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Antiepileptic drugs and prostate cancer risk in the Finnish Randomized Study of Screening for Prostate Cancer

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Abstract

Antiepileptic drugs (AEDs) with histone deacetylase (HDAC) inhibitor properties decrease prostate cancer (PCa) cell proliferation in vitro. A population-based cohort of 78 615 men was used to evaluate the risk of PCa among users of AEDs. Study population was linked to the Finnish national prescription database to obtain information on individual medication reimbursements in 1996 to 2015. Cox regression with antiepileptic medication use as a time-dependent variable was used to analyze PCa risk overall, and low, medium and high-risk PCa separately. The analysis was adjusted for age, screening trial arm, and other drugs in use, including statins, antidiabetic drugs, antihypertensive drugs, aspirin, and nonsteroidal anti-inflammatory drugs. Compared to the nonusers of AEDs, overall PCa risk was decreased among AED users (hazard ratio [HR] = 0.86, 95% confidence interval [CI] = 0.76-0.96). A similar PCa risk decrease was observed among users of HDACi AEDs (HR = 0.87, 95% CI = 0.76-1.01), but no risk difference was found when comparing HDACi AED users to users of other AEDs (HR = 0.98, 95% CI = 0.76-1.27). Our study showed a decrease in overall PCa risk among men using AEDs compared to nonusers. The risk associations were similar for HDAC inhibitors as for AEDs in general.

KEYWORDS
antiepileptic drugs, HDAC inhibition, prostate cancer

1 | INTRODUCTION

Prostate cancer (PCa) is the most common malignancy and the second most common cause of cancer death among Western men.[1-3] Recent studies have demonstrated that valproic acid (VPA), an antiepileptic drug (AED) with histone deacetylase inhibitor (HDACi) activity, decreases proliferation of PCa cells in vitro and reduces tumor volume in vivo.[4-6] Carbamazepine and topiramate are also known to have HDACi properties.[7-9]

VPA increases the expression of p21 and p27 in tumor cells in vitro leading to inhibition of cell cycle and increase in differentiation. VPA also has an antiangiogenic effect on PCa cells.[10]

Abbreviations: AED, antiepileptic drug; BMI, body mass index; FinRSPC, Finnish Randomized Study of Screening for Prostate Cancer; HDAC, histone deacetylase; HDACi, histone deacetylase inhibitor; HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; PCa, prostate cancer; PSA, prostate-specific antigen; VPA, valproic acid.

Previous epidemiological studies on association of AEDs on PCa risk have given conflicting results. In a small UK cohort study, VPA users showed a nonsignificant trend of increased PCa risk.[11] Another study found that VPA, carbamazepine, oxcarbazepine, lamotrigine, and levetiracetam may decrease serum levels of prostate-specific antigen (PSA).[12] Two studies have reported no association between PCa risk and VPA usage.[13,14] In our previous case-control study, we found a decreased risk of PCa associated with usage of VPA, carbamazepine, and phenobarbital.[15] We did not analyze HDACi AEDs as a group or compared to users of other types of AEDs.

People with epilepsy are known to have increased risk of cancer and increased cancer mortality overall.[16,17] The mechanism behind the association is unclear, but is believed to be due to conditions associated with epilepsy. There are, however, no data available of PCa risk in people with epilepsy that we know of.

We examined the association between AEDs and PCa risk among men in the Finnish Randomized Study of Prostate Cancer Screening (FinRSPC) during 1996 to 2015. To our knowledge, this is the first study to evaluate PCa risk comprehensively among AED users.

What's new?

Valproic acid, an antiepileptic drug with histone deacetylase inhibitor activity, has been shown to decrease proliferation of prostate cancer cells in vitro and reduce tumor volume in vivo. Epidemiological studies on the association of antiepileptic drugs and prostate cancer risk have yielded conflicting results. This is the first epidemiological study to comprehensively evaluate prostate cancer risk and use of antiepileptic drugs with histone deacetylase inhibitory properties at population level. The results showed a decrease in overall prostate cancer risk among men using antiepileptic drugs compared to non-users. The risk associations were similar for histone deacetylase inhibitors and antiepileptics in general.

2 | MATERIALS AND METHODS

2.1 | The study cohort

The Finnish Randomized Study of Prostate Cancer Screening includes 80 458 men residing in the metropolitan areas of Helsinki and Tampere. In 1996 to 1999, all men aged 55, 59, 63 and 67 in the target population were identified annually from the Population Register in Finland. After exclusion of prevalent PCa cases, they were randomly assigned 1:1.5 into two groups: the screening arm (32 000 men) and the control arm (48 458 men). Family history of PCa was obtained at baseline participating in the screening arm. Men in the screening arm were invited to screening with PSA test every 4 years until the age of 71 years, excluding men who were diagnosed with PCa, had moved abroad or died. They were considered screening positive if the PSA was above 4 ng/mL, or if they had PSA at 3.0 to 3.9 ng/mL and percentage of free PSA less or equal to 15%. No intervention was offered to the men in the control arm.

