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ORIGINAL PAPER

The association between antihypertensive drug use and incidence of prostate cancer in Finland: a population-based case–control study

Kimmo J. Kemppainen · Teuvo L. J. Tammela · Anssi Auvinen · Teemu J. Murtola

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Abstract Some studies have suggested that use of antihypertensive drugs could decrease prostate cancer risk. We evaluated this association at the population level. All prostate cancer cases in Finland during 1995–2002 and matched controls (24,657 case–control pairs) were identified from the Finnish Cancer Registry and the Population Register Center, respectively. Detailed information on antihypertensive drug purchases was obtained from a national prescription database. Data were analyzed using multivariable-adjusted conditional logistic regression model. Ever use of antihypertensive drugs was associated with marginally elevated overall prostate cancer risk (OR 1.16; 95% CI, 1.12–1.21). Risk of advanced prostate cancer did not differ from the nonusers (OR 1.08, 95% CI 0.98–1.18). The risk increase was observed constantly in all classes of antihypertensive drugs. Our large population-based study generally does not support decreased risk of prostate cancer among antihypertensive drug users. Conversely, an increased overall prostate cancer risk was observed. The association being similar for all drug groups suggests that it is probably caused by a systematic difference between medication users and nonusers, such as differing PSA testing activity.

Keywords Antihypertensive drugs · Case–control · Prostatic neoplasms

K. J. Kemppainen · T. L. J. Tammela · T. J. Murtola (✉)
School of Medicine, University of Tampere,
33014 Tampere, Finland
e-mail: teemu.murtola@uta.fi

T. L. J. Tammela
Department of Urology, Tampere University Hospital, Tampere, Finland

A. Auvinen
School of Health Sciences, University of Tampere, Tampere, Finland

T. J. Murtola
Department of Surgery, Central Finland Central Hospital, Jyväskylä, Finland

Introduction

Prostate cancer causes great losses in terms of health care costs and life years. No less importantly, the treatments used in disease management often bear comorbidity impairing the quality of life of those affected. Thus, disease prevention would be highly desirable.

Although prostate cancer is a medical issue of major importance, we still lack satisfactory knowledge of its etiology. Hypertension has been suggested to be a prostate cancer risk factor [1]. It has been suggested that the same factors that are associated with hypertension, such as obesity, hypertension, heart rate, activation of the autonomic nervous system, and the renin-angiotensin system [1–3] might be associated with an elevated risk of prostate cancer as well.

Not surprisingly, the question has risen whether the use of antihypertensive medication might be associated with a reduced risk of prostate cancer. Several studies have been conducted on the subject, with conflicting results. Positive results are reported for individual drugs, classes of drugs (such as calcium-channel blockers and beta-blockers), and blood pressure medication as a whole, but there are also studies that fail to report such findings [2, 4–7].

Antihypertensive medication is widely used in the developed countries. Thus, any effects these drugs might have on prostate cancer risk are likely to have public health

relevance. The aim of the present study was to comprehensively evaluate population-level associations between antihypertensive drug use and prostate cancer incidence.

Materials and methods

Study design

The data on all newly diagnosed prostate cancer cases in Finland during the years 1995–2002 were obtained from the Finnish Cancer Registry. This data set included 25,029 cases. The Finnish Cancer Registry covers more than 99% of cases diagnosed annually in Finland [8], as health care units are required to report all cancer diagnoses to the Registry. The Registry collects data on the primary site of cancer, histology, and the method of diagnosis. However, the information does generally not include data on tumor differentiation or serum prostate specific antigen (PSA) values. Tumor stage was available for 55% of the cases. Of these, a clear majority (73%) of the tumors were localized.

The method of diagnosis was mostly histology from the primary tumor (99.3%). In a fraction of cases, the diagnosis was only based on clinical (0.4%), radiological (0.3%), or specific laboratory findings (0.02%). All these cases were included in the present study, while 185 cases with missing information on diagnosis were excluded. Additionally, 66 cases appearing twice in the population were excluded.

