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Prostate cancer risk among users of finasteride and alpha-blockers – A population based case–control study

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ABSTRACT

Finasteride has been reported to reduce prostate cancer risk in asymptomatic men. However, in clinical practice finasteride and alpha-blockers are used to treat benign prostatic hyperplasia (BPH). We evaluated prostate cancer risk among users of BPH pharmacotherapy at the population level. Comprehensive Finnish national registries provided information on 24723 prostate cancer cases and controls. Overall, prostate cancer risk was elevated among users of both drug categories compared to non-users (odds ratio, OR = 1.41; 95% confidence interval, CI 1.31–1.51 for finasteride and OR = 1.79; 95% CI 1.67–1.91 for alpha-blockers). However, the risk was lower among finasteride users when compared with alpha-blocker users (OR = 0.80; 95% CI 0.64–1.00). Regular finasteride users had the lowest risk. The increased risk is probably due to enhanced diagnostics of prostate cancer in men with BPH. Finasteride use does not decrease prostate cancer incidence compared with non-users. Nevertheless, the risk is lower when compared with alpha-blocker users.

1. Introduction

Prostate cancer is the most common malignancy among men in most countries.[1] An estimated 225227 new cases of prostate cancer were diagnosed in Europe in 2002.[1] Prostate cancer is among the three most common causes of cancer death in men in most European countries.[1]

Benign prostatic hyperplasia (BPH) is a common disease affecting up to 40% of men in the oldest age groups.[2] Incidence of both BPH and prostate cancer increases with age. However, association between these two conditions has not been established.[3]

Alpha-blockers and 5α-reductase inhibitors are currently used for medical management of BPH.[4] The 5α-reductase inhibitors decrease prostate size by inhibiting formation of the active androgen metabolite, dihydrotestosterone. Finasteride was the only 5α-reductase inhibitor licensed in Finland during the study period. Alpha-blockers reduce lower urinary tract symptoms (LUTS) of BPH by relaxing smooth muscle in the prostate.[4] The principal indication for both drug groups is symptomatic BPH. However, the effect of alpha-blocker treatment commences more rapidly than finasteride. Thus, men with severe BPH symptoms are more often treated with alpha-blockers.

Results from the Prostate Cancer Prevention Trial (PCPT) have shown a reduction in prostate cancer risk in finasteride users.[5] To be eligible for inclusion in the trial, the men had to have only little or no LUTS.[5] However, currently the only

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official indications for finasteride use are treatment of symptomatic BPH and male pattern baldness.

Some alpha-blockers have been reported to inhibit growth of prostate cancer cells *in vitro*.[6] Alpha-blockers licensed in Finland are tamsulosin and alfuzosin.

This study was undertaken to examine prostate cancer risk among users of BPH pharmacotherapy at the population level.

2. Patients and methods

2.1. Study population

All 25029 newly diagnosed prostate cancer cases in Finland during 1995–2002 were identified from the Finnish Cancer Registry, which covers more than 99% of all prostate cancer patients in Finland.[7] The register information includes primary site of cancer, histology, date and method of diagnosis. Information on stage was available in 55% of cases (13616 patients). Of these 73% were localised. The registry does not routinely record differentiation, such as Gleason score, nor serum prostate specific antigen (PSA) values.

Practically all the cases were histologically confirmed (99.3%). Also cases with the diagnosis based solely on clinical (0.4%), radiological (0.3%) or specific laboratory findings (0.02% of cases) were included. A total of 185 cases (0.7%) with an unknown method of diagnosis were excluded.

The Population Register Centre of Finland selected 24723 male controls with individual matching on age and geographical area of the cases at the time of the diagnosis. A total of 963 controls were subsequently diagnosed with prostate cancer during the study period, thus appearing twice in the analysis. Population size in Finnish municipalities ranges from less than 200 to 560000.[8] For 121 cases in the oldest age group, matched controls could not be found from the same municipality, resulting in their exclusion. A total of 24723 case–control pairs were included in the analyses.

Following approval from the ethics committee of the Pirkanmaa health care district, Finland, obtaining informed consent from the study population was not undertaken due to the large size of the population, and due to part of the population being unattainable (deceased or moved abroad) by the time of the study.