Incident cases in the control arm and in the screening arm were identified from the Finnish Cancer Registry, which covers practically all cancer cases in Finland.[18] The clinical information on Gleason grade (available for 97.3% of cases), stage (97.7%) and serum PSA values were acquired from the medical records.

Information on body mass index (BMI) was available for 11 698 participants of the third screening round (14.5% of all men), who responded to a questionnaire mailed along with the third-round screening invitations (93% response among participants). Information on marital status (available for 59 887 men [74.4%]) were obtained from the Population Register Center and occupational status (employed, unemployed or retired) (available for 64 109 men [79.7%]) were obtained from Statistics Finland (authorization number TK-53-1330-18).

2.2 | Information on medication use

The trial database was linked to the national prescription database of the Social Insurance Institution (SII) of Finland to obtain individual level information on reimbursements for physician-prescribed antiepileptic medication purchases during 1995 to 2015. The unique personal identification numbers were used as the key in the deterministic linkage. Information on medication usage was obtained for 78 615 men in the study (97.7%).

The SII is a governmental agency providing reimbursements for the cost of prescription medication. Reimbursement is available for all Finnish residents, usually obtained as price subsidy at purchase at the pharmacy. For every reimbursed purchase, the date, number of packages, dose and number of doses of the purchase are entered into the database. Drugs dispensed to hospital inpatients or in other way institutionalized patients are not covered by the prescription database.[19]

In Finland, all patients with epilepsy have 100% reimbursement for AEDs. Epilepsy diagnosis is made by neurologist and it is based on clinical neurological assessment, electroclinical findings and neuroimaging. The SII database was used to identify participants with 100% reimbursement for AEDs. Data of 100% reimbursement were only available for years 1995 to 2009. Reimbursement entitlements made before 1995 were not available.

The AEDs licensed in Finland during 1995 to 2015 were ethosuximide, phenobarbital, phenytoin, gabapentin, carbamazepine, clonazepam, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, primidone, tiagabine, topiramate, zonisamide, lacosamide, VPA and vigabatrin. The drugs were identified based on drug-specific Anatomical Therapeutic Chemical (ATC) codes. Clonazepam, phenobarbital, pregabalin and primidone were excluded from the analysis either because of their common usage for other indications than epilepsy (clonazepam and pregabalin) or because of very small number of users in the study population during the follow-up (phenobarbital and primidone). Additionally, information on usage of statins, antidiabetic

medication, antihypertensive medication, nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin were obtained as potential confounders from the database.

2.3 | Statistical analysis

Cox regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for PCa by medication usage. The time metric was years and months (as decimals of year) since the screening trial randomization (the baseline). Cox regression was adjusted for age at randomization and in the multivariable analyses also for simultaneous usage of other drugs. Analyses of the full trial cohort were also adjusted for the screening trial arm. Validity of proportional hazards assumption was not formally tested as exposure of interest is analyzed as time-dependent variable.

PCa risk overall and separately the risk of low-, medium- and high-risk PCa were compared between users and nonusers of AEDs. A low-risk PCa was required to fill all the following criteria: Gleason score 6 or below, stage T1-2 and PSA under 10. Medium-risk PCa had at least one of the following characteristics: Gleason 7, stage T3 or PSA 10 to 20. High-risk PCa was defined as having one of the following properties: Gleason score 8 to 10, stage T4, metastases or PSA over 20. Separate analyses were performed comparing HDACi AEDs to other AEDs. Carbamazepine, topiramate, oxcarbazepine and VPA were classified as HDACi medication and other AEDs as non-HDACi. VPA was also analyzed separately compared to non-HDACi because in vitro studies on the subject have almost exclusively evaluated the effect of VPA on cancer growth. Oxcarbazepine was considered as a HDAC inhibitor due to close pharmacological similarity to carbamazepine.

AED use was included into the Cox regression as a time-dependent variable. Medication usage status was updated yearly after the baseline. Men who were not AED users at baseline were considered nonusers until the year of the first purchase. Men who switched from one drug group to another (eg, from non-HDACi AEDs to HDACi AEDs) remained as users of both drug groups.

The quantity of medication use was standardized between different drugs by dividing the annual usage in milligrams by the defined daily dose listed by the World Health Organization. The duration of medication use was measured as years with recorded purchases. The intensity of AED use (doses per year) was calculated by dividing the yearly dosage by years of usage.

