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Bladder cancer survival in men using 5-alpha-reductase inhibitors

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ABSTRACT

Purpose: Androgens may have a role in bladder carcinogenesis. We studied whether use of 5-alpha-reductase inhibitors (5-ARIs) associates with bladder cancer (BCa)-specific mortality in a population-based cohort of men with BCa.

Materials and methods: The study cohort consists of 10,720 Finnish men with newly diagnosed BCa during 1997-2012, identified from national cancer registry. Median follow-up was 4.17 years after BCa diagnosis.

Hazard ratios (HRs) and 95% confidence intervals (CI) for the risk of BCa death by 5-ARI use were analyzed using Cox regression adjusted for age, gender, co-morbidities, primary bladder cancer treatment and tumor extent at diagnosis. Lag time analyses were performed to assess long-term risk association. Simultaneous use of alpha-blockers was taken into account to estimate possible confounding by indication.

Results: 5-ARI use before BCa diagnosis was associated with lowered risk of BCa death (HR 0.84, 95% CI 0.73-0.97). The risk decrease became stronger along with years of use. Conversely, pre-diagnostic use of alpha-blockers did not associate with BCa survival (HR 1.02, 95% CI 0.91-1.13). Similarly, use of 5-ARIs after the diagnosis was associated with decreased risk of BCa death (HR 0.77, 95% CI 0.68-0.88). Again, the use of alpha-blockers did not associate with BCa survival (HR 0.98, 95% CI 0.90-1.07). The risk decrease by 5-ARI use persisted with up to five years' time lag.

Conclusions: 5-ARI users have improved disease-specific survival after BCa diagnosis compared to non-users, whereas alpha-blocker use does not associate with the survival. This supports the benefits of 5-alpha-reductase inhibition in bladder cancer.

INTRODUCTION

Urothelial bladder cancer is the sixth most common cancer type among men worldwide.[1] More than 70-80% of bladder cancers are superficial and treatable with transurethral resection (TURB), often combined with intravesical instillations. In 25% of cases bladder cancer infiltrates the muscle layer of the bladder wall. In these cases, a radical cystectomy combined with chemotherapy is often needed. Less than 10% of bladder cancers have already metastasized at diagnosis and are palliatively treated with chemotherapy and radiation. Tumors are also classified by cytology into low-grade or high-grade, high-grade being the most malignant and potentially invasive.[2]

Superficial low-grade bladder cancer often recurs, but disease-specific survival is excellent. This is not the case for muscle-infiltrating invasive cancer, which has five-year survival rate of 50-65%. Metastatic disease is still incurable and the life expectancy is less than 16 months.[3]

The prevalence of bladder cancer is higher among men than women. The reason for the gender difference is unknown but androgens have been proposed to have an impact on urothelial carcinogenesis; androgen receptor signaling may promote growth of urothelial cancer cells.[4] Importance of androgens in urothelial bladder cancer was supported by a recent study reporting reduced incidence of bladder cancer in men using 5α-reductase inhibitors (5-ARIs) finasteride or dutasteride compared to the non-users.[5] These drugs inhibit conversion of testosterone to dihydrotestosterone (DHT), a more potent activator of androgen signalling. The enzyme 5α-reductase is expressed mainly in the prostate, and 5-ARIs are mainly used for management of benign prostatic hyperplasia. However, 5α-reductase is also expressed by urothelial cancer cells, and DHT has been found to affect their growth.[6,7] Therefore it can be presumed that use of 5-ARIs would have benefits

in bladder cancer patients, but currently no published studies have examined how 5-ARIs may affect bladder cancer prognosis.

We performed a population-based cohort study in Finland to estimate whether use of 5-ARIs is associated with bladder cancer prognosis, with the hypothesis that the prognosis is better among 5-ARI users. As 5-ARIs are used to treat benign prostate hyperplasia (BPH) and lower urinary tract symptoms (LUTS) caused by BPH, 5-ARI users are more likely than non-users to be under urologist's supervision, creating possible selection bias. To assess and control for this bias we additionally analyzed the risk association for alpha-blockers that are used partly for the same indications.

