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ORIGINAL ARTICLE

Prostate Cancer

Antiarrhythmic drug usage and prostate cancer: a population-based cohort study

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Even though the relationship between antiarrhythmic drug usage and subsequent prostate cancer (PCa) risk has recently been highlighted, relevant findings in the previous literature are still inconsistent. In addition, very few studies have attempted to investigate the association between sodium channel blockers or potassium channel blockers for arrhythmia and the subsequent PCa risk. Therefore, this cohort study aimed to find the relationship between antiarrhythmic drug usage and the subsequent PCa risk using a population-based dataset. The data used in this study were derived from the Longitudinal Health Insurance Database 2005, Taiwan, China. We respectively identified 9988 sodium channel blocker users, 3663 potassium channel blocker users, 65 966 beta-blocker users, 23 366 calcium channel blockers users, and 7031 digoxin users as the study cohorts. The matched comparison cohorts (one comparison subject for each antiarrhythmic drug user) were selected from the same dataset. Each patient was tracked for a 5-year period to define those who were subsequently diagnosed with PCa. After adjusting for sociodemographic characteristics, comorbidities, and age, Cox proportional hazard regressions found that the hazard ratio (HR) of subsequent PCa for sodium channel blocker users was 1.12 (95% confidence interval [CI]: 0.84–1.50), for potassium channel blocker users was 0.89 (95% CI: 0.59–1.34), for beta-blocker users was 1.08 (95% CI: 0.96–1.22), for calcium channel blocker users was 1.14 (95% CI: 0.95–1.36), and for digoxin users was 0.89 (95% CI: 0.67–1.18), compared to their matched nonusers. We concluded that there were no statistical associations between different types of antiarrhythmic drug usage and subsequent PCa risk.

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INTRODUCTION

Prostate cancer (PCa) is a prevalent urological malignancy in elderly male populations.[1] Even though this disease affected over 899 000 patients and contributed to 258 000 deaths in 2008 worldwide, the actual pathophysiology and risk factors of PCa remain unclear.[2,3] Therefore, finding protective factors, exploring risk factors, and further developing prevention strategies for PCa are recognized as important public health issues.

To date, increasing experimental evidence has supported that channels for potassium, sodium, and calcium are frequently overexpressed in PCa cells, and these ion channels are thought to regulate PCa cell proliferation and metastasis.[4–10] In addition, previous studies reported that cardiac glycosides which inhibit Na^+/K^+ ATPase and contribute to elevated intracellular calcium concentrations can affect prostate-specific antigen (PSA) levels and suppress tumor growth.[11,12] Thus, many studies supposed that ion channel blockers and cardiac glycosides, which were developed for other indications, including arrhythmia and epilepsy, could potentially be novel therapeutic strategies against PCa.[13,14]

Recently, as many of the elderly are regularly using antiarrhythmic drugs (including sodium channel blockers, potassium channel blockers, beta-blockers, calcium channel blockers, and digoxin), the relationship between antiarrhythmic drug usage and the subsequent PCa risk has been highlighted. Nevertheless, very few studies have investigated the subsequent PCa risk in sodium channel blocker users or potassium channel blocker users.[15,16] Most of the literature only attempted to find the PCa risk in beta-blocker users, calcium channel blocker users, and digoxin users. For instance, some prior studies showed that beta-blocker users, calcium channel blocker users, and digoxin users might have a decreased risk of PCa.[17–20] Other studies observed that the use of beta-blockers or calcium channel blockers was not associated with a PCa risk.[15,21–24] Conversely, recent meta-analyses presented increased risks of PCa in beta-blocker users and calcium channel blocker users.[25] Accordingly, relevant findings in previous studies are still inconclusive today. Consequently, this retrospective cohort study aimed to explore the associations between the use of different types of antiarrhythmic drugs and the subsequent PCa risk using a large population-based dataset in Taiwan, China.