The cumulative amount, duration and intensity of AED use were updated during the follow-up according to the reimbursed medication

TABLE 1 Population characteristics

	Antiepileptic drug use		
	None	Any	HDAC inhibitor use[b]
N of men	72 384	6231	4096
N of prostate cancer cases	8548 (11.8%)	713 (11.4%)	427 (10.4%)
N of (a) low	2903 (35.9%)	229 (33.3%)	133 (32.7%)
(b) medium	2843 (35.2%)	276 (40.2%)	166 (40.8%)
(c) high risk PCa	2330 (28.9%)	182 (26.5%)	108 (26.5%)
Median age	59	59	59
Median BMI[a]	26.3	26.2	26.0
Screening arm	27 845 (38.5%)	2349 (37.7%)	1545 (37.7%)
Use of other drugs			
Antidiabetic drugs, n (%)	13 010 (18.0%)	1234 (19.8%)	699 (17.1%)
Statins, n (%)	35 157 (48.6%)	3352 (53.8%)	2110 (51.5%)
Antihypertensive drugs, n (%)	52 661 (72.8%)	4992 (80.1%)	3224 (78.7%)
Aspirin, n (%)	12 003 (16.6%)	1413 (22.7%)	938 (22.9%)
NSAIDs, n (%)	59 085 (81.6%)	5419 (87.0%)	3480 (85.0%)
Marital status			
Single, divorced or widowed	9578 (13.2%)	918 (14.7%)	592 (14.5%)
Married or registered relationship	45 631 (63.0%)	3760 (60.3%)	2382 (58.2%)
Occupational status			
Employed	29 570 (40.9%)	2012 (32.3%)	1211 (29.6%)
Unemployed	7435 (10.3%)	568 (9.1%)	395 (9.6%)
Retired	22 045 (30.5%)	2479 (39.8%)	1711 (41.8%)

Note: Population-based cohort of 78 615 Finnish men.
Abbreviations: BMI, body mass index; HDAC, histone deacetylase; NSAID, nonsteroidal anti-inflammatory drugs; PCa, prostate cancer.
[a]Available for 15% of men in the entire study population.
[b]Includes any use of valproic acid, carbamazepine, oxcarbazepine or topiramate.

TABLE 2 Prostate cancer risk among antiepileptic drug users compared to nonusers of AEDs

	Overall PCa		Low-risk PCa		Medium-risk PCa		High-risk PCa	
	HR (95% CI) Age-adjusted	HR (95% CI) Multivariable adjusted*	HR (95% CI) Age-adjusted	HR (95% CI) Multivariable adjusted*	HR (95% CI) Age-adjusted	HR (95% CI) Multivariable adjusted*	HR (95% CI) Age-adjusted	HR (95% CI) Multivariable adjusted*
No AED use	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Any AED use	0.85 (0.76-0.96)	0.86 (0.76-0.96)	0.74 (0.59-0.92)	0.76 (0.61-0.95)	0.98 (0.82-1.18)	0.96 (0.80-1.16)	0.80 (0.64-0.99)	0.80 (0.64-1.01)
Intensity of usage								
First tertile	0.97 (0.80-1.17)	0.99 (0.82-1.20)	1.05 (0.74-1.47)	1.11 (0.79-1.56)	1.18 (0.88-1.59)	1.20 (0.89-1.62)	0.67 (0.44-1.03)	0.65 (0.42-1.01)
Second tertile	0.80 (0.65-0.98)	0.81 (0.65-1.00)	0.66 (0.43-1.00)	0.67 (0.44-1.03)	0.86 (0.61-1.21)	0.84 (0.59-1.20)	0.73 (0.49-1.10)	0.78 (0.52-1.17)
Third tertile	0.81 (0.67-0.98)	0.79 (0.65-0.97)	0.57 (0.38-0.85)	0.57 (0.38-0.86)	0.92 (0.68-1.24)	0.87 (0.63-1.19)	0.96 (0.69-1.32)	0.96 (0.68-1.33)

Note: Population-based cohort of 78 615 Finnish men.

Abbreviations: AED, antiepileptic drug; CI, confidence interval; FinRSPC, Finnish Randomized Study of Screening for Prostate Cancer; HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; PCa, prostate cancer.

*Calculated with Cox regression adjusted for age, FinRSPC study arm, use of cholesterol-lowering, antidiabetic and antihypertensive drugs and use of NSAIDs and aspirin.

purchases. After discontinuation, the participants retained the level they had reached before stopping the usage.

Use of other drugs was analyzed as dichotomous variables stratified as ever-users and never-users during the entire follow-up.

To evaluate delayed associations between AED use and PCa risk and to minimize the impact of protopathic bias, we performed lag-time analyses where exposure occurring 1 to 3 years before the outcome was censored. For instance, outcomes occurring in the year 2002 by AED use in 2001 were analyzed in the 1-year lag-time analysis.

To further evaluate influence of PSA testing to the PCa risk, we performed a sensitivity analysis where we included only men with at least one PSA test during the follow-up. We also performed a sensitivity analysis where we included only users of AEDs without AED usage prior to the FinRSPC baseline to evaluate whether time-dependent exposure variable allow for adequate exposure classification.