MATERIALS AND METHODS

Study population

We collected all urothelial cancers of the bladder diagnosed in Finland during 1997-2012 from the comprehensive national Finnish Cancer Registry (FCR) based on ICD-10 codes (C67.0-C67.9).[8] A total of 10,720 men were included in the study. The available data included date of cancer diagnosis, tumor extent (localized, locally advanced or metastatic), primary treatment (surgery versus other), the date and the cause of death. The FCR data were linked to the information from Care Register for Health Care (HILMO) based on personal unique identification number. HILMO data contained diagnoses and procedures recorded at hospital contacts in Finnish healthcare units in 1997-2012.[9] Data on HILMO was used to evaluate comorbidities (diabetes, hypercholesterolemia and hypertension) and to obtain information on timing and number of endoscopic and open surgical procedures for bladder cancer after diagnosis. Surgical procedures were identified using procedure codes KCD02, KCD05, KCD32, KCC00, KCC10 and KCC20. **(Supplement table 1)**

Information on medication use

The study cohort was linked to national prescription database managed by Social Insurance Institution of Finland (SII) to obtain data on 5-ARI (finasteride, dutasteride) medication purchases in 1997-2012. Additionally, data on cholesterol-lowering, antihypertensive and antidiabetic drug purchases was also collected. The database provided detailed information on each medication purchase, including the date of purchase, ATC-coding, package size and dosage.

As part of national health insurance available to all Finnish citizens, SII partly covers costs for physician prescribed drug purchases.[10] The reimbursement is available to all Finnish citizens. Each reimbursed prescription purchase is recorded, regardless of the rate of SII cost coverage. Alpha-

blockers and 5-ARIs are available in Finland solely by prescription, thus comprehensively recorded by the database. The only exception is 1 mg finasteride used for treatment of androgenetic alopecia. **Also,** over-the-counter medications and medications used during inpatient are not recorded by the database.

Statistical analysis

Age distribution, tumor and treatment characteristics and the prevalence of co-morbidities were compared by 5-ARI use before and after bladder cancer diagnosis. We used Chi-square test to test for statistical significance of difference in categorical variables and Mann-Whitney U-test for non-categorical variables. Analyses on pre- and post-diagnostic use were made in separate models.

Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (95% CI) for the risk of having more than two or more than five TURBs after bladder cancer diagnosis. Logistic regression model was adjusted for age and co-morbidities.

Hazard ratios (HRs) and 95% CIs for the risk of bladder cancer death were analyzed using Cox regression adjusted for age, gender, co-morbidities, primary bladder cancer treatment (surgery vs. other) and tumor extent at diagnosis (localized vs metastatic). The unknown tumor extent was included in the analysis as one category. The time-metric was years and months since bladder cancer diagnosis. Follow-up continued until death, emigration or common closing date 31.Dec. 2012, whichever came first.

Medication use was divided to pre-diagnostic and post-diagnostic usage according to the year of drug purchases. Usage at the year of diagnosis was included in post-diagnostic use. Users of 5-ARIs were

stratified into two subgroups by median number of 5-ARI doses used/year. Similar stratifications were done for alpha-blockers.

Pre-diagnostic 5-ARI use was analyzed as time-fixed variable taking into account all usage occurring between 1997 and the year of diagnosis. Post-diagnostic 5-ARI use was analyzed as time-dependent variable, where user status and annual dosage were updated separately for each follow-up year based on the annual recorded purchases. Alpha-blocker use and 5-ARI use were entered into the regression model together to take into account simultaneous usage.

Long-term risk associations were evaluated in lag-time analyses where medication use was lagged forward in follow-up time. In 3-year lag-time analysis we estimated effects of 5-ARI use occurring three years earlier; e.g. for end-points occurring in 2005 we used 5-ARI exposure in 2002.

