548-0.993)	0.045
Comorbidities				
BPH	6.33 (4.470-8.963)	< 0.001	5.15 (3.605-7.369)	< 0.001
DM	1.09 (0.834-1.434)	0.516	1.02 (0.770-1.342)	0.908
Cirrhosis	0.85 (0.523-1.375)	0.504	0.84 (0.518-1.371)	0.491
COPD	1.76 (1.259-2.461)	0.001	1.03 (0.731-1.459)	0.857
CKD	1.22 (0.929-1.598)	0.153	0.99 (0.746-1.300)	0.913
Hypertension	1.48 (0.890-2.467)	0.130	0.89 (0.530-1.503)	0.669
Hyperthyroidism	1.04 (0.511-2.101)	0.920	1.21 (0.595-2.461)	0.598

BPH = benign prostatic hyperplasia; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; HR = hazard ratio.

Taiwanese and Chinese are known to have a lower incidence of PCa compared to African Americans or Caucasians. Therefore, the effects of cardiac glycosides seen in this study need to be examined in cohorts of other ethnicities using other population-based databases. Second, detailed data on cancer such as prostate-specific antigen levels, cancer staging, Gleason grading, treatment responses, mortality, digoxin dosages, personal and family histories, and detailed look at the symptoms/signs are not available in the NHIRD, and therefore it was not possible to show the effects of cardiac glycosides on the incidence of PCa stratified by risk groups. Further clinical studies are needed to investigate the effect of digoxin on the incidence of different risk groups using clinical information from hospital-based databases. Third, the study was limited to a certain age range, and patients diagnosed with PCa who were younger than 30 years or older than 80 years were not included. However, our cohort included more than 99% of all registered cases with PCa. Fourth, the users of digoxin in this study were all prescribed with cardiac glycoside treatment due to heart failure, and we did not have data showing the effects of cardiac glycosides on the incidence of PCa in patients without underlying cardiac conditions. Randomized clinical trials on the use of cardiac glycosides in patients without underlying cardiac conditions may be warranted if the ethical concerns are justified. Sixth, the present data do not prove the role of digoxin in treating confirmed PCa. A randomized controlled trial is necessary to answer this question.

In conclusion, using the NHIRD, we confirmed that the use of digoxin in the patients with heart failure had a significant effect in reducing the incidence of PCa in a time-dependent manner.

Our findings may have implication of the potential use of cardiac glycosides in the prevention of PCa or in the management of CRPC.

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