The Population Register Center of Finland selected controls that were individually matched to the cases for age (±1 year) and area of residence (municipality) at the time of diagnosis. As matching for place of residence was not possible for 121 cases in the oldest age group, these cases were dropped. The 963 individuals, who were included in the study as controls but were later diagnosed with prostate cancer, were included in the study population twice, both as controls and as cases in another case–control pair. The final number of case–control pairs was 24,657.

The prescription database of the Social Insurance Institution of Finland (SII) is a comprehensive nationwide registry covering all reimbursements provided by the Institution. The reimbursements are part of the national public health insurance. They are available for all Finnish residents for all purchases of a drug prescribed by a physician and approved as reimbursable. The prescription database includes information on the amount and dose of drugs as well as the dates of purchase [9].

The classes of drugs used in pharmacological management of hypertension in Finland are diuretics (including thiazides, loop diuretics, and potassium-sparing diuretics), beta-blockers, calcium-channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor (AT II) antagonists. Besides hypertension, all of these drug groups have also other indications for use; diuretics are used in the treatment for edema caused by various conditions such as cardiac or liver insufficiency; beta-blockers are used in management and prevention of cardiac arrhythmias and secondary prevention of cardiovascular disease; calcium-channel blockers are used in the management of angina pectoris and Raynaud's disease; ACE inhibitors and AT II antagonists are used in the management of cardiac insufficiency.

All antihypertensive drugs were only available through a physician's prescription. As the purchase of these drugs was also reimbursable to the patient by the SII, a nearly complete record of the quantity and duration of drug use could be obtained. Drugs prescribed to hospital inpatients were not registered by the SII and were thus unavailable for our study.

The study was granted approval by the ethics committee of the Pirkanmaa health care district, Finland (ETL R03290).

Statistical analysis

For the cases, all drugs purchased during the period from 1 January 1995 to the month of diagnosis were included in the analysis. For their controls, all drugs purchased during the period from 1 January 1995 to the index date (the date of diagnosis for the corresponding case) were similarly included.

The yearly mg amount of a drug purchased by each patient was divided by the defined daily dose (DDD) recommended by the WHO [10] for the drug in question, thus yielding the yearly number of DDDs purchased by each patient.

The data were analyzed using Stata 8.2 software (College Station, Texas). The odds ratios (OR) and 95% confidence intervals (CI) for prostate cancer related to antihypertensive drug use were calculated using conditional logistic regression. The analyses were separately performed for each individual drug and for drug classes. The overall risk of prostate cancer and the risk of advanced disease were calculated separately. Nonusers of any antihypertensive medication were used as reference group. Additionally, a sub-analysis was performed where the OR of prostate cancer among users of each antihypertensive drug group was calculated with users of other groups of antihypertensive drugs as a reference group.

Age-adjusted and multivariable-adjusted analyses were performed. The covariates included in the multivariable-adjusted model were age, place of residence, and use of alpha-blockers, finasteride, cholesterol-lowering drugs, and antidiabetic drugs.

For analyses of cumulative dose and duration, the study population was stratified into quartiles according to the number of DDDs or years of medication use. The OR was then calculated for each quartile. Trends in prostate cancer

risk by quantity or length of medication use were calculated by including the cumulative number of DDDs or years of antihypertensive drug use into the multivariable-adjusted logistic regression model as a continuous variable.

Results

Overall prostate cancer risk

The population characteristics are presented in Table 1. Usage of drugs used in the management of benign prostatic hyperplasia (BPH) (finasteride or alpha-blockers) was more frequent among the cases than the controls (18.7 vs. 12.5%, respectively). The use of any antihypertensive drug was associated with a marginally elevated risk of prostate cancer (Multivariable-adjusted OR 1.16, 95% CI 1.12–1.21.). An elevated risk was observed for several drug classes, namely diuretics in general (OR 1.10, 95% CI 1.06–1.15), thiazides (OR 1.14, 95% CI 1.08–1.20), potassium-sparing diuretics (OR 1.11, 95% CI 1.05–1.17), beta-blockers (OR 1.05, 95% CI 1.00–1.09), calcium-channel blockers (OR 1.12, 95% CI 1.07–1.17), ACE inhibitors (OR 1.12, 95% CI 1.06–1.17), and AT II antagonists (OR 1.18, 95% CI 1.05–1.33) (Table 2).

