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Is digoxin use for cardiovascular disease associated with risk of prostate cancer?

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Abstract

Purpose—Digoxin is a commonly used medication for heart failure and cardiac arrhythmias that has recently been suggested as a novel chemotherapeutic agent. Preclinical studies of prostate cancer (PCa) have shown anti-tumor activity with digoxin. We explore the relationship between use of digoxin and PCa risk.

Methods—Data from a population-based case-control study of incident cases aged 35 – 74 years at PCa diagnosis in 2002 – 2005 in King County, Washington were available. Controls were identified by random digit dialing and frequency matched by age. Use of digoxin was determined from in-person questionnaires regarding medical and prescription history. The relationship of digoxin use with PCa risk was evaluated with logistic regression.

Results—1,001 cases of PCa and 942 controls were analyzed. The prevalence of digoxin use in controls was 2.7%, and use was positively correlated with age. In multivariate analysis adjusting for age, race, PSA screening and family history of PCa, digoxin use was associated with a reduction in the odds ratio of PCa (OR 0.58, 95% CI 0.30 – 1.10). Among those with ≥ 3 PSA tests over the preceding 5 years (546 cases, 380 controls), digoxin use was associated with a stronger reduction of PCa risk (OR 0.44, 95% CI 0.20—0.98).

Conclusion—These data indicate digoxin use may be associated with a reduction in risk of PCa. Given the potential mechanisms by which digoxin may exert an anti-neoplastic effect and other recent studies showing a negative association between digoxin use and PCa, further research is warranted.

Keywords

Prostate cancer; Risk; Digoxin; Population Based; Case Control study

Introduction

Cardiac glycosides (e.g., digitalis, digoxin, digitoxin, ouabain) have been used for hundreds of years in the treatment of congestive heart failure and cardiac arrhythmias. Their cardiac effects are mediated through inhibition of the Na+/K+ ATPase, which leads to increased intracellular calcium concentrations and increased cardiac contractility.(4) Cardiac glycosides have also been found to have a number of other effects, including altering serum

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androgen levels (6, 12) and inhibiting tumor growth and development.(9) Recently, digoxin has been proposed as both a potential therapeutic in cancer therapy as well as a cancer prevention agent.(9)

Prostate cancer (PCa) is the most common cancer diagnosed in men in the United States with a 1 in 6 lifetime risk of developing the disease.(1) Identification of factors that could reduce the incidence and progression of PCa is an important public health goal. Cardiac glycosides are of substantial interest in this regard. Studies of digoxin effects on PCa cell lines have shown growth inhibitory actions in both androgen dependent and androgen independent cells.(8, 13, 14) Recently, a report from the Health Professionals Follow-up Study found that regular use of digoxin was associated with a 24% reduction (95% CI 0.61 – 0.95) in the relative risk of PCa.(10) To further evaluate the digoxin-PCa relationship, we analyzed data from a population-based case-control study of risk factors for this disease.

Materials and Methods

Study Participants

The study population consists of participants in a population-based case-control study of risk factors for PCa, which was specifically designed to assess use of several classes of medications. Details of the study participants and data collection have previously been described.(2) Briefly, cases were residents of King County, Washington with histologically confirmed PCa ascertained from the Seattle-Puget Sound SEER cancer registry and diagnosed between January 1, 2002, and December 31, 2005. Of those eligible men identified, 75% (n = 1,001) agreed to participate. Male residents of King County, Washington with no history of PCa were identified as a comparison group using random digit telephone dialing. Controls were frequency matched to cases by five-year age groups, and recruited evenly throughout the ascertainment period for cases. During the first step of random digit dialing, complete household census information was obtained for 81% of the 24,106 residential telephone numbers contacted. Of eligible men who were identified and met the study eligibility criteria, 63% (n = 942) completed the study interview.

Data Collection

Subjects completed in-person interviews conducted by trained interviewers that collected information about demographic and lifestyle factors, medical history, specific medications used, family history of PCa, and PCa screening in the previous five years. Participants were asked if they had ever taken brand name (Cystodigin, Digitek, Lanoxicaps, Lanoxin) or generic digoxin (digitoxin, digoxin) at least once a week for three months or longer. Subjects were also asked about dates of use (start and stop dates for each episode), duration of use and frequency of use of digoxin. Similar data were also collected on ACE inhibitor, diuretic, aspirin and non-steroidal anti-inflammatory (NSAID) use, medications often taken with digoxin.