2.2. Drug exposure data

Information on BPH pharmacotherapy prescribed to the study population and reimbursed by the Social Insurance Institution of Finland during 1995–2002 was obtained from the comprehensive nationwide prescription database of the Social Insurance Institution of Finland (SII). The database provided individual information on quantity and time of the medication use.

SII manages the national public health insurance in Finland, providing reimbursements for the cost of medicines prescribed by a physician (with the exception of hospital inpatients).[9] The prescription database covers all reimbursements paid by the SII, which are available for all Finnish citizens for every drug purchase. However, not all drugs are approved as reimbursable, thus not covered in the prescription database.

Finasteride was licensed for use and approved for reimbursement for treatment of BPH in Finland in 1992. Therefore, information on finasteride use for this indication was available for the entire follow-up period. Finasteride is not reimbursed for treatment of androgen-induced alopecia; thus information on this use was not available. Tamsulosin was approved for basic reimbursement in 1996 and alfuzosin in 1997. The only official indication for both alpha-blockers is the symptoms of BPH.

The defined daily doses (DDDs) of finasteride, tamsulosin and alfuzosin available for the treatment of BPH in Finland are 5 mg, 0.4 mg and 10 mg, respectively. Medication use was quantified by calculating the number of DDDs bought each year based on package size and the number of packages bought.

2.3. Statistical analysis

Only the medication purchases prior to the month of diagnosis were included in the analyses. For controls, the month of diagnosis of their matched case was used as the reference month for medication purchases.

Prostate cancer may cause symptoms similar to BPH. Therefore, some medication purchases were likely prescribed to treat symptoms of prostate cancer while diagnostic process was under way. To reduce this bias, all cases and controls whose only purchases were 100 DDD or less of either drug-group within six months preceding the reference month were excluded from the analysis. Thus 1910 cases and 375 controls were excluded.

A conditional logistic regression model stratified by age and geographical area was used to calculate odds ratios (OR) and 95% confidence intervals (95% CI) for prostate cancer related to pharmacotherapy using STATA 8.2 software. For analyses comparing the risk between finasteride and alpha-blocker users, a stratified unconditional model was used due to low number of matched case–control pairs available in these two groups.

To estimate the time relation between medication use and prostate cancer diagnosis, the time period preceding the diagnosis was extended 12 months at a time running backwards from the reference month. Only the case–control pairs with the information available for the entire time period (1–8 years prior to the reference month) were included in these analyses.

Regularity of medication use was assessed based on two variables: the number of years during which each person had reimbursements and the number of DDDs reimbursed each year. Regular users had been reimbursed at least 365 DDDs during each year of the analysed time period. Irregular users' reimbursements covered each year, but were less than 365 DDD/year. Short-term users had at least one year without reimbursements during the analysed time period. Also analyses were carried out, where persons who had been reimbursed 350 DDD or more per year were considered regular users. However, the results were not changed.

For analyses on prostate cancer stage a four year cutoff point was used for duration of medication use, since the number of men with longer duration would not have allowed

stratified analyses. Additionally, the prostate cancer risk difference between treatment arms in the PCPT was evident already after four years of treatment.[5]

3. Results

3.1. Prevalence of BPH pharmacotherapy

A total of 7715 men (15.6% of the overall study population) had used BPH pharmacotherapy. Of them 1578 had used both types of formulations. Finasteride use was more frequent among cases than controls (Table 1). The difference was greatest among users of smallest quantities of finasteride and diminished with increasing total cumulative quantity.

A similar pattern in prevalence was observed in tamsulosin users (Table 1). In alfuzosin users the prevalence differed only when the total cumulative quantity was 365 DDD or less.

3.2. Finasteride and prostate cancer risk

Overall, finasteride use was associated with an increased prostate cancer risk (OR = 1.41; 95% CI 1.31–1.51). The risk was increased among short-term users regardless of length of the analysed time period (Table 2a). Among the irregular users the risk was elevated only when the analysed time period was the year preceding the reference month. Prostate cancer risk among regular finasteride users did not differ from that of the non-users.