Positive association between antihypertensive drug use and prostate cancer risk was similar regardless of cumulative dose and duration of use. The OR of prostate cancer slightly decreased by quartiles of increasing cumulative DDD dose of antihypertensive use, but no significant trend in OR was detected when the DDD dose was analyzed as a continuous variable (Table 3). Only the cumulative dose and duration of beta-blockers use were inversely related with the risk of prostate cancer (p for trend < 0.01 and < 0.01, respectively; Table 3).

Risk of advanced prostate cancer

Use of antihypertensive drugs was not associated with the risk of advanced prostate cancer (OR 1.08, 95% CI 0.98–1.18, Table 2). Only the use of thiazides was associated both with an increased overall risk of prostate cancer (OR 1.14, 95% CI 1.08–1.20) as well as an increased risk of an advanced form of the disease (OR 1.18, 95% CI 1.03–1.36).

Although the use of calcium-channel blockers was not associated with the risk of advanced prostate cancer in any quartile of cumulative dose or duration, there was a significant inverse trend with cumulative quantity and length of use (p for trend $= 0.03$ and $= 0.01$, respectively; Table 4). None of the other drug groups were associated with the risk of advanced prostate cancer.

Comparison of prostate cancer risk between users of different groups of antihypertensive drugs and by BPH medication usage status

When the analyses were repeated for each drug group with the men using other groups of antihypertensive drugs, instead of nonusers, as a reference group, the results did not

Table 1 Study population characteristics

	Cases		Controls	
	n	% of total	*n*	% of total
Total	24,657	100	24,657	100
Nonusers	11,938	48.4	12,908	52.4
Any antihypertensive drug use	12,719	51.6	11,749	47.6
Diuretic use	5,969	24.2	5,534	22.4
>1500 DDD[a]	1,637	6.6	1,514	6.1
Beta-blocker use	7,609	30.9	7,292	29.6
>1,500 DDD	879	3.6	906	3.7
Calcium-channel blocker use	5,018	20.4	4,524	18.3
>1,500 DDD	1,033	4.2	915	3.7
ACE inhibitor use	4,444	18.0	4,041	16.4
>1,500 DDD	1.518	6.1	1,384	5.6
Angiotensin II antagonist use	643	2.6	539	2.2
>1,500 DDD	55	0.2	33	0.1
Use of other types of antihypertensive drugs[b]	654	2.7	539	2.2
>1,500 DDD	41	0.2	49	0.2
Statin use	2,621	10.6	2,439	9.9
Antidiabetic drug use	2,209	9.0	2,391	9.7
BPH medication[c] use	4,603	18.7	3,086	12.5

Case–control study of all newly diagnosed prostate cancer cases in Finland during 1995–2002 and matched controls

[a] DDD = defined daily dose

[b] Includes users of centrally acting and peripherally acting antiadrenergic agents

[c] BPH medication: drugs used in management of benign prostatic hyperplasia; finasteride, tamsulosin, and alfuzosin

Table 2 Overall prostate cancer risk and risk of advanced cancer among ever users of antihypertensive drug users compared to never users

	Overall prostate cancer			Advanced prostate cancer		
	No. of discordant case–control pairs (case exposed/control exposed)	$OR_{age\text{-}adjusted}$ (95% CI)	$OR_{multivariable\text{-}adjusted}$[a] (95% CI)	No. of discordant case–control pairs	$OR_{age\text{-}adjusted}$ (95% CI)	$OR_{multivariable\text{-}adjusted}$[a] (95% CI)
All antihypertensives	6,301/5,404	1.18 (1.14– 1.22)	1.16 (1.12– 1.21)	875/857	1.02 (0.93–1.12)	1.08 (0.98–1.18)
Diuretics	2,972/2,518	1.11 (1.06–1.15)	1.10 (1.06–1.15)	446/402	1.12 (1.01–1.25)	1.16 (1.04–1.30)
Beta-blockers	3,750/3,344	1.06 (1.02– 1.11)	1.05 (1.00–1.09)	507/507	0.95 (0.86–1.05)	1.01 (0.91– 1.12)
Calcium-channel blockers	2,534/2,048	1.14 (1.09–1.19)	1.12 (1.07– 1.17)	314/319	0.92 (0.81–1.04)	0.96 (0.85–1.09)
ACE inhibitors	2,273/1,905	1.12 (1.07–1.17)	1.12 (1.06–1.17)	291/290	0.98 (0.86–1.11)	1.03 (0.90–1.17)
Angiotensin II antagonists	327/252	1.20 (1.07–1.35)	1.18 (1.05–1.33)	29/34	0.94 (0.66–1.34)	0.99 (0.69–1.42)
Other types of antihypertensive drugs[b]	233/190	1.22 (1.07–1.37)	1.15 (1.02–1.29)	37/28	1.20 (0.87–1.66)	1.23 (0.89–1.70)