PATIENTS AND METHODS

Database

This retrospective cohort study used medical records derived from the Longitudinal Health Insurance Database 2005 (LHID2005,

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Taiwan, China). This database consists of claims data for 1 million individuals randomly selected from the National Health Insurance (NHI, Taiwan, China) program in 2005 (n = 25.68 million). The NHI (Taiwan, China) program was founded in 1995. It provides comprehensive and affordable medical services for over 99% of citizens from Taiwan, China. The LHID2005 consists of de-identified secondary data released to the public for academic purposes and was exempted from full review following consultation with the Taipei Medical University Institutional Review Board (TMU-JIRB 201612057), Taiwan, China.

Study sample

This population-based cohort study identified patients who received a prescription of antiarrhythmic drugs during an ambulatory care visit from 1 January 2001 to 31 December 2008. Selected patients were categorized as having been exposed to sodium channel blockers (disopyramide, quinidine, flecainide, lidocaine, procainamide, propafenone, phenytoin, mexiletine, and prajmaline), potassium channel blockers (amiodarone, dronedarone, and sotalol), beta-blockers (atenolol, bisoprolol, carvedilol, esmolol, metoprolol, propranolol, and timolol), calcium channel blockers (diltiazem and verapamil), or digoxin. The date of the first ambulatory care visit for receiving each antiarrhythmic drug was identified as the index date for each study participant. We then excluded female patients, to limit the study to the male population. Patients aged <40 years were also excluded from this study, because very few patients receive antiarrhythmic drugs in that age group. We further excluded those patients who had been diagnosed with PCa (ICD-9-CM code 185) prior to the index date. Finally, 9988 sodium channel blocker users, 3663 potassium channel blocker users, 65 966 beta-blocker users, 23 366 calcium channel blocker users, and 7031 digoxin users were identified as study cohorts in this study.

The matched comparison cohorts (one comparison subject per patient who received an antiarrhythmic drug) were selected from the remaining beneficiaries of the LHID2005. The comparison cohorts were selected by matching male patients receiving an antiarrhythmic drug in terms of age group (40–49 years and ≥50 years) and year of the index date. For the comparison cohorts, the year of the index date was simply a matched year in which the comparison subjects had a medical utilization. We assured that none of the comparison subjects had a medical history of PCa prior to the index date. Ultimately, 9988 sodium channel blocker nonusers, 3663 potassium channel blocker nonusers, 65 966 beta-blocker nonusers, 23 366 calcium channel blocker nonusers, and 7031 digoxin nonusers were defined as comparison cohorts in this study.

Outcome measures

This retrospective cohort study attempted to investigate the association between the use of antiarrhythmic drugs and subsequent PCa. Each patient was individually tracked for a 5-year period from their index date to define those who were subsequently diagnosed with PCa (ICD-9-CM code 185, malignant neoplasm of the prostate).

Statistical analysis

The SAS System for Windows (version 9.2, SAS Institute, Cary, NC, USA) was used to perform all analyses in this study. Chi-squared tests were conducted to investigate differences in monthly income, geographic location (Northern, Central, Eastern, and Southern Taiwan, China), urbanization level (five levels, with level 1 being the most urbanized and level 5 being the least), hypertension, hyperlipidemia, and diabetes between the study cohorts and matched comparison cohorts. Conditional Cox proportional hazard regression analyses were used to evaluate the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for PCa during the 5-year study period between the study cohorts and their matched comparison cohorts. In addition, the adjustments were made for patients' monthly income, geographical region, urbanization level, age, hypertension, diabetes, hyperlipidemia, and obesity. We used a two-sided P = 0.05 to define statistical significance in this study.

RESULTS

Distributions of demographic characteristics and medical comorbidities between patients who received antiarrhythmic drugs and their matched comparison subjects are shown in **Table 1** and **2**. **Table 1** and **2** show that there were statistical differences between sodium channel blocker users, beta-blocker users, digoxin users, and their matched nonusers in the distributions of monthly income, geographic location, urbanization level, hypertension, hyperlipidemia, diabetes, and obesity (all $P < 0.001$). **Table 1** also shows that there were statistical differences in urbanization level ($P = 0.041$), hypertension ($P < 0.001$), hyperlipidemia ($P < 0.001$), and diabetes ($P < 0.001$) between potassium channel blocker users and their matched nonusers, respectively. However, there was no difference in monthly income or geographic location between potassium channel blocker users and their matched nonusers. In addition, there were statistical differences between calcium channel blocker users and matched nonusers in terms of monthly income ($P = 0.044$), geographical location ($P < 0.001$), urbanization level ($P < 0.001$), hypertension ($P < 0.001$), hyperlipidemia ($P < 0.001$), and diabetes ($P < 0.001$).