Risk trends by cumulative usage of AEDs were analyzed by stratifying medication users by tertiles of amount, duration and intensity of medication usage. Tertiles of cumulative usage were analyzed as a continuous time-dependent variable. To assess effect modification by the background variables serving as potential cofounders (age, trial arm, other medications), the analysis was stratified according to the background variables and interaction with medication usage was evaluated by adding an interaction term to the Cox regression model. Improvement in model fit was assessed using likelihood ratio tests.

Cox regression analyses were performed using IBM SPSS statistical software version 25 (Chicago, IL).

3 | RESULTS

3.1 | Population characteristics

Prevalence of AED use was 11.4%. The median age at randomization and BMI were comparable between AED users and nonusers (Table 1). During median follow-up of 17 years, 9261 prostate cancers were diagnosed, of which 713 among AED users. AED users were more often also users of other drug groups, such as NSAIDs, antihypertensive drugs and statins (Table 1). AED users were more often retired compared to nonusers of AEDs (Table 1).

3.2 | AEDs and PCa risk

The age-adjusted incidence of PCa was 78.5/10 000 person years for users of any AED, 74.1/10 000 person years for those using HDACi AED and 78.9/10 000 person years for men not using AED. When compared to the nonusers, overall PCa risk was lower among AED users (multivariable-adjusted HR = 0.86, 95% CI = 0.76-0.96), with a decreasing trend with intensity of AED use (Table 2). The risk

TABLE 3 Prostate cancer risk among users of HDAC inhibitory antiepileptic drugs compared to men using AEDs without HDAC inhibition activity

	Overall PCa		Low-risk PCa		Medium-risk PCa		High-risk PCa	
	HR (95% CI) Age-adjusted	HR (95% CI) Multivariable adjusted*	HR (95% CI) Age-adjusted	HR (95% CI) Multivariable adjusted*	HR (95% CI) Age-adjusted	HR (95% CI) Multivariable adjusted*	HR (95% CI) Age-adjusted	HR (95% CI) Multivariable adjusted*
Men using non-HDAC AEDs	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
HDAC AED users	1.02 (0.79-1.30)	0.98 (0.76-1.27)	0.85 (0.52-1.38)	0.81 (0.49-1.31)	0.96 (0.65-1.43)	0.89 (0.60-1.33)	1.06 (0.66-1.71)	1.12 (0.68-1.85)
Intensity of usage								
First tertile	1.10 (0.82-1.49)	1.09 (0.80-1.48)	1.04 (0.58-1.85)	1.00 (0.56-1.79)	1.01 (0.63-1.64)	0.95 (0.58-1.56)	1.02 (0.56-1.86)	1.05 (0.57-1.96)
Second tertile	0.99 (0.71-1.37)	0.98 (0.71-1.37)	1.00 (0.54-1.84)	0.95 (0.51-1.76)	0.75 (0.43-1.30)	0.73 (0.41-1.28)	1.04 (0.56-1.95)	1.16 (0.61-2.20)
Third tertile	0.96 (0.70-1.30)	0.91 (0.67-1.25)	0.56 (0.29-1.09)	0.54 (0.18-1.05)	1.08 (0.68-1.72)	0.96 (0.60-1.55)	1.11 (0.62-1.99)	1.16 (0.64-2.10)
Men with confirmed epilepsy†								
Men using non-HDAC AEDs	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
HDAC AED users	0.94 (0.43-2.05)	0.81 (0.37-1.76)	0.55 (0.16-1.87)	0.46 (0.13-1.59)	3.11 (0.43-22.76)	2.54 (0.35-18.71)	0.84 (0.20-3.57)	0.74 (0.17-3.20)

Note: Population-based cohort of 78 615 Finnish men.

Abbreviations: AED, antiepileptic drug; CI, confidence interval; FinRSPC, Finnish Randomized Study of Screening for Prostate Cancer; HDAC, histone deacetylase; HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; PCa, prostate cancer.

*Calculated with Cox regression adjusted for age, FinRSPC study arm, use of cholesterol-lowering, antidiabetic and antihypertensive drugs and use of NSAIDs and aspirin.

†1197 men with confirmed purchases of AEDs under entitlement for special reimbursement for epilepsy during 1995 to 2009.

decrease was significant only for low-risk PCa. Decreased risk estimates were observed also for the high-risk PCa (HR = 0.80, 95% CI = 0.64-1.01).

3.3 | HDAC inhibitors and PCa risk

Users of HDACi AEDs had decreased risk estimate of PCa when compared to nonusers of AEDs (HR = 0.87, 95% CI = 0.76-1.01), and again risk decreased in inverse trend with intensity of HDACi AED use (Table S1) and was significant only for low-risk PCa. No difference in the PCa risk was found when comparing users of HDACi AEDs to users of AEDs with no HDACi properties (HR = 0.98, 95% CI = 0.76-1.27) (Table 3). The results were similar for all PCa risk classes and when limiting the analysis to men with confirmed epilepsy (Table 3). Users of VPA had nonsignificantly lower PCa risk compared to nonusers of AEDs (HR = 0.84, 95% CI = 0.65-1.09). (Table S2).