Case–control study of all newly diagnosed prostate cancer cases in Finland during 1995–2002 and matched controls

[a] Calculated using logistic regression model adjusted for age, place of residence, and use of cholesterol-lowering drugs, antidiabetic drugs, finasteride, or alpha-blockers

[b] Includes users of centrally acting and peripherally acting antiadrenergic agents

display any notable changes. In this analysis, the use of loop diuretics and beta-blockers was negatively associated with the overall risk of prostate cancer (OR 0.91, 95% CI 0.84–1.00 and OR 0.91, 95% CI 0.85–0.98, respectively). The use of thiazides continued to be positively associated with the risk of advanced cancer (OR 1.24, 95% CI 1.00–1.54). The use of calcium-channel blockers was negatively associated with the risk of advanced prostate cancer (OR 0.77, 95% CI 0.63–0.94), and there was a significant decreasing trend in the risk by increasing cumulative DDD dose and years of usage (p for trend = 0.029 and 0.023, respectively). However, no drug class was consistently associated with prostate cancer risk when both the overall risk and the risk of advanced cancer were considered.

We also performed a sub-analysis where the study population was stratified by BPH medication usage. Among ever users of BPH medication, usage of antihypertensive drugs was not associated with increased risk of prostate cancer, either overall or for advanced cancer (Table 5). Conversely, in this sub-analysis, usage of calcium-channel blockers and ACE inhibitors was associated with decreased overall prostate cancer risk and ACE inhibitor users had even decreased risk of advanced cancer. However, significant inverse association with the cumulative amount of medication use was only observed for overall prostate cancer risk among ACE inhibitor users ($p = 0.045$ for a decreasing trend). The results obtained with never users of BPH medication were similar to the results from the overall analysis (Table 5).

Finally, we performed a sensitivity analysis where all prescriptions within 5 years prior to the diagnosis/index date were excluded in order to analyze biologically plausible lag times between antihypertensive use and prostate cancer risk. In this analysis, the statistically significant positive associations remained between overall prostate cancer risk and usage of any antihypertensive drug (OR 1.08; 95% CI 1.02–1.13), diuretics (OR 1.12; 95% CI 1.05–1.20), and ACE inhibitors (OR 1.13; 95% CI 1.05–1.21). None of the drug groups was associated with risk of advanced prostate cancer nor showed protective association for the overall risk.

Discussion

We have demonstrated with a large, population-level dataset that antihypertensive drug use is generally not associated with a decreased prostate cancer risk, either overall or for advanced cancer. Previous research has suggested that antihypertensive drug usage might be associated with a diminished risk of prostate cancer [2]. The argument has been made for antihypertensives in

Table 3 Overall prostate cancer risk by cumulative amount and duration of antihypertensive drug use compared to never users