Table 3 shows the incidence rates for PCa among the sampled patients. The findings indicate that the incidence rates of PCa per 1000 person-years within the 5-year follow-up period were 2.65 (95% CI: 2.21–3.14) and 1.93 (95% CI: 1.57–2.36) for sodium channel blocker users and matched nonusers, respectively. Moreover, incidence rates of PCa per 1000 person-years within the 5-year study period were 3.36 (95% CI: 2.57–4.32) and 3.08 (95% CI: 2.32–3.99) for potassium channel blocker users and their matched nonusers, respectively. The Cox proportional hazard regression analyses further revealed that the adjusted HR of subsequent PCa for sodium channel blocker users was 1.12 (95% CI: 0.84–1.50, $P = 0.423$) compared to matched nonusers after adjusting for demographic characteristics and comorbidities. The adjusted HR was 0.89 (95% CI: 0.59–1.34, $P = 0.585$) for potassium channel blocker users compared to the matched nonusers (**Table 3**).

Table 4 reveals that incidence rates per 1000 person-years for subsequent PCa in beta-blocker users and matched nonusers were 2.19 (95% CI: 2.04–2.36) and 1.81 (95% CI: 1.66–1.96), respectively. Incidence rates of PCa per 1000 person-years were 3.07 (95% CI: 2.76–3.41) and 2.18 (95% CI: 1.92–2.46) for calcium channel blocker users and their matched nonusers, respectively. **Table 4** also presents that the incidence rates of PCa per 1000 person-years were 3.65 (95% CI: 3.04–4.34) and 3.12 (95% CI: 2.56–3.76) for digoxin users and their matched nonusers, respectively. In addition, the HRs for subsequent PCa in beta-blocker users, calcium channel blocker users, and digoxin users compared to their matched nonusers are also shown in **Table 4**. The adjusted HRs for subsequent PCa in beta-blocker users, calcium channel blocker users, and digoxin users were 1.08 (95% CI: 0.96–1.22, $P = 0.212$), 1.14 (95% CI: 0.95–1.36, $P = 0.162$), and 0.89 (95% CI: 0.67–1.18, $P = 0.406$), compared to their matched nonusers, respectively.

Table 1: Demographic characteristics of sampled patients who received antiarrhythmic drugs and their matched comparison patients

Variable	*Sodium channel blockers (Class I antiarrhythmic drugs)*			*Potassium channel blockers (Class III antiarrhythmic drugs)*		
	Users (n=9988)	*Nonusers (n=9988)*	*P*	*Users (n=3663)*	*Nonusers (n=3663)*	*P*
Age (year, *n* [%])						
40–49	2037 (20.4)	2037 (20.4)	>0.999	358 (9.8)	358 (9.8)	>0.999
≥50	7951 (79.6)	7951 (79.6)		3305 (90.2)	3305 (90.2)	
Monthly income (US Dollar, *n* [%])						
1–530	4757 (47.6)	4558 (45.6)	<0.001	1916 (52.3)	1879 (51.3)	0.667
530–830	3554 (35.6)	3464 (34.7)		1243 (33.9)	1276 (34.8)	
≥830	1677 (16.8)	1966 (19.7)		504 (13.8)	508 (13.9)	
Geographical region,[a] *n* (%)						
Northern	3927 (39.3)	4684 (46.9)	<0.001	1571 (42.9)	1662 (45.4)	0.148
Central	2813 (28.2)	2246 (22.5)		888 (24.2)	872 (23.8)	
Southern	2881 (28.8)	2803 (28.1)		1099 (30.0)	1024 (28.0)	
Eastern	367 (3.7)	255 (2.6)		105 (2.9)	105 (2.9)	
Urbanization level, *n* (%)						
1 (most urbanized)	2313 (23.2)	2885 (28.9)	<0.001	976 (26.6)	986 (26.9)	0.041
2	2813 (28.2)	2612 (26.2)		1041 (28.4)	937 (25.6)	
3	1585 (15.9)	1559 (15.6)		529 (14.4)	556 (15.2)	
4	1772 (17.7)	1552 (15.5)		593 (16.2)	595 (16.2)	
5 (least urbanized)	1505 (15.1)	1380 (13.8)		524 (14.3)	589 (16.1)	
Comorbidities, *n* (%)						
Hypertension	5217 (52.2)	2091 (20.9)	<0.001	2342 (63.9)	847 (23.1)	<0.001
Diabetes	2227 (22.3)	1255 (12.6)	<0.001	968 (26.4)	486 (13.3)	<0.001
Hyperlipidemia	2056 (20.6)	1144 (11.5)	<0.001	943 (25.7)	466 (12.7)	<0.001
Obesity	155 (1.6)	90 (0.9)	<0.001	68 (1.9)	21 (0.6)	<0.001