Statistical Analysis

Baseline characteristics between cases and controls, and between controls exposed and unexposed to digoxin, were compared with chi-squared tests. The relative risk of PCa associated with digoxin use was calculated by logistic regression. Two models were created. First, a model adjusting only for age; and second, a multivariate model adjusting for known risk factors for PCa (age, race, family history of PCa, and PSA screening history). ACE inhibitor, diuretic, statin, and aspirin use were evaluated as potential confounders as well to determine if any observed effect of digoxin on PCa risk varied by concomitant use of these medications. We also evaluated risk according to current use and duration of digoxin use (based on median duration of exposure). Duration of use was determined from reported start

and stop dates of the medication. Current use was defined as use at the time of reference date (date of diagnosis for cases and a randomly assigned date for controls that approximated the distribution of diagnosis dates in the cases). Owing to concerns over potential co-occurrence of PSA screening and use of prescription medications (due to both requiring a visit to a physician), an analysis was performed limiting to those men with at least 3 PSAs over the preceding 5 years. Additionally, we performed polytomous regression to determine the risk associated with digoxin use according to disease aggressiveness (controls compared to less aggressive and more aggressive PCa cases). Disease aggressiveness was based on a composite variable incorporating Gleason score, stage and PSA where more aggressive PCa was defined as: Gleason 4+3 or greater; or non-localized stage; or PSA ≥ 20 ng/mL at time of diagnosis. All statistical analyses were conducted using Stata software, Version 8 (Stata, Inc., College Station, TX).

Results

Selected characteristics for cases and controls are shown in Table 1. Compared to controls, cases were likely to be African American (16% vs. 10%, $p < 0.001$), to report a family history of PCa (23% vs. 12%, $p < 0.001$), and to have had three or more PSAs within the five years before reference date (55% vs. 40%, $p < 0.001$). The prevalence of any digoxin use was 1.7% and 2.7% in cases and controls, respectively. Of those reporting any use of digoxin, 78% were currently taking the medication. Of the men taking digoxin (n = 42), two did not know the brand/generic name of the medication they took whereas for the remainder, reported use was: Lanoxin (n = 30), Digitek (n = 8) and digoxin (n = 7). Overall, 76% of users reported a specific medical indication for taking digoxin. Of these, 72% of use was for treatment of arrhythmias, 16% for myocardial infarction/congestive heart failure, and 10% for hypertension. Participants not reporting dates of usage were excluded from analyses of current use and duration of use (n=3).

Table 2 shows the characteristics of controls stratified by use of digoxin. Increasing age was associated with digoxin use; no men under the age of 55 reported taking digoxin, whereas the proportion of users increased to 2.5% of men aged 55 – 64 and 4.3% for men aged 65 – 74. Digoxin use was also associated with PSA screening history. Men who had more frequent PSA testing were also more likely to use digoxin. Race, family history of PCa, income, and education were not associated with digoxin use.

As shown in Table 3, ever compared to never use of digoxin was associated with a 39% (OR 0.61, 95% CI 0.33 – 1.14) reduction in the age-adjusted odds ratio for PCa. In the multivariate model adjusting for age, race, family history of PCa and PSA screening history, the risk estimate was similar (OR 0.58, 95% CI 0.30 – 1.10), although this did not reach statistical significance ($p = 0.09$). The estimated risk reduction was similar for prior users and current users, with no difference based on duration of use (median duration of use was 4.5 years). In the polytomous regression model, ever use of digoxin was associated with a non-significant reduction in PCa risk for both less aggressive (0.59, 95% CI 0.26 – 1.35) and more aggressive (0.68, 95% CI 0.23 – 2.07) phenotypes compared to controls. Use of ACE inhibitors, diuretics, statins or NSAIDs did not significantly change the risk estimates associated with digoxin use.

Table 4 shows the results of the logistic regression analysis in men with at least three PSA tests over the preceding five years. Whereas the prevalence of digoxin use did not change in the cases limited to those with greater PSA screening, the prevalence of digoxin use in the control population with greater PSA screening was approximately 70% higher (4.5% of the frequently screened control group compared to 2.7% of the entire control population). In each category of digoxin use, the magnitude of the effect on the reduction in the odds ratio

was greater. Ever use of digoxin in this subset of men was associated with a significant reduction in the estimated relative risk of PCa (OR 0.44, 95% CI 0.20 – 0.98).

Discussion

In this population-based case-control study, we observe a non-significant reduction in the relative risk of PCa in men taking digoxin for cardiovascular disease. This effect was stronger and became statistically significant when the analysis was limited to those men with more frequent PSA testing in the previous 5 years. These results are consistent with findings from earlier epidemiologic studies of overall PCa risk and with pre-clinical studies demonstrating anti-tumor activity of digoxin.