	All antihypertensives	Diuretics	Beta-blockers	Calcium-channel blockers	ACE inhibitors	AT II antagonists
Cumulative amount of use	OR (95% CI)[a]	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
1st quartile[b]	1.19 (1.12–1.26)	1.16 (1.08–1.26)	1.08 (1.01–1.16)	1.18 (1.09–1.28)	1.23 (1.13–1.34)	1.30 (1.03–1.64)
2nd quartile	1.15 (1.08–1.22)	1.08 (1.00–1.16)	1.04 (0.97–1.11)	1.04 (0.96–1.14)	1.03 (0.94–1.13)	1.05 (0.84–1.33)
3rd quartile	1.16 (1.10–1.23)	1.08 (1.00–1.17)	1.02 (0.95–1.10)	1.11 (1.02–1.20)	1.11 (1.02–1.22)	1.11 (0.88–1.40)
4th quartile	1.11 (1.05–1.18)	1.10 (1.01–1.19)	1.04 (0.96 –1.11)	1.14 (1.05–1.24)	1.11 (1.01–1.21)	1.27 (1.00–1.60)
p^{c}_{trend}	0.798	0.262	0.003[d]	0.633	0.314	0.194
Cumulative duration of use						
1 year or less	1.22 (1.14–1.30)	1.15 (1.07–1.23)	1.10 (1.02–1.18)	1.18 (1.08–1.28)	1.19 (1.09–1.30)	1.24 (0.99–1.55)
2–3 years	1.15 (1.08–1.21)	1.07 (1.00–1.14)	1.04 (0.98–1.11)	1.09 (1.01–1.18)	1.08 (1.00–1.17)	1.03 (0.85–1.26)
4–5 years	1.12 (1.05–1.19)	1.09 (1.00–1.19)	1.00 (0.93–1.08)	1.05 (0.96–1.15)	1.12 (1.02–1.23)	1.41 (1.02–1.95)
6 years or longer	1.14 (1.07–1.21)	1.12 (1.02–1.24)	1.05 (0.97–1.13)	1.15 (1.04–1.28)	1.09 (0.98–1.21)	1.46 (0.79–2.67)
p^{c}_{trend}	0.337	0.245	0.002[d]	0.993	0.433	0.233

Case–control study of all newly diagnosed prostate cancer cases in Finland during 1995–2002 and matched controls

[a] Calculated using logistic regression model adjusted for age, place of residence, and use of cholesterol-lowering drugs, antidiabetic drugs, finasteride, or alpha-blockers

[b] DDD quartiles for all antihypertensives combined: 1–372, 373–1,078, 1,079–2,550, ≥2,551 DDD; diuretics: 6–249, 250–686, 687–1,599, ≥1,600 DDD; beta-blockers: 1–144, 145–434, 435–980, ≥981 DDD, calcium-channel blockers: 1–200, 201–599, 600–1,300, ≥1,301 DDD, ACE inhibitors: 3–256, 257–816, 817–2,020, ≥2,021 DDD; AT II antagonists: 7–150, 151–405, 406–826, ≥827 DDD

[c] Calculated by entering cumulative amount of DDDs or years of medication use as continuous variables into multivariable-adjusted logistic regression model

[d] Decreasing trend in prostate cancer risk

Table 4 Risk of advanced prostate cancer by cumulative amount and duration of antihypertensive drug use compared to never users

	All antihypertensives	Diuretics	Beta-blockers	Calcium-channel blockers	ACE inhibitors	AT II antagonists
Cumulative amount of use	OR (95% CI)[a]	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
1st quartile[b]	1.04 (0.90–1.20)	1.25 (1.03–1.51)	0.95 (0.80–1.14)	0.97 (0.79–1.21)	1.11 (0.88–1.40)	1.02 (0.51–2.04)
2nd quartile	1.15 (1.00–1.33)	1.22 (1.00–1.49)	0.96 (0.81–1.14)	0.91 (0.73–1.14)	0.93 (0.74–1.17)	0.79 (0.40–1.54)
3rd quartile	1.01 (0.87–1.17)	1.19 (0.97–1.45)	1.01 (0.84–1.22)	0.92 (0.74–1.14)	0.96 (0.75–1.23)	0.96 (0.48–1.90)
4th quartile	1.07 (0.90–1.26)	0.99 (0.81–1.22)	1.18 (0.96–1.44)	1.07 (0.83–1.37)	1.14 (0.88–1.48)	1.42 (0.62–3.27)
p^{c}_{trend}	0.366	0.778	0.794	0.029[d]	0.962	0.741
Cumulative duration of use						
1 year or less	1.10 (0.94–1.29)	1.21 (1.01–1.45)	0.99 (0.82–1.19)	0.91 (0.74–1.12)	1.02 (0.82–1.28)	1.61 (0.80–3.24)
2–3 years	1.05 (0.92–1.21)	1.24 (1.05–1.47)	1.05 (0.90–1.22)	0.98 (0.81–1.18)	1.01 (0.82–1.23)	0.68 (0.36–1.31)
4–5 years	0.98 (0.83–1.16)	0.99 (0.79–1.23)	0.88 (0.72–1.08)	0.91 (0.72–1.16)	1.03 (0.80–1.32)	2.08 (0.76–5.67)
6 years or longer	1.15 (0.95–1.38)	1.15 (0.86–1.52)	1.14 (0.91–1.44)	1.12 (0.83–1.53)	1.10 (0.80–1.50)	2.02 (0.18–22.56)
p^{c}_{trend}	0.763	0.219	0.782	0.007[d]	0.721	0.700