Finasteride use did not affect prostate cancer risk if usage had been discontinued prior to the reference month (data not shown). The effect of finasteride did not significantly vary between age groups (data not shown).

Finasteride use for less than four years was associated with an increased risk for localised prostate cancer (Table 3). However, the risk of advanced cancer was not affected by finasteride usage.

Table 1 – Prevalence of BPH pharmacotherapy among Finnish prostate cancer cases diagnosed in 1995–2002 and their matched controls

Pattern of use[a]	Finasteride		Tamsulosin		Alfuzosin	
	Cases	Controls	Cases	Controls	Cases	Controls
Ever-users	2534	1761	4244	2108	410	186
Never-users	22189	22962	20479	22615	24313	24537
Cumulative dose (DDD)[b]						
0	89.4	92.9	80.6	90.7	97.9	99.0
1–365	6.5	3.5	15.8	6.6	1.9	0.8
366–730	1.8	1.5	2.0	1.3	0.1	0.1
731–1095	0.95	0.8	0.9	0.6	0.05	0.05
1096–1460	0.5	0.5	0.4	0.4	0.01	0.01
1461–1825	0.35	0.4	0.2	0.2	–	–
1826–2190	0.2	0.3	0.1	0.0	–	–
⩾2191	0.1	0.1	0.01	0.005	–	–

Distribution of users according to the total cumulative quantity of medication reimbursements.
a Total number of men in each category.
b Total cumulative quantity of DDDs reimbursed during the study period. Reported as percentages of men in each category.

Table 2a – Odds ratios of prostate cancer among finasteride users in the study population of all Finnish prostate cancer cases diagnosed in 1995–2002 and their matched controls

Period of exposure[a]	Regular use[b]			Irregular use[c]			Short-term use[d]		
	No. of discordant pairs[e]	OR	95% CI	No. of discordant pairs	OR	95% CI	No. of discordant pairs	OR	95% CI
1 year	345/332	1.04	0.90–1.21	394/277	1.42	1.21–1.65	415/256	1.62	1.39–1.89
2 years	111/113	0.98	0.76–1.28	312/286	1.09	0.93–1.28	1102/755	1.46	1.33–1.61
3 years	49/36	1.36	0.88–2.09	235/240	0.98	0.82–1.18	1181/772	1.53	1.40–1.68
4 years	56/72	0.78	0.55–1.10	114/113	1.00	0.77–1.30	1132/745	1.52	1.39–1.67
5 years or more	25/26	0.96	0.56–1.66	98/100	0.98	0.74–1.29	1067/721	1.48	1.34–1.62

a Length of the time period included in the analysis. Measured as consecutive years running backwards from the reference month.
b Each person categorised as regular user has been reimbursed at least 365 DDD of finasteride during each year of the exposure period.
c Irregular users have been reimbursed less than 365 DDD of finasteride during each year of the exposure period.
d Finasteride users with one or more years without reimbursements during the exposure period are categorised as short-term users.
e Number of case–control pairs discordant to finasteride use. Case: user – control: non-user/Case: non-user – control: user.

Table 2b – Odds ratios of prostate cancer among alpha-blocker users in the study population of all Finnish prostate cancer cases diagnosed in 1995–2002 and their matched controls

Period of exposure[a]	Regular use[b]			Irregular use[c]			Short-term use[d]		
	No. of discordant pairs[e]	OR	95% CI	No. of discordant pairs	OR	95% CI	No. of discordant pairs	OR	95% CI
1 year	96/49	1.95	1.34–2.83	996/524	1.90	1.70–2.13	595/242	2.46	2.10–2.88
2 years	199/141	1.41	1.11–1.77	290/180	1.61	1.32–1.96	1227/529	2.32	2.09–2.57
3 years	109/78	1.40	1.01–1.94	174/117	1.49	1.15–1.92	1183/616	1.92	1.74–2.12
4 years	54/34	1.60	0.97–2.64	116/73	1.59	1.14–2.20	1052/581	1.81	1.63–2.00
5 years or more	15/5	2.79	1.00–7.74	53/27	1.96	1.22–3.14	1704/1058	1.61	1.47–1.77

a Length of the time period included in the analysis. Measured as consecutive years running backwards from the reference month.
b Each person categorised as regular user has been reimbursed at least 365 DDD during each year of the exposure period.
c Irregular users have been reimbursed less than 365 DDD during each year of the exposure period.
d Users with one or more years without reimbursements during the exposure period are categorised as short-term users.
e Number of case–control pairs discordant to alpha-blocker use. Case: user – control: non-user/Case: non-user – control: user.