[a]Taiwan, China

Table 2: Demographic characteristics of sampled patients who received beta-blockers, calcium channel blockers, or digoxin and their matched comparison patients

Variable	*Beta-blockers (Class II antiarrhythmic drugs)*			*Calcium channel blockers (Class IV antiarrhythmic drugs)*			*Digoxin*		
	Users (n=65 966)	*Nonusers (n=65 966)*	*P*	*Users (n=23 366)*	*Nonusers (n=23 366)*	*P*	*Users (n=7031)*	*Nonusers (n=7031)*	*P*
Age (year, *n* [%])									
40–49	18542 (28.1)	18542 (28.1)	>0.999	3830 (16.4)	3830 (16.4)	>0.999	541 (7.7)	541 (7.7)	>0.999
≥50	47424 (71.9)	47424 (71.9)		19536 (83.6)	19536 (83.6)		6490 (92.3)	6490 (92.3)	
Monthly income (US Dollar, *n* [%])									
1–530	26622 (40.4)	27292 (41.4)	<0.001	10735 (45.9)	10964 (46.9)	0.044	3805 (54.1)	3731 (53.1)	<0.001
530–830	23194 (35.2)	23585 (35.8)		8614 (36.9)	8361 (35.8)		2629 (37.4)	2480 (35.3)	
≥830	16150 (24.5)	15089 (22.9)		4017 (17.2)	4041 (17.3)		597 (8.5)	820 (11.7)	
Geographical region,[a] *n* (%)									
Northern	28120 (42.6)	30977 (47.0)	<0.001	9290 (39.8)	10842 (46.4)	<0.001	2909 (41.4)	3230 (45.9)	<0.001
Central	17073 (25.9)	14720 (22.3)		6878 (29.4)	5318 (22.8)		2076 (29.5)	1631 (23.2)	
Southern	18870 (28.6)	18503 (28.1)		6457 (27.6)	6544 (28.0)		1774 (25.2)	1963 (27.9)	
Eastern	1903 (2.9)	1766 (2.7)		741 (3.2)	662 (2.8)		272 (3.9)	207 (2.9)	
Urbanization level, *n* (%)									
1 (most urbanized)	17864 (27.1)	19076 (28.9)	<0.001	5481 (23.5)	6535 (28.0)	<0.001	1583 (22.5)	1915 (27.2)	<0.001
2	18510 (28.1)	17922 (27.2)		6279 (26.9)	6035 (25.8)		1775 (25.3)	1795 (25.5)	
3	10519 (16.0)	10398 (15.8)		3724 (15.9)	3624 (15.5)		1060 (15.1)	1082 (15.4)	
4	10200 (15.5)	9889 (15.0)		4193 (17.9)	3750 (16.1)		1336 (19.0)	1146 (16.3)	
5 (least urbanized)	8873 (13.5)	8681 (13.2)		3689 (15.8)	3422 (14.7)		1277 (18.2)	1093 (15.6)	
Comorbidities, *n* (%)									
Hypertension	40195 (60.9)	12255 (18.6)	<0.001	15336 (65.6)	5113 (21.9)	<0.001	4456 (63.4)	1710 (24.3)	<0.001
Diabetes	14401 (21.8)	7984 (12.1)	<0.001	5976 (25.6)	3072 (13.2)	<0.001	1953 (27.8)	927 (13.2)	<0.001
Hyperlipidemia	17155 (26.0)	7640 (11.6)	<0.001	6467 (27.7)	2758 (11.8)	<0.001	1512 (21.5)	865 (12.3)	<0.001
Obesity	1302 (2.0)	582 (0.9)	<0.001	485 (2.1)	184 (0.8)	<0.001	95 (1.4)	33 (0.5)	<0.001

[a]Taiwan, China

Table 3: Incidence rates, hazard ratios, and 95% confidence intervals for prostate cancer among sampled patients during a 5-year follow-up period

Subsequent incidence of prostate cancer	*Sodium channel blockers (Class I antiarrhythmic drugs)*			*Potassium channel blockers (Class III antiarrhythmic drugs)*		
	Total sample (n=19 976)	*Users (n=9988)*	*Nonusers (n=9988)*	*Total sample (n=7326)*	*Users (n=3663)*	*Nonusers (n=3663)*
Incidence rate per 1000 person-years (95% CI)	2.29 (2.00–2.61)	2.65 (2.21–3.14)	1.93 (1.57–2.36)	3.22 (2.66–3.86)	3.36 (2.57–4.32)	3.08 (2.32–3.99)
Crude HR (95% CI)		1.37* (1.05–1.78)	1.00		1.09 (0.76–1.57)	1.00
Adjusted[a] HR (95% CI)		1.12 (0.84–1.50)	1.00		0.89 (0.59–1.34)	1.00

The adjusted HR was calculated by a Cox proportional hazard regression stratified by age group and the index year. [a]Adjusted for monthly income, geographical region, urbanization level, comorbidities, and age. *$P \leq 0.05$, statistically significant when users compared to the nonusers. HR: hazard ratio; CI: confidence interval

DISCUSSION

This population-based cohort study found no relationship between the PCa incidence and antiarrhythmic drug usage (including sodium channel blockers, potassium channel blockers, beta-blockers, calcium channel blockers, and digoxin). To our knowledge, very few studies have mentioned the association between PCa risk and prior use of sodium channel blockers or potassium channel blockers, even though ion channel blockers are considered to be new therapeutic strategies against PCa in some experimental studies. Most previous studies only investigated the connection between the risk of PCa and the use of beta-blockers, calcium channel blockers, or digoxin. In addition, relevant findings in the literature are still conflicting.

Our study showed no increased risk of subsequent PCa for sodium channel blocker users or potassium channel blocker users compared to their matched nonusers, respectively. The findings in our study are similar to two western studies. One population-based case–control study in Finland showed that sodium channel blockers and potassium channel blockers for arrhythmia did not have a PCa preventive effect.[15] Another cohort study in the United Kingdom showed that the use of Class I antiarrhythmic drugs (sodium channel blockers for arrhythmia) was not associated with the risk of cancer (HR: 1.11, 95% CI: 0.98–1.24, $P = 0.09$).[16]

In addition, results of our study showed no relationship between the subsequent risk of PCa and the use of beta-blockers, calcium channel blockers, or digoxin. These findings are consistent with some previous studies. For instance, three cohort studies, one nested case–control study, and one meta-analysis consistently observed that beta-blocker use was not associated with PCa-specific mortality.[26–30] A meta-analysis and some observational studies in the United States, Canada, and the United Kingdom all found that the use of calcium channel blockers did not increase the risk of PCa.[23,24,31–33] Furthermore, abundant research in Finland, the United Kingdom, and Ireland found no clear association between digoxin use and PCa.[15,21,22,34,35]

Nonetheless, results of several studies are inconsistent with our findings. One recent meta-analysis reported that the use of beta-blockers was associated with a decreased PCa-specific mortality (HR: 0.85, 95% CI: 0.77–0.94).[17] One case–control study and a population-based cohort study found that beta-blocker use and propranolol use (a type of beta-blocker) were related with a reduced risk of PCa.[18,32] In addition, an American study using a self-administered questionnaire showed an inverse association between calcium channel blocker usage and PCa risk (HR: 0.55; 95% CI: 0.31–0.97).[20] However, a slightly elevated PCa risk in calcium channel blocker users (HR: 1.08, 95% CI: 1.00–1.16) was observed in a meta-analysis which included six cohort studies and eight case–control studies.[25] Furthermore, a mailed questionnaire cohort study mentioned that regular digoxin users had a lower PCa risk compared to nonusers (RR: 0.76, 95% CI: 0.61–0.95).[36] Another case–control study in the United States also reported that digoxin use was negatively associated with PCa in patients with more frequent PSA testing in the prior 5 years (OR: 0.44, 95% CI: 0.20–0.98).[19] These inconsistent findings in the previous literature may have been due to several methodological limitations. For example, using a case–control study design may contribute to a selection bias. A small sample size of a cohort study might cause an insufficient statistical power. In addition, lacking information of some potential confounders might affect the actual relationship between antiarrhythmic drug use and the subsequent risk of PCa.

Our study has a number of specific strengths. First, this retrospective cohort study used a large population-based dataset which is representative of the entire population from Taiwan, China. The characteristic of the LHID2005 could provide a sufficiently large sample size of the results and further minimize selection bias in this study. The use of this dataset may also have increased the statistical power to detect an association between antiarrhythmic drug use and the subsequent PCa risk. Second, this study was performed in Taiwan, China, and most selected patients were of Chinese ethnicity. Because ethnicity is considered a risk factor for PCa, the homogeneity of the ethnicity in the selected cohorts may have eliminated a possible confounding effect on the results.[37]

Nevertheless, several limitations still must be considered. First, the LHID2005 used in this study provides no information regarding dietary habits, body mass index, family history, *etc*., which are considered as potential risk factors for PCa.[38] However, we have adjusted the patients' obesity in order to eliminate the potential influence about body-mass index. Second, the PCa diagnoses in this study relied on administrative claims data and ICD-9 codes. These diagnoses might be less accurate than those made according to standardized diagnostic examinations. Third, medical records on the PCa grade and stage, including prostate biopsy, pathologic data, and tumor-node-metastasis (TNM) classification of malignant tumors, were not available in this dataset. The PCa stage and severity might have confounded the relationship between antiarrhythmic drug use and the PCa risk. Finally, this study did not evaluate the potential effects of the length or dose of antiarrhythmic drugs exposure. This factor might affect the findings in this study. Therefore, more studies are still warranted to identify the association between length of antiarrhythmic drug exposure and the following PCa risk.

AUTHOR CONTRIBUTIONS

LTK and CCH participated in the design of the study and drafted the manuscript. HCL performed the statistical analysis and helped to draft the manuscript. CYH conceived of the study, participated in its design and coordination, and drafted the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

Table 4: Incidence rates, hazard ratios, and 95% confidence intervals for prostate cancer among sampled patients during a 5-year follow-up period

Subsequent incidence of prostate cancer	*Beta-blockers (Class II antiarrhythmic drugs)*			*Calcium channel blockers (Class IV antiarrhythmic drugs)*			*Digoxin*		
	Total sample (n=131 932)	*Users (n=65 966)*	*Nonusers (n=65 966)*	*Total sample (n=46 732)*	*Users (n=23 366)*	*Nonusers (n=23 366)*	*Total sample (n=14 062)*	*Users (n=7031)*	*Nonusers (n=7031)*
Incidence rate per 1000 person-years (95% CI)	2.00 (1.89–2.11)	2.19 (2.04–2.36)	1.81 (1.66–1.96)	2.62 (2.42–2.84)	3.07 (2.76–3.41)	2.18 (1.92–2.46)	3.38 (2.97–3.84)	3.65 (3.04–4.34)	3.12 (2.56–3.76)
Crude HR (95% CI)		1.21* (1.09–1.35)	1.00		1.41** (1.20–1.66)	1.00		1.17 (0.90–1.51)	1.00
Adjusted[a] HR (95% CI)		1.08 (0.96–1.22)	1.00		1.14 (0.95–1.36)	1.00		0.89 (0.67–1.18)	1.00

The adjusted HR was calculated by a Cox proportional hazard regression stratified by age group and the index year. [a]Adjusted for monthly income, geographical region, urbanization level, comorbidities, and age. *P≤0.05; **P≤0.001, users compared to the nonusers. HR: hazard ratio; CI: confidence interval

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