Case–control study of all newly diagnosed prostate cancer cases in Finland during 1995–2002 and matched controls

[a] Calculated using logistic regression model adjusted for age, place of residence, and use of cholesterol-lowering drugs, antidiabetic drugs, finasteride, or alpha-blockers

[b] DDD quartiles for all antihypertensives combined: 1–372, 373–1,078, 1,079–2,550, ≥2,551 DDD; diuretics: 6–249, 250–686, 687–1,599, ≥1,600 DDD; beta-blockers: 1–144, 145–434, 435–980, ≥981 DDD, calcium-channel blockers: 1–200, 201–599, 600–1,300, ≥1,301 DDD, ACE inhibitors: 3–256, 257–816, 817–2,020, ≥2,021 DDD; AT II antagonists: 7–150, 151–405, 406–826, ≥827 DDD

[c] Calculated by entering cumulative amount of DDDs or years of medication use as continuous variables into multivariable-adjusted logistic regression model

[d] Decreasing trend in prostate cancer risk

Table 5 Overall prostate cancer risk and risk of advanced cancer among users of antihypertensive drugs compared to never users

	Overall prostate cancer OR (95% CI)[a]	Advanced prostate cancer OR (95% CI)
BPH medication[b] ever users		
Any antihypertensive	0.80 (0.64–1.00)	0.42 (0.17–1.09)
Diuretics	0.85 (0.69–1.06)	0.79 (0.35–1.78)
Beta-blockers	0.79 (0.63–0.98)	1.41 (0.62–3.17)
Calcium-channel blockers	0.77 (0.61–0.97)	0.51 (0.19–1.37)
ACE inhibitors	0.76 (0.60–0.97)	0.31 (0.13–0.75)
ATII-blockers	0.87 (0.53–1.42)	0.19 (0.02–2.29)
Never-users of BPH medication		
Any antihypertensive	1.23 (1.17–1.28)	1.12 (1.01–1.25)
Diuretics	1.15 (1.09–1.21)	1.22 (1.07–1.38)
Beta-blockers	1.08 (1.03–1.14)	1.04 (0.92–1.18)
Calcium-channel blockers	1.20 (1.14–1.27)	1.00 (0.87–1.15)
ACE inhibitors	1.14 (1.08–1.21)	1.06 (0.92–1.23)
ATII-blockers	1.25 (1.07–1.46)	1.11 (0.72–1.72)

Analysis stratified by BPH medication usage. Case–control study of all newly diagnosed prostate cancer cases in Finland during 1995–2002 and matched controls

[a] Calculated using logistic regression model adjusted for age, place of residence, use of cholesterol-lowering drugs, and use of antidiabetic drugs

[b] BPH medication: drugs used in management of benign prostatic hyperplasia; finasteride, tamsulosin, and alfuzosin

general, as well as for individual drugs and drug classes, such as beta-blockers, calcium-channel blockers, and captopril [2, 4–6]. The present study generally does not corroborate these findings. On the contrary, we found that the use of antihypertensives was associated with a marginally elevated overall risk of prostate cancer. We did, however, observe a statistically significant decreasing trend in the risk of advanced prostate cancer by cumulative amount and duration of calcium-channel blocker use, which was not observed in users of any other drug group. Thus, we cannot entirely rule out the beneficial effects of calcium-channel blockers against prostate cancer.