TABLE 4 Prostate cancer risk among users of HDAC inhibitor antiepileptic drugs compared to men using other types of AEDs and among AED users compared to nonusers of AEDs in a 1-year and 3-year lag time analyses

Prostate cancer risk among users of AEDs compared to nonusers of AEDs				
	1-year lag time		**3-year lag time**	
	HR (95% CI) $_{\text{age-adjusted}}$	**HR (95% CI) $_{\text{multivar.adjusted}}$***	**HR (95% CI) $_{\text{age-adjusted}}$**	**HR (95% CI) $_{\text{multivar.adjusted}}$***
Non-AED users	Ref	Ref	Ref	Ref
Any AED users	0.84 (0.74-0.95)	0.84 (0.75-0.95)	0.84 (0.73-0.96)	0.84 (0.74-0.97)
Prostate cancer risk among users of HDAC inhibitor antiepileptic drugs compared to users of other types of AEDs				
	1-year lag time		**3-year lag time**	
	HR (95% CI) $_{\text{age-adjusted}}$	**HR (95% CI) $_{\text{multivar.adjusted}}$***	**HR (95% CI) $_{\text{age-adjusted}}$**	**HR (95% CI) $_{\text{multivar.adjusted}}$***
Men using non-HDAC AEDs	Ref	Ref	Ref	Ref
HDAC AED users	1.08 (0.83-1.43)	1.06 (0.80-1.39)	1.18 (0.86-1.63)	1.16 (0.84-1.61)

Note: Population-based cohort of 78 615 Finnish men.
Abbreviations: AED, antiepileptic drug; CI, confidence interval; FinRSPC, Finnish Randomized Study of Screening for Prostate Cancer; HDAC, histone deacetylase; HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs.
*Calculated with Cox regression adjusted for age, FinRSPC study arm, use of cholesterol-lowering, antidiabetic and antihypertensive drugs and use of NSAIDs and aspirin.

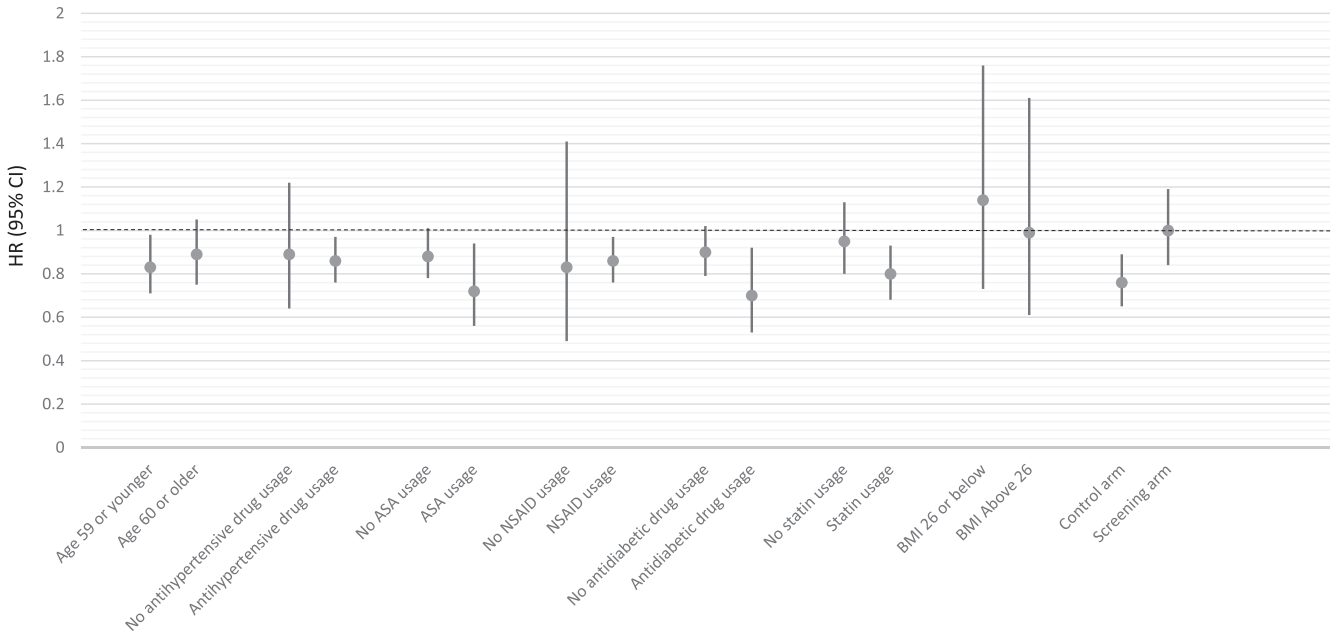

FIGURE 1 Prostate cancer risk among men using any antiepileptic drugs compared to nonusers. Analysis stratified by background characteristics. Population-based cohort of 78 615 Finnish men