All statistical p-values are two-sided. All analyses were performed using IBM SPSS Statistic software.

RESULTS

Population characteristics

In the study population of 10,720 men, the median follow-up was 4.17 years after bladder cancer diagnosis. In total 6,100 (56.9%) participants died during the follow-up. The number of deaths caused by bladder cancer was 2,332 (21.8%).

Drug users before the diagnosis

Both 5-ARI and alpha-blocker users were generally slightly older than non-users. Median age among 5-ARI was two years higher (78 years) compared to alpha-blocker users. There was no **statistically significant** difference in the proportions of all-cause or bladder cancer deaths between 5-ARI and alpha-blocker users. However, when compared to non-users, both 5-ARI and alpha-blocker users had significantly lower all-cause and bladder cancer specific mortalities. At diagnosis, 5-ARI users had more often metastatic bladder cancers than alpha-blocker users (14.5% vs. 13.0%). However, there were more localized bladder cancers among alpha-blocker than 5-ARI users (60.8 vs. 59.0). (Table 1)

TABLE 1. Population characteristics

	Non-users	5-ARI users		alpha-blocker users	
		Pre-diagnosis*	Post-diagnosis*	Pre-diagnosis	Post-diagnosis
N of participants	5090	1328	1880	2353	4250
Median age (IQR) at diagnosis	70 (61-78)	78 (72-83)	75 (68-81)	76 (70-82)	74 (66-80)
Median (IQR) follow-up time	3,75 (1,25-8.08)	3.25 (1.5-5.75)	5.17 (2.5-9.3)	3.25 (1.5-6.17)	5.1 (2.4-9.1)

N (%) deaths	3088 (60.7)	725 (54.6)	856 (45.5)	1286 (54.7)	2176 (51.2)
Overall mortality	607/1,000	546/1,000	455/1,000	547/1,000	512/1,000
N (%) bladder cancer deaths	1246 (40.3)	288 (21.7)	266 (14.1)	514 (21.8)	761 (17.9)
Overall bladder cancer specific mortality	245/1,000	217/1,000	141/1,000	218/1,000	179/1,000
Tumor extent; n (%)					
Localized	3,176 (60.4)	784 (59.0)	1257 (66.9)	1430 (60.8)	2782 (65.5)
Metastatic	698 (13.3)	193 (14.5)	162 (8.6)	306 (13.0)	404 (9.5)
Unknown	1,388 (26.4)	351 (26.4)	461 (24.5)	617 (26.2)	1064 (25.0)
P-value	Ref	0.01	0.00	0.19	0.12
Median (IQR) number of surgical procedures	2 (1-9)	2 (1-9)	1 (1-7)	2 (1-9)	2 (1-8)
P-value	Ref	0.00	0.00	0.00	0.04
Median (IQR) Charlson co-morbidity index	4 (3-4)	4 (3-4)	4 (3-4)	4 (3-4)	4 (3-4)
P-value	Ref	0.79	0.21	0.17	0.56
N (%) of men treated with cystectomy	749 (14.7)	141 (10.6)	127 (6.8)	297 (12.6)	398 (9.4)
P-value	Ref	0.06	0.00	0.51	0.00
N (%) of men receiving radiation therapy	616 (12.1)	167 (12.6)	158 (6.4)	292 (12.4)	488 (11.5)
P-value	Ref	0.00	0.00	0.00	0.04
N (%) of men receiving chemotherapy	1021 (20.1)	274 (20.6)	378 (20.1)	487 (20.7)	968 (22.8)
P-value	Ref	0.01	0.13	0.00	0.50

* Simultaneous use of 5-ARIs and alpha-blockers: N=897 (67.5 % of 5-ARI users) before BCa diagnosis, N=1,389 (73.9%) after it

There was no statistically significant difference between 5-ARI and alpha-blocker users in median Charlson co-morbidity index or in the median number of surgical procedures after bladder cancer diagnosis. Alpha-blocker users were treated more often with cystoprostatectomