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Karasneh, R. A., Murray, L. J., Hughes, C. M., & Cardwell, C. R. (2016). Digoxin use after diagnosis of prostate cancer and survival: a population-based cohort study. Pharmacoepidemiology and Drug Safety, 25(9), 1099-1103. DOI: 10.1002/pds.4018

Published in:
Pharmacoepidemiology and Drug Safety

Digoxin use after diagnosis of prostate cancer and survival: A population-based cohort study

Running title: Digoxin after prostate cancer diagnosis and survival

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Key words: prostate cancer, digoxin, mortality, cardiac glycosides, epidemiology.

Key points:

- No evidence of a reduction in prostate cancer-specific mortality with digoxin use after diagnosis
- No dose response associations were apparent.

Aknowledgments

This study is based partly on data from the CPRD obtained under license from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this study are those of the authors alone. None of the authors have any conflicts of interest to declare.

The work was supported by the Health and Social Care, Research and Development, Public Health Agency, Northern Ireland who funded a UK NIHR Career Development Fellowship [to C.R. Cardwell] and access to the CPRD dataset; and Yarmouk University, Jordon, who funded a PhD studentship [to R.A. Karasneh]. The funders had no role in the study design; collection, analysis, and interpretation of data; writing of the report; or the decision to submit for publication.

Conflict of Interest: The authors declare that they have no conflict of interest

Word count: 1,492

Abstract

Purpose: Preclinical studies have shown that digoxin exerts anti-cancer effects on different cancer cell lines including prostate cancer. A recent observational study has shown that digoxin use was associated with a 25% reduction in prostate cancer risk. The aim of this study is to investigate whether digoxin use after diagnosis of prostate cancer is associated with decreased prostate cancer-specific mortality.

Methods: A cohort of 13,134 prostate cancer patients newly diagnosed from 1998 to 2009 was identified from English cancer registries and linked to the UK Clinical Practice Research Datalink (to provide digoxin and other prescription records) and to the Office of National Statistics mortality data (to identify 2,010 prostate cancer-specific deaths). Using time-dependent Cox regression models, unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CIs) were calculated for the association between post-diagnostic exposure to digoxin and prostate cancer-specific mortality.

Results: Overall, 701 (5%) prostate cancer patients used digoxin after diagnosis. Digoxin use was associated with an increase in prostate cancer-specific mortality before adjustment (HR=1.59; 95% CI 1.32-1.91), but after adjustment for confounders, the association was attenuated (adjusted HR=1.13; 95% CI 0.93-1.37) and there was no evidence of a dose response.

Conclusions: In this large population-based prostate cancer cohort, there was no evidence of a reduction in prostate cancer-specific mortality with digoxin use after diagnosis.

Introduction

Preclinical studies suggest that digoxin, a cardiac glycoside, exerts anti-cancer effects on various types of cancer including prostate cancer [1]. Digoxin was found to enhance apoptosis of prostate cancer cell lines through several mechanisms such as inhibition of the Na^+/K^+ pump activity leading to reductions in the proliferation of prostate cancer cell lines [2,3]. A recent *in vitro* screen of 3,817 compounds identified digoxin as the candidate with the most potential for use in prostate cancer treatment based upon its ability to inhibit proliferation in prostate cancer cell lines [4]. The researchers also conducted observational epidemiology showing, in the Health Professionals Follow-up Study, that digoxin users had a significant 24% reduction in prostate cancer risk [4]. However, there have not been any epidemiological studies which have investigated the effect of digoxin use after prostate cancer diagnosis on survival. A recent study has investigated the association between digoxin use before prostate cancer diagnosis and survival from prostate cancer [5], but this is a less relevant time period, as intervening prior to a cancer diagnosis in order to improve survival is of questionable clinical applicability. The aim of our population-based study was to investigate whether prostate cancer patients using digoxin after diagnosis had reduced prostate cancer-specific mortality.

Materials and Methods

Data source

This study was conducted using three databases. The Clinical Practice Research Datalink (CPRD), the National Cancer Data Repository (NCDR) and the Office of National Statistics (ONS). These datasets were linked using a deterministic algorithm based upon National Health Service (NHS) number, gender, date of birth, and postcode. Ethical approval for all observational research using the CPRD has been obtained from a multicentre research ethics committee.