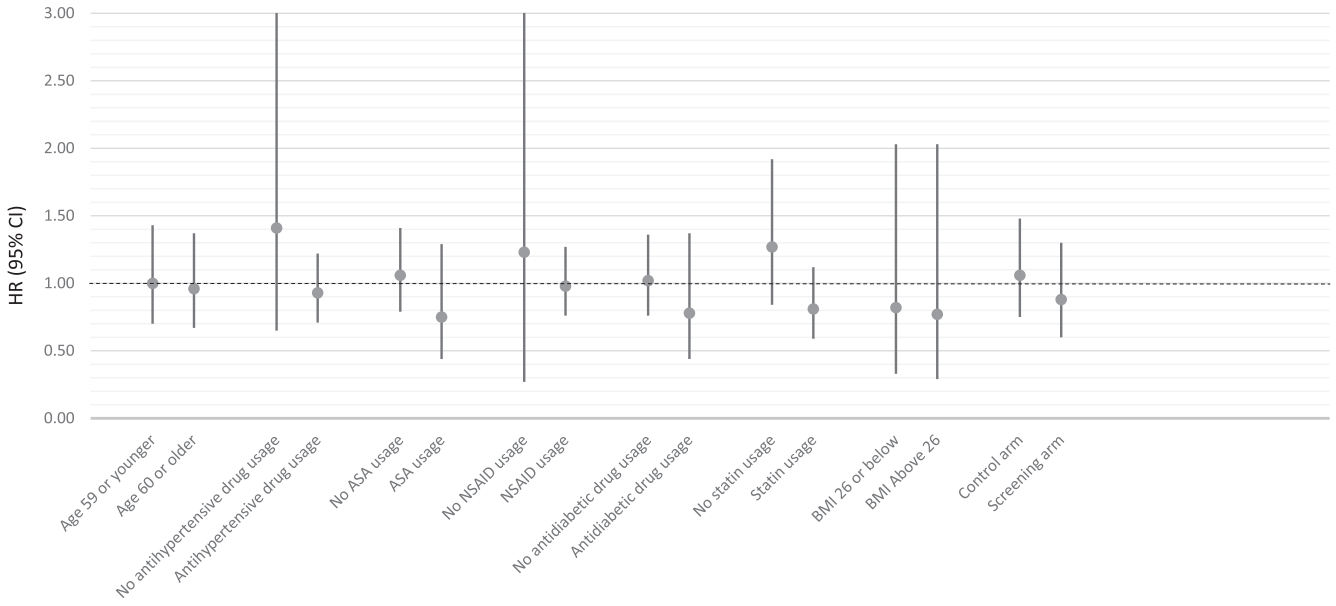

FIGURE 2 Prostate cancer risk among men using HDAC inhibitory antiepileptic drugs compared to men using other types of antiepileptic drugs. Analysis stratified by background characteristics. Population-based cohort of 78 615 Finnish men. HDAC, histone deacetylase

3.4 | Lag-time analyses

Users of AEDs had lower PCa risk compared to nonusers of AEDs also in 1-year (HR = 0.84, 95% CI = 0.75-0.95) and 3-year (HR = 0.84, 95% CI = 0.74-0.97) lag time analyses (Table 4). PCa risk was similar between users of HDACi AEDs and other AEDs in both 1- and 3-year lag-time analyses.

3.5 | Sensitivity analyses

When limiting users of AEDs to those men not using AEDs before randomization, risk of PCa was lower compared to nonusers AEDs (HR = 0.89, 95% CI = 0.78-1.01 in multivariable adjusted analysis). When comparing users of HDACi AEDs and other types of AEDs including only men with no AED use before baseline, no difference in PCa risk was seen (HR = 0.89, 95% CI = 0.76-1.05 in multivariable adjusted analysis).

We performed a sensitivity analysis were only men with at least one PSA test during the follow-up were included to the analysis. Users of AEDs had lower PCa risk compared to nonusers also in this analysis (HR = 0.84, 95% CI = 0.75-0.95), and comparison of PCa risk among users of HDACi AEDs and users of other AEDs yielded also results similar with main analysis (HR = 0.99, 95% CI = 0.77-1.29).

3.6 | Subgroup analyses

PCa risk reduction seen among users of AEDs was only seen in FinRSPC control arm (HR = 0.76, 95% CI = 0.65-0.89), while in the screening arm PCa risk was similar to nonusers of AEDs (HR = 1.00, 95% CI = 0.84-1.19). However, no statistically significant subgroup difference was found (*P* for interaction .281) (Figure 1). Similarly, use of other drugs, age, BMI, marital or occupational status had no significant effect modification.

When comparing users of HDACi AEDs to users of other types of AEDs, no significant effect modification by background characteristics was found, although most subgroup analyses had low statistical power (Figure 2).

4 | DISCUSSION

Our study showed a decreased risk of PCa among users of AEDs compared to nonusers. This finding was significant only for low-risk PCa; nonsignificant risk reduction was found also for high-risk cancer. Similar risk reductions were found in users of HDACi AEDs and users of other types of AEDs.

Our findings might indicate lower frequency of opportunistic PSA testing among users of AEDs, explaining the risk difference for low-risk PCa. Systematic PCa screening regardless of AED use abolishes the impact of differing attendance on PSA testing, and no significant PCa risk difference was seen in this setting in the FinRSPC screening arm. However, this does not seem to comprehensively explain our results, since no statistically significant subgroup difference was found between screening and control arms. Also, when we analyzed PCa risk in men with at least one PSA test during the follow-up, AED users had lower PCa risk compared to nonusers of AEDs similar to the main analysis. However, we did not have information on actual healthcare utilization during the study period,

which limits the interpretation of these results since opportunistic PSA screening is usually linked to outpatient visits. Also, the risk for high-risk PCa was almost significantly lower among users of AEDs compared to nonusers in main analysis. These findings suggest that use of AEDs also has a direct PCa protective effect. However, no evidence was found to support the role of HDAC inhibition in lowering PCa risk indicating that there is some other factor behind our findings.

Men under long-term treatment with HDACi AEDs had lower age-corrected PSA levels compared with control groups in one study of 106 patients.[13] Since finding of low-risk PCa is highly dependent on PSA-testing, this might be one explanation behind the decreased risk of low-risk PCa in patients using HDACi AEDs.

In vitro studies have shown VPA, a HDACi AED, to decrease PCa cell proliferation.[4-6] Our findings do not support clinical relevance of these findings, since no difference in PCa risk reduction was seen when comparing HDACi drug users to users of other AEDs. Users of VPA had nonsignificantly reduced risk of PCa risk (HR = 0.84, 95% CI = 0.65-1.09) when compared to nonusers of AEDs.

Results of previous epidemiological studies on the subject have been inconsistent. In our previous study, we found a significant PCa risk reduction among users of VPA, carbamazepine and phenobarbital.[15] However, only users of carbamazepine had a significant risk reduction for advanced (lymph-node positive or metastatic) disease. A cohort study of 26 911 US veterans found no association between VPA use and PCa risk overall.[14] A Danish population-based case-control study found no decrease in PCa risk among VPA users, but their follow-up time was only 5 years, with no more than six exposed cases.[13] A British cohort study of 3000 patients with epilepsy found increased PCa risk among men using VPA, but it was based on only eight exposed cases.[11]

In lag-time analyses, PCa risk was lower in AED users in both 1-year and 3-year analysis. These findings indicate that PCa protective association with AED use is most likely associated with long-term influence of drug use on development of PCa or related to properties of men using AEDs in long-term, that is, people with epilepsy rather than protopathic bias due to cancer-related condition, such as brain-metastases.

Our study has several strengths. A large population-based cohort was used to evaluate PCa risk among AED users. We were able to obtain accurate information on PCa cases and AED use through comprehensive nationwide registers. Since the detailed exposure information was obtained objectively from a prescription database, which comprehensively records drug reimbursements including the number of packages, amount and dose for the drug purchased, no recall bias affected the estimation of exposure. Our study setting also allowed analyzing PCa risk for both AED users with and without systematic screening for PCa. Exceptional accuracy in our information on medication purchases allowed analyzing usage in time-dependent manner to minimize immortal time bias.

Our study also has some limitations. We did not know the indication for the drug usage except for a small subgroup of people with confirmed epilepsy, although we had information on background comorbidities and of diagnoses within the study population. Some AEDs are also used in management of nonepileptic conditions, such as neuropathic pain and migraine. No significant PCa risk difference was found between users of HDACi AEDs and other types of AEDs when analysis was limited only to people with confirmed epilepsy, which is in line with the findings in the whole study population. We had only information on special reimbursement for years 1995 to 2009, so the statistical power of this subgroup analysis is limited. Drugs administered for hospital inpatients are not recorded in the prescription database causing underestimation and misclassification of the exposure. Also, we did not have information of the actual intake of medication, which might lead to overestimation of the exposure. However, continued unused medication purchases should be uncommon. Alcohol usage, smoking and physical activity are lifestyle factors that could cause confounding in our results and we did not have information on these, but their role as a risk factor for PCa is not well defined.

Our results show that AED use is associated with a reduced risk of PCa. However, the risk reduction does not depend on HDAC inhibitory properties. Further studies are required to evaluate whether this risk reduction leads to lower PCa mortality.