Considering the risk increase being comparable for the large majority of antihypertensive drug users and the lack of dose-dependent associations, we find it justified to conclude that the increased risk among antihypertensive drug users is most probably caused by systematic differences between medication users and nonusers unrelated to the medication. Those who receive treatment for hypertension likely have regular contact with health care and may also be more likely to be screened for prostate cancer, although the prevalence of PSA testing in Finland was very low during the study period [11]. Further, it has been suggested that hypertension may be associated with increased serum PSA [12, 13]. More active PSA testing and thus enhanced detection of early-stage tumors could explain why we observed an increased overall prostate cancer risk among antihypertensive drug users, while the risk of advanced prostate cancer did not differ from that of nonusers. Further, the increased risk was not observed in our subpopulation of BPH medication users, which further supports our inference of the result being affected by PSA testing activity. In this sub-analysis, the effect of differing PSA testing was diminished, as all BPH medication users undergo the test as part of a routine diagnostic work-up. On the other hand, hypertension, the common indication for the use of antihypertensive drugs, could be associated with an increased prostate cancer risk or the two diseases may share common risk factors [1]. Men using antihypertensive drugs likely have a long history of elevated blood pressure, which could have affected carcinogenesis in the prostate. This was not controlled for in our study, since we did not have information on blood pressure at the time of the study nor in the past. However, our analysis covered all purchases of antihypertensive medications, regardless of indication and, e.g., medications used for heart failure or angina pectoris are included. Therefore, the focus of analysis is on the drugs rather than indication.

According to some studies, hypertension and prostate cancer may ultimately have a common cause, for which both sympathetic activation and the RAS system have been identified as candidates; this would, of course, explain why beta-blockers and ACE inhibitors in particular might reduce the risk of prostate cancer [2, 3]. One clinical study has suggested that use of ACE inhibitor captopril might delay PSA relapse following radical prostatectomy [14]. We observed a decreasing trend in overall prostate cancer risk among men using beta-blockers, but not among ACE

inhibitor users. Calcium-channel blockers may diminish the risk of prostate cancer through a different mechanism, by inhibiting the proliferation of cancer cells and by inducing apoptosis [5]. Thus, in theory, calcium-channel blockers could be effective in preventing progression of early-stage tumors into advanced cancers. Our results partly support this, as we observed significant inverse association between cumulative duration and dose of calcium-channel blocker use and prostate cancer risk. However, even in our large dataset, the OR of prostate cancer was not significantly affected when the risk was compared between users of calcium-channel blockers and nonusers of antihypertensives. Thus, uncertainty remains.

The present study is based on very large material that is unaffected by recall bias. The racially homogeneous population of Finland (over 98% Caucasian) and the nearly complete registers of purchased drugs and diagnosed malignancies offer an excellent opportunity to explore the associations between drug use and cancer.

There were, still, many variables that could not be controlled for in this study. Firstly, we did not have data on the frequency of PSA testing and thus could not know surely whether the increased overall prostate cancer risk among medication users was really due to more active PSA testing. Secondly, the stage of cancer was only known for 55% of the cases. However, this is not likely to bias our results as the proportion of cases with missing information on stage did not differ by medication use. Thirdly, we did not have records of the antihypertensive use prior to 1995. This could lead to exposure misclassification, as some men with the index date early in the study period could have had a longer history of medication use than what appeared in our analysis. This would bias our results toward the null. However, the effect of this bias is likely minimal, as the results were similar for the case–control pairs with an index date occurring late in the study period (during 2000–2002) and thus with more complete exposure information. Thirdly, we could not directly control for propensity to seek health care services, as the information was not available. Adjusting our analysis for place of residence and simultaneous use of other types of medications served as a proxy for this, but likely some residual confounding remained. Possibly antihypertensive medication users were still more likely to have a health care contact and a PSA test, raising the observed OR of prostate cancer among drug users. Finally, we did not have information on some other exposures that might affect prostate cancer risk, such as obesity, vitamin ingestion, and physical activity. These could have caused bias in either direction, depending on their association with antihypertensive drug use.

Despite these weaknesses, the present study provides convincing evidence against any substantial protective effect that antihypertensives might have against prostate cancer. Even if the proposed theories of the common cause of hypertension and prostate cancer are correct, the currently used antihypertensives are unlikely to have any great value in primary prevention of prostatic malignancies, with the possible exception of calcium-channel blockers.

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