3.3. *Alpha-blockers and prostate cancer risk*

Alpha-blocker use was associated with substantially increased prostate cancer risk (OR = 1.79; 1.67–1.91). The risk remained elevated regardless of regularity of use or length of the analysed time period (Table 2b).

Alpha-blocker use did not affect prostate cancer risk among men who had discontinued medication prior to the reference month (data not shown). The risk increase tended to be stronger among the youngest age group (60 years or younger) compared to the oldest age group (77 years or older) (OR = 2.78, 2.38–3.25 *versus* OR = 1.45, 1.23–1.71, respectively).

Only the risk of localised prostate cancer was affected among alpha-blocker users (Table 3). The risk was increased among regular users for less than four years and non-regular users for both duration categories.

3.4. *Prostate cancer risk among BPH medication users*

The risk among users of both drug categories was elevated compared with that among non-users (OR = 1.49; 95% CI 1.34–1.65).

However, when compared with the alpha-blocker users the overall prostate cancer risk in finasteride users was decreased (OR = 0.80; 95% CI 0.64–1.00). A significant decrease was observed among regular and irregular users (Table 4). The odds ratio tended to be less than one also among the short-term users, but significant differences were not observed. There were no clear trends in risk associated with duration of finasteride use.

4. Discussion

Our results show an increased risk of prostate cancer in men using either group of BPH phrarmacotherapy. The risk increase is most likely caused by increased detection of latent prostate cancers due to differential diagnostics of BPH. However, the risk was lower among finasteride users compared with the alpha-blocker users. Our results emphasise that prostate cancer risk in symptomatic finasteride users is strongly affected by not only the biological effect of finasteride , but by the clinical practices and diagnostics in the management of LUTS and BPH as well.

Ours is the first study to examine prostate cancer risk among finasteride users in a population-based setting and compare it to that of alpha-blocker users.

Due to the comprehensive national health care registers of Finland, we were able to evaluate the effect of medication use on prostate cancer risk at the population level. Enrollment of

Table 3 – Prostate cancer stage in finasteride and alpha-blocker users in the study population of all Finnish prostate cancer cases diagnosed in 1995–2002 and their matched controls

Duration of medication use		Pattern of use	Localised cancer			Non-localised cancer		
			No. of discordant pairs[a]	OR	95% CI	No. of discordant pairs	OR	95% CI
Finasteride	<4 years	Regular	133/101	1.32	1.01–1.72	35/41	0.86	0.54–1.34
		Non-regular[b]	623/319	1.95	1.71–2.23	114/128	0.89	0.69–1.14
	⩾4 years	Regular	20/13	1.60	0.52–4.89	–	–	–
		Non-regular	428/360	1.19	0.92–1.53	47/76	0.62	0.37–1.04
Alpha-blockers	<4 years	Regular	119/77	1.55	1.16–2.06	28/26	1.08	0.63–1.84
		Non-regular	707/347	2.04	1.79-2.32	132/119	1.11	0.87–1.43
	⩾4 years	Regular	12/7	1.71	0.67–4.35	–	–	–
		Non-regular	447/178	2.51	2.11–2.99	63/84	0.75	0.54–1.05

a Number of case–control pairs discordant to medication use. Case: user – control: non-user/Case: non-user – control: user.
b Includes irregular and short-term medication users.

Table 4 – Prostate cancer risk among finasteride users compared with alpha-blocker users

Period of exposure[a]	Regular use[b]			Irregular use[c]			Short-term use[d]		
	No. of exposed cases	OR	95% CI	No. of exposed cases	OR	95% CI	No. of exposed cases	OR	95% CI
1 year	356	0.61	0.51–0.72	423	0.83	0.69–0.99	1042	1.06	0.89–1.26
2 years	114	0.65	0.49–0.85	323	0.72	0.60–0.85	1507	0.88	0.78–1.00
3 years	45	0.93	0.59–1.45	221	0.64	0.53–0.78	1041	0.98	0.87–1.11
4 years	52	0.57	0.39–0.82	102	0.71	0.54–0.95	1041	0.99	0.87–1.13
5 years or more	24	0.72	0.41–1.26	96	0.76	0.57–1.02	1135	1.04	0.92–1.19

Study population of all Finnish prostate cancer cases diagnosed in 1995–2002 and their matched controls.
a Length of the time period included in the analysis. Measured as consecutive years running backwards from the reference month.
b Each person categorised as regular user has been reimbursed at least 365 DDD during each year of the exposure period.
c Irregular users have been reimbursed less than 365 DDD during each year of the exposure period.
d Medication users with one or more years without reimbursements during the exposure period are categorised as short-term users.

all the prostate cancer cases in Finland during 1995–2002 and their controls led to a large study population with minimal influence of chance or selection bias.

Finasteride and alpha-blocker use for BPH was fully documented by the prescription database since they were available only through physician's prescription during the study period. Thus we were able to estimate detailed exposure information from the prescription database in an unbiased fashion and with extensive coverage. In 2002, a total of 4.69 DDD/1000 persons/day of finasteride and 6.41 DDD/1000/day of alpha-blockers were purchased in Finland for BPH treatment.[10] In our data, the men had been reimbursed 4.42 DDD/1000/day of finasteride and 6.15 DDD/1000/day of alpha-blockers. Hence the validity and representativeness of our results are high.

An 89% prevalence of LUTS has been estimated among Finnish men 50 years of age or older, with 24% having severe symptoms.[11] The 15.6% overall prevalence of BPH pharmacotherapy observed in our study population suggests that only a small portion of these men seek medical help, presumably those with most severe LUTS. Severe symptoms are more often treated with quicker acting alpha-blockers, explaining their observed greater prevalence of use.

A portion of BPH pharmacotherapy was used to treat symptoms of prostate cancer, as shown by the substantially increased risk among men whose only medication purchases had occurred within six months of the reference date (OR = 3.19; 95% CI 2.60–3.90 and OR = 6.02; 95% CI 5.25–6.89 for finasteride and alpha-blockers, respectively). However, exclusion from the analyses controlled the bias caused by these men.

Finasteride was licensed in Finland in 1992, though information on medication purchases was available since 1995. As a result some of the users may have longer history of use than appeared in our study and some previous users may appear falsely as non-users, thus diluting the observed effect of finasteride. However, the distortion is likely to be small as the estimates based on cases diagnosed during the early period (with less complete coverage of recent use) gave similar results than analyses based on later cases.

The observed difference in prostate cancer risk between alpha-blocker and finasteride users could have been slightly diluted by the fact that alpha-blockers were licensed in Finland later than finasteride, as 681 previous finasteride users switched to alpha-blockers in 1996 and 1997. However, the exclusion of these men from the analyses changed the results only marginally.

Finasteride used in the treatment of androgen-induced alopecia is not recorded by the prescription database, possibly leading to underestimation of the treatment effect. However, finasteride is not commonly used for this indication; in 2002 the consumption in Finland was 0.41 DDD/1000 persons/day.[10]

Age and ethnicity are well known risk factors for prostate cancer.[12] We controlled the confounding effect of age by individual matching of cases and controls. Confounding by ethnicity is minimal due to the homogeneity of the Finnish population with over 98% being Caucasian.[8] Inherited predisposition for prostate cancer is a strong risk factor, estimated to account for 5–10% of all Finnish prostate cancers.[13] Thus if the medical treatment for BPH is assumed to be 1.1–1.5 times more common among men with a family history of prostate cancer, this confounding factor could have caused 0.5–5% of excess risk observed in our study. However, hereditary prostate cancer has not been found to affect the risk of BPH.[14]

Other possible risk factors such as body mass index, dietary fat, vitamin D and vitamin E[12] were not accounted for in the selection of study population, since data were not available. Thus, they can potentially cause a confounding factor in our results, but their role as risk factors has not been well established.