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CONFLICT OF INTEREST

T. L. J. T. has served as a paid consultant for Amgen, Astellas, Bayer, Ferring and Roche. T. J. M. has served as a paid consultant for Astellas, GSK and Janssen Cilag. K. T. has received support from research funding from Medivation/Astellas/Pfizer, Orion and Myovant. J. P. has participated in clinical trials for Eisai, UCB and Bial; received research grants from Eisai, Medtronic, UCB and Liva-Nova; received speaker honoraria from LivaNova, Eisai, Medtronic, Orion Pharma and UCB; received support for travel to congresses from LivaNova, Eisai, Medtronic and UCB and participated in advisory boards for Arvelle, Novartis, LivaNova, Eisai, Medtronic, UCB and Pfizer. The other authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT AND CONSENT TO PARTICIPATE

The study was performed in accordance with the Declaration of Helsinki and the protocol was approved by the ethics committee of Pirkanmaa Hospital District. The informed consent was waived as the study is retrospective.

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REFERENCES

1. Ferlay J, Parkin DM, Steliarova-Fourcher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer*. 2010;46:765-781.
2. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev*. 2010;19:1893-1907.
3. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin*. 2011;61:212-236.
4. Iacopino F, Urbano R, Graziani G, Muzi A, Navarra R, Sica G. Valproic acid activity in androgen-sensitive and -insensitive human prostate cancer cells. *Int J Oncol*. 2008;32:1293-1303.
5. Xia Q, Sung J, Chowdhury W, et al. Chronic administration of valproic acid inhibits prostate cancer cell growth in vitro and in vivo. *Cancer Res*. 2006;66:7237-7244.
6. Shabbeer S, Kortenhorst MS, Kachhap S, Galloway N, Rodriguez R, Carducci MA. Multiple molecular pathways explain the anti-proliferative effect of valproic acid on prostate cancer cells in vitro and in vivo. *Prostate*. 2007;67:1099-1110.
7. Eyal S, Yagen B, Sobol E, Altschuler Y, Shmuel M, Bialer M. The activity of antiepileptic drugs as histone deacetylase inhibitors. *Epilepsia*. 2004;45:737-744.
8. Beutler AS, Li S, Nicol R, Walsh MJ. Carbamazepine is an inhibitor of histone deacetylases. *Life Sci*. 2005;76:3107-3115.
9. Meng Q, Chen X, Sun L, Zhao C, Sui G, Cai L. Carbamazepine promotes Her-2 protein degradation in breast cancer cells by modulating HDAC6 activity and acetylation of Hsp90. *Mol Cell Biochem*. 2011;348:165-171.
10. Sidana A, Wang M, Shabbeer S, et al. Mechanism of growth inhibition of prostate cancer xenografts by valproic acid. *J Biomed Biotechnol*. 2012;2012:180363. https://doi.org/10.1155/2012/180363.
11. Singh G, Bell GS, Driever PH, Sander JW. Cancer risk in people with epilepsy using valproate-sodium. *Acta Neurol Scand*. 2012;125:234-240.
12. Stettner M, Kramer G, Strauss A, et al. Long-term antiepileptic treatment with histone deacetylase inhibitors may reduce the risk of prostate cancer. *Eur J Cancer Prev*. 2012;21:55-64.
13. Hallas J, Friis S, Bjerrum L, et al. Cancer risk in long-term users of valproate: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev*. 2009;18:1714-1719.
14. Kang H, Gillespie TW, Goodman M, et al. Long-term use of valproic acid in US veterans is associated with a reduced risk of smoking-related cases of head and neck cancer. *Cancer*. 2014;120:1394-1400.
15. Salminen JK, Tammela TL, Auvinen A, Murtola TJ. Antiepileptic drugs with histone deacetylase inhibition activity and prostate cancer risk: a population-based case-control study. *Cancer Causes Control*. 2016;27:637-645.
16. Kaae J, Carstensen L, Wohlfahrt J, Melbye M, Allison Boyd H. Epilepsy, anti-epileptic medication use and risk of cancer. *Int J Cancer*. 2014;134:932-938.
17. Nevalainen O, Raitanen J, Ansakorpi H, Artama M, Isojärvi J, Auvinen A. Long-term mortality risk by cause of death in newly diagnosed patients with epilepsy in Finland: a nationwide register-based study. *Eur J Epidemiol*. 2013;28:981-990.
18. Leinonen MK, Miettinen J, Heikkinen S, Pitkäniemi J, Malila N. Quality measures of the population-based Finnish Cancer Registry indicate sound data quality for solid malignant tumours. *Eur J Cancer*. 2017;77:31-39.
19. Martikainen J, Rajaniemi S. *Drug Reimbursement Systems in EU Member States, Iceland and Norway*. Social Security And Health Reports 54. Helsinki, Finland: The Social Insurance Institution, Finland; 2003. Accessed January 2020. https://helda.helsinki.fi/bitstream/handle/10138/13932/Drug_reimbursement.pdf?sequence=1&isAllowed=y.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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