Digoxin is a cardiac glycoside (including digitalis, digitoxin, ouabain) used for treatment of congestive heart failure and cardiac arrhythmias. The cardiac glycosides function through Na+/K+ ATPase inhibition leading to increased intracellular calcium concentrations, thereby increasing cardiac contractility. A number of other actions of cardiac glycosides have been identified, including several that are involved in anti-neoplastic activity.(9) In both LNCaP and PC3 PCa cell lines, digoxin treatment has been demonstrated to induce apoptosis (6, 8, 13, 14) and inhibit tumor cell proliferation.(13, 14) Recently, cardiac glycosides were shown to inhibit hypoxia inducible factor 1α (HIF-1α) protein expression both *in vivo* and in a mouse model.(3, 14) HIF-1α is involved in tissue response to hypoxia. In cancer tissue, increased HIF-1α levels result in increased angiogenesis that is required for tumor growth. In one study, 3,120 medications were surveyed and 20 were found to reduce HIF-1α levels by > 88%. Interestingly, of these, 11 were cardiac glycosides.(10)

Few studies of cardiac glycoside use in humans have examined their potential role in cancer prevention. In an observational cohort of women with breast cancer (n = 175), a lower cancer-specific death rate (6% vs. 34%, $p < 0.005$) in those taking digitalis (n = 32) was observed after long-term follow-up (median 22.3 years). In addition, there was decreased cell proliferation and aneuploidy in the tumors of patients on digitalis.(11) In another investigation, Haux et al. prospectively followed a cohort of digitoxin users without a history of cancer at baseline. Higher serum digitoxin levels were associated with a decreased risk of developing leukemia/lymphoma, kidney and urinary organ cancers (all $p \leq 0.05$).(5) Interestingly, digoxin use is associated with alterations in serum hormone levels. Stoffer et al. demonstrated that compared to controls, patients taking digoxin for two or more years had significantly higher estrogen and LH levels along with lower testosterone levels (all $p < 0.005$).(12) Further work showed that this was due to a direct negative effect of the medication on the testicles.(7) Considering that androgens have an important role in the initiation and progression of PCa, the ability of digoxin to influence androgen exposure is a potential mechanism whereby this drug may alter PCa risk.

In a recent study, Platz et al. screened a library of medications for their growth inhibition activity in LNCaP cells.(10) Cardiac glycosides were one of the most potent inhibitors. The authors then utilized data from the Health Professionals Follow-up Study to evaluate the relationship between digoxin use and PCa incidence. At baseline (in 1986), 2% of the men reported digoxin use. Compared to nonusers, regular users of digoxin had a statistically significant 24% (95% CI 0.60 – 0.95) reduction in the relative risk of PCa, and those with ≥ 10 years of use had the lowest risk estimate. Interestingly, the prevalence of digoxin use in controls (2.7%) and the magnitude of risk reduction in relation to digoxin use in our study are comparable, although our results did not achieve statistical significance. However, when our analysis was restricted to those with ≥ 3 PSA tests over the preceding 5 years (as a proxy for access to healthcare), the results became stronger with 4.5% of controls reporting digoxin use and a significant reduction in risk was observed (OR 0.44, 95% CI 0.20 – 0.98).

There are strengths and limitations of our study that should be considered. The population-based case-control study was specifically designed to evaluate digoxin in relation to risk of prostate cancer. Thus, the collection of detailed exposure data enabled assessment of ever use, duration of use, and recency of use. However, the low prevalence of digoxin use limited study power. Selection bias is also a concern given that only 63% of eligible controls agreed to participate. We have no data on non-participants, but if controls who refused were less healthy and thereby more likely to be taking digoxin than participating controls, we may have underestimated the reduced risk of PCa associated with this exposure. In addition, digoxin use was based on participant report rather than pharmacy records. A separate analysis of a subset of this study population that was designed to validate use of statin medications found 87% agreement between self-reported use and computerized pharmacy records,(2) suggesting that self-report is reliable for some medications in this population.

Despite the limitations, these findings support the growing evidence from preclinical and epidemiological data suggesting that digoxin has potential anti-tumor activity. These results indicate that larger studies are warranted to evaluate the potential role of digoxin in relation to PCa development and progression.

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Table 1
Selected Characteristics of Prostate Cancer Cases and Controls

	Cases N (%)	Controls N (%)	P-value
Total	1,001	942	
Age at reference date (years)			
35-54	201 (20.1)	209 (22.2)	
55-64	402 (40.2)	361 (38.3)	
65-74	398 (39.8)	372 (39.5)	
Race			
Caucasian	843 (84.2)	844 (89.6)	< 0.001
African-American	158 (15.8)	98 (10.4)	
First-degree family history of PCa			
No	775 (77.4)	833 (88.4)	< 0.001
Yes	226 (22.6)	109 (11.6)	
PSA screening within the past 5 years			
None	220 (22.0)	240 (25.5)	< 0.001
1 – 2 PSAs	172 (17.2)	168 (17.8)	
≥ 3 PSAs	546 (54.6)	380 (40.3)	
Unknown	63 (6.3)	154 (16.4)	
Income (annual)			
< $50,000	322 (33.6)	309 (33.7)	0.96
$50,000 +	637 (66.4)	608 (66.3)	
Education			
High school only	196 (19.6)	181 (19.2)	0.76
Some college/vocational	241 (24.1)	210 (22.3)	
Bachelors degree	262 (26.2)	261 (27.7)	
Graduate degree	301 (30.1)	289 (30.7)	