We found the odds ratio of prostate cancer to be increased similarly in users of both drug groups of BPH pharmacotherapy, even though the drugs act through very distinct mechanisms. Since BPH is not associated with prostate cancer risk,[3] non-causal explanations must be considered. Differential diagnostics in men with LUTS includes measuring of serum PSA and performing a digital rectal examination, with prostate biopsy for the exclusion of prostate cancer in men with suspicious findings.

Prostate cancer is a disease of slow growth rate and long latency. Autopsy studies have reported a 34% prevalence of latent prostate cancer for men older than 50 years.[15,16] A 42% average prevalence of incidental prostate cancer has been reported in men undergoing cystoprostatectomy for

bladder cancer.[17,18] The autopsy and cystoprostatectomy prevalences have been estimated to exceed the lifetime risk of death from prostate cancer by at least 10-fold.[19] The present diagnostic techniques have been shown to be capable of diagnosing a large proportion of these latent cancers, leading to overdetection.[20]

Routine prostate cancer screening with PSA-test in asymptomatic men was not recommended in Finland during the study period. The exception was men participating in the Finnish Prostate Cancer screening trial, initiated in 1996.[21] The overall prevalence of opportunistic screening has been reported to be 10% in Finnish population during 1996–1999.[22]. Since a majority of the population was unscreened, the prevalence of undiagnosed latent malignancies of prostate was presumably high leading to increased detection rate in men whose PSA was systematically measured due to LUTS, causing detection bias. The observed risk being increased only for localised prostate cancer supports this assumption.

Prostate cancer risk was increased among alpha-blocker users regardless of regularity of use. However, in finasteride users the risk increase was observed only among short-term users in all categories of exposure time and irregular users when the analysed time period was the year preceding the reference month. Among regular finasteride users the risk was not elevated at any time period. It is likely that the risk is elevated also among regular users at the initiation of the therapy, but the subsequent decrease in risk among long-term regular users diminishes the overall increase observed.

BPH is a progressive disease,[23] and discontinuation of medication use eventually leads to recurrence of LUTS unless surgery is commenced. Thus irregular and short-term users likely had more frequent contacts with a physician due to LUTS than the regular users, leading to more frequent PSA measurements and an increased likelihood of prostate cancer diagnosis.

The biological effect of finasteride use could more properly be evaluated when prostate cancer risk among finasteride users was compared to that of alpha-blocker users since both groups undergo differential diagnostics of BPH, increasing comparability. The risk did not differ between short-term medication users with one or more years without purchases during the analysed time periods. However, in men with purchases each year, i.e. regular and irregular users, the risk decrease was significant. It is plausible that only consistent exposure to finasteride on a yearly basis is sufficient for a risk decreasing effect. Among regular and irregular finasteride users for five years or longer the odds ratios were below one, but the difference was not significant due to small number of men in these categories.

The risk difference between finasteride and alpha-blocker users could also be affected by the PSA lowering effect of finasteride.[24] Due to lower average PSA-level there could have been fewer indications for prostate biopsies among finasteride users. However, the PSA lowering effect has been reported to be stronger when PSA is elevated due to BPH than when elevated due to cancer.[25] Thus the prostate cancer detection sensitivity of PSA has been reported to improve during finasteride therapy, presumably counterbalancing the detection bias caused by lower PSA-levels.

We report an increased prostate cancer risk among BPH pharmacotherapy users compared to non-users in previously mainly unscreened population. The increase is due to enhanced detection of latent prostate cancers associated with clinical practice of BPH diagnosis and management. However, the risk is decreased among finasteride users when compared with alpha-blocker users, who are subject to similar diagnostics. The results suggest a chemopreventive effect of finasteride on prostate cancer at the population level in men treated for BPH. Nevertheless, possible detection bias caused by the PSA lowering effect of finasteride must be considered when interpreting the results.

Conflict of interest statement

None.

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