Study design

A cohort of newly diagnosed prostate cancer patients was identified on the basis of a NCDR recorded primary diagnosis of prostate cancer (based upon International Classification of Diseases (ICD)) from an English cancer registry between 1998 and 2009. Cohort members with a previous NCDR cancer diagnosis, apart from *in situ* neoplasms and non-melanoma skin cancers, were excluded. Deaths were identified from the ONS with information on deaths up to January 2012, with prostate cancer-specific deaths defined as those with underlying cause of death based upon ICD codes. Patients were removed if their cancer diagnosis date occurred before they were registered at a CPRD practice, if their cancer diagnosis date occurred before the CPRD records at their General Practitioner (GP) practice were of research quality (up to standard), if their cancer diagnosis date occurred after the last date of data collection from their general practice, or if they received androgen deprivation therapy (ADT) more than 8 weeks prior to the date of their cancer diagnosis. Follow-up started one year after prostate cancer diagnosis to remove deaths in the first year after diagnosis.

Exposure data

Digoxin was determined from GP prescribing records. A quantity of 28 tablets was assumed for approximately 1% of prescriptions where quantity was missing or assumed incorrect. The Defined Daily Doses (DDDs) in each prescription were calculated. Digoxin use was investigated as a time varying covariate [6]. The use of a lag is recommended [7] and in this study, prescriptions in the 6 months prior to death were removed by the lag as these may reflect end of life treatment. Dose-response analyses were conducted.

Covariates

Data available from NCDR included histological grade and treatment in the six months after diagnosis. ADT use was determined from GP prescription records. Smoking, alcohol, and body mass index (BMI) were determined from the closest GP record prior to prostate cancer diagnosis. Comorbidities prior to diagnosis were determined prior to diagnosis from GP diagnosis codes using comorbidities comprising a recent adaptation of the Charlson comorbidity index to Read coding databases such as CPRD [8]. Deprivation was based upon postcode of residence using the 2004 Index of Multiple Deprivation for England [9]. Statin, metformin, angiotensin-converting-enzyme inhibitors (ACEI), spironolactone and aspirin use was determined from GP prescription records.

Statistical analysis

The patients were followed from one year after prostate cancer diagnosis to death, end of registration with their general practice, last date of data collection from their general practice or end of ONS mortality death registration data follow-up. In the main analysis, time-dependent Cox regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for prostate cancer-specific death for digoxin users compared with non-users. Adjusted analyses were conducted including potential confounders. Further analyses were conducted by considering the number of digoxin prescriptions and number of DDDs. Analyses were repeated for all-cause mortality. Subgroup and sensitivity analyses were also conducted.

Results

Figure 1 shows that the final cohort included 13,134 prostate cancer patients with a mean of 5 years of follow-up from diagnosis, in whom there were 2,010 prostate cancer-specific deaths,

and 1,885 deaths from other causes. Smaller proportions of digoxin users compared with non-users were younger, and were current smokers. Digoxin users were much less likely to receive surgery or radiotherapy but more likely to receive hormone therapy. Digoxin users were more likely to have comorbidities (particularly for cerebrovascular disease, chronic pulmonary disease, congestive heart disease, diabetes and myocardial infarction) and use other medications (such as low- dose aspirin, spironolactone, statins, metformin, and ACEI). Other characteristics, including Gleason score and grade, were generally similar in digoxin users compared with non-users.

The findings for prostate cancer-specific and all-cause mortality are shown in Table 1. Digoxin use was associated with increased prostate cancer-specific mortality before adjustment (HR=1.59; 95% CI 1.32-1.91) but after adjustment for confounders, the association was attenuated (adjusted HR=1.13; 95% CI 0.93-1.37). This attenuation was largely due to adjustment for age (HR adjusted for age=1.22; 95% CI 1.02-1.47) and no dose response associations were apparent.

There was a large increase in all-cause mortality in digoxin users prior to adjustments (HR=2.24; 95% CI 2.00-2.51) and after adjustment for confounders, a weak association remained (HR=1.39; 95% CI 1.23-1.56). This increase was most marked for cardiovascular deaths (adjusted HR=1.85; 95% CI 1.49-2.31), as expected, and there was only a modest increase in the risk of death for non-cardiovascular causes (adjusted HR=1.25; 95% CI 1.08-1.44).

In sub-group analyses, the results were little altered when the cohort was restricted to individuals with digoxin indications (in which the digoxin non-users are likely to be more

similar to the digoxin users) (adjusted HR=1.07; 95% CI 0.78-1.46), and when the cohort was restricted to individuals receiving ADT (adjusted HR=1.18; 95% CI 0.95-1.46). A simplified analysis for prostate cancer-specific mortality, based upon digoxin use in the year after diagnosis, also revealed little evidence of association (adjusted HR=1.20; 95% CI 0.97- 1.49). A further sensitivity analyses revealed a small increase in prostate cancer-mortality with digoxin use in the year before diagnosis (adjusted HR=1.25; 95% CI 1.03- 1.52). Finally, there was no evidence of a difference in cancer-specific mortality in digoxin users compared with non-users when the analysis was restricted to those for whom Gleason score was available and additionally adjusted for (adjusted HR=0.94; 95% CI 0.67-1.31).

Discussion

In this study, there was no evidence of reduced prostate cancer-specific mortality in prostate cancer patients who used digoxin.

This study is the first population-based cohort to investigate digoxin use after diagnosis of prostate cancer and mortality. Our findings are similar to the lack of association between digoxin and prostate cancer-specific mortality observed in an Irish study of digoxin and mortality [5], but that study only investigated digoxin use prior to diagnosis of prostate cancer. Our findings do not support preclinical studies which suggest digoxin has anticancer properties [10]. Epidemiological studies have suggested reductions in prostate cancer risk in digoxin users [4,11], our findings suggest that any reductions in risk may not translate to survival possibly because different mechanisms may be involved in metastasis and tumour initiation.

The main strengths of our study include its large size and long duration of follow-up but we cannot rule out the possibility of a type 2 error. Although verification of cancer diagnosis and death facilitated using NCDR and ONS data respectively were robust, misclassification of prostate cancer cause of death is possible; however, methodological studies suggest that comparative risk estimates are unlikely to be greatly affected where misclassification is unlikely to be differential [12]. Recall bias was eliminated by using routinely collected GP-prescribed drug data that included detailed timing of digoxin use; nevertheless it did not capture hospital or hospice prescriptions. Confounding by indication, often a problem in pharmacoepidemiology, is unlikely to have influenced our main finding for prostate cancer-specific mortality, but would explain the increase in all-cause mortality due largely to raised cardiovascular mortality in digoxin users [13]. Misclassification of digoxin usage is possible because it is unknown whether patients fully complied with their prescriptions. However, most digoxin prescribing will have been captured as digoxin is not available over-the-counter in the UK. As with all observational studies, confounding caused by unrecorded\unavailable variables (such as stage) or incomplete potential confounders cannot be ruled out.

Conclusion

There was no evidence of a reduction in prostate cancer-specific mortality with digoxin use after diagnosis.

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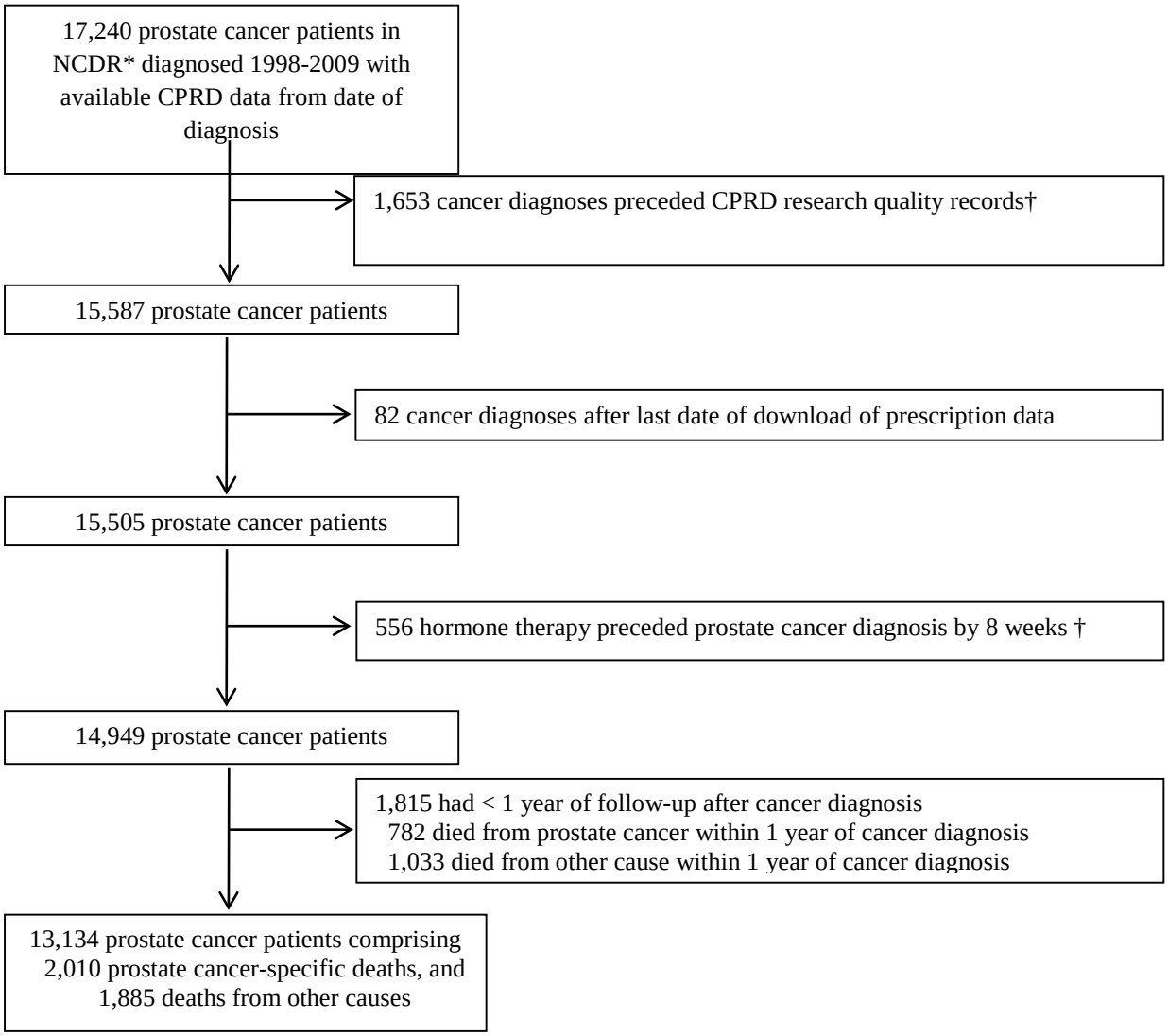

Figure 1.

* With no history of other cancers in NCDR, excluding in situ neoplasms and non-melanoma skin cancers.
† Indicating date of diagnosis may not be correctly recorded in cancer registry.

Table 1. Association between digoxin usage after cancer diagnosis and prostate cancer-specific and all-cause mortality.

Medication usage after diagnosis	Cancer-specific/ all-cause mortality	All patients	Person years	Unadjusted HR (95%CI)	Adjusted[a] HR (95%CI)
Prostate cancer-specific mortality					
Number of patients			*[13,134]*		
Digoxin non-user	1,890	12,433	50,736	1.00	1.00
Digoxin user [b]	120	701	2,106	1.59 (1.32, 1.91)	1.13 (0.93, 1.37)
Digoxin non-user	1,890	12,433	50,736	1.00	1.00
1 to 11 Digoxin prescriptions [c]	57	268	916	1.61 (1.23, 2.09)	1.15 (0.88, 1.50)
≥ 12 Digoxin prescriptions [c]	63	433	1,190	1.57 (1.22, 2.02)	1.10 (0.85, 1.43)
Digoxin non-user	1,890	12,433	50,736	1.00	1.00
1 to 365 ddds [c]	76	362	1,147	1.73 (1.38, 2.18)	1.17 (0.92, 1.48)
≥ 365 ddds [c]	44	339	959	1.38 (1.03, 1.87)	1.06 (0.78, 1.44)
All-cause mortality					
Number of patients			*[13,134]*		
Digoxin non-user	3,566	12,433	50,736	1.00	1.00
Digoxin user [b]	329	701	2,106	2.24 (2.00, 2.51)	1.39 (1.23, 1.56)
Digoxin non-user	3,566	12,433	50,736	1.00	1.00
1 to 11 Digoxin prescriptions [c]	135	268	916	2.06 (1.73, 2.45)	1.30 (1.09, 1.55)
≥ 12 Digoxin prescriptions [c]	194	433	1,190	2.40 (2.07, 2.77)	1.46 (1.25, 1.70)
Digoxin non-user	3,566	12,433	50,736	1.00	1.00
1 to 365 ddds [c]	191	362	1,147	2.34 (2.03, 2.71)	1.36 (1.17, 1.58)
≥ 365 ddds [c]	138	339	959	2.12 (1.78, 2.51)	1.42 (1.19, 1.70)

ddds, defined daily doses.

[a] Model includes year of diagnosis, age at diagnosis, surgery within 6 months, radiotherapy within 6 months, chemotherapy within 6 months, androgen deprivation therapy within 6 months, estrogen therapy within 6 months, comorbidities prior to diagnosis (including cerebrovascular disease, chronic pulmonary disease, congestive heart disease, diabetes, diabetes with complications, myocardial infarction, peptic ulcer disease, peripheral vascular disease, renal disease) and other medication use (after diagnosis, as time varying covariates, specifically low-dose aspirin, statins, metformin, ACEI and spironolactone) and deprivation (in fifth).

[b] Medication use modelled as a time varying covariate with an individual considered a non-user prior to 6 months after first medication usage and a user after this time, excludes deaths in the year after cancer diagnosis.

[c] Medication use modelled as a time varying covariate with an individual considered a non-user prior to 6 months after first medication usage, a user of 0 to 12 prescriptions (or 365th defined daily doses) from 6 months after first prescription to 6 months after 12th prescription (or 365th defined daily dose) and a greater user after this time, excludes deaths in the year after cancer diagnosis.