Table 2
Selected Characteristics of Population-Based Controls By Digoxin Use

	Digoxin Use		P-value
	No N (%)	Yes N (%)	
Total	917 (97.4)	25 (2.7)	
Age at reference date (years)			
35-54	209 (22.8)	0 (0.0)	0.008
55- 64	352 (38.4)	9 (36.0)	
65-74	356 (38.8)	16 (64.0)	
Race			
Caucasian	820 (89.4)	24 (96.0)	0.29
African-American	97 (10.6)	1 (4.0)	
First-degree family history of PCa			
No	106 (11.6)	3 (12.0)	0.95
Yes	811 (88.4)	22 (88.0)	
PSA screening within the past 5 years			
None	238 (26.0)	2 (8.0)	0.03
1 – 2 PSAs	166 (18.1)	2 (8.0)	
≥ 3 PSAs	363 (39.6)	17 (68.0)	
Unknown	150 (16.4)	4 (16.0)	
Income (annual)			
< $50,000	300 (33.6)	9 (37.5)	0.69
$50,000 +	593 (66.4)	15 (62.5)	
Education			
High school only	176 (19.2)	5 (20.0)	0.90
Some college/vocational	206 (22.2)	7 (28.0)	
Bachelors degree	255 (27.8)	6 (24.0)	
Graduate degree	282 (30.8)	7 (28.0)	

Table 3

Odds Ratios (OR) for Prostate Cancer Associated with Digoxin Use

Digoxin Use	Cases N (%)	Controls N (%)	Age-Adjusted OR (95% CI)	P-value	Multivariate * OR (95% CI)	P-value
Ever/Never Use						
Never	984 (98.3)	917 (97.4)	1.00		1.00	
Ever	17 (1.7)	25 (2.7)	0.61 (0.33 – 1.14)	0.12	0.58 (0.30 – 1.10)	0.09
Recency of Use^						
Never	984 (98.3)	917 (97.7)	1.00		1.00	
Past	4 (0.4)	5 (0.5)	0.71 (0.19 – 2.67)	0.61	0.65 (0.17 – 2.48)	0.53
Current	13 (1.3)	18 (1.9)	0.65 (0.31 – 1.34)	0.24	0.62 (0.29 – 1.30)	0.20
Duration of Use^						
Never	984 (98.3)	917 (97.7)	1.00		1.00	
< 4.5 years	6 (0.6)	9 (1.0)	0.61 (0.21 – 1.71)	0.34	0.60 (0.21 – 1.76)	0.36
≥ 4.5 years	7 (0.7)	8 (0.9)	0.79 (0.28 – 2.2)	0.64	0.69 (0.24 – 2.00)	0.50

*Adjusted for age, race, family history of prostate cancer and PSA screening history

^Excluded participants who did not answer questions on current use or duration of use

Table 4

Odds Ratios (OR) for Prostate Cancer Associated with Digoxin Use in Patients with at least 3 PSA tests over the preceding 5-years

Digoxin Use	Cases N (%)	Controls N (%)	Age-Adjusted OR (95% CI)	P-value	Multivariate * OR (95% CI)	P-value
Ever/Never Use						
Never	536 (98.2)	363 (95.5)	1.00		1.00	
Ever	10 (1.8)	17 (4.5)	0.43 (0.19 – 0.95)	0.04	0.44 (0.20 – 0.98)	0.04
Recency of Use^						
Never	536 (98.2)	363 (95.8)	1.00		1.00	
Past	2 (0.4)	3 (0.8)	0.49 (0.08 – 2.96)	0.44	0.51 (0.08 – 3.10)	0.46
Current	8 (1.5)	13 (3.4)	0.45 (0.18 – 1.09)	0.08	0.47 (0.19 – 1.14)	0.10
Duration of Use^						
Never	536 (98.2)	363 (95.8)	1.00		1.00	
< 4.5 years	4 (0.7)	6 (1.6)	0.49 (0.08 – 1.76)	0.44	0.53 (0.15 – 1.91)	0.33
≥ 4.5 years	4 (0.7)	7 (1.9)	0.41 (0.14 – 1.40)	0.28	0.41 (0.12 – 1.43)	0.16

*Adjusted for age, race, family history of prostate cancer and PSA screening history

^Excluded participants who did not answer questions on current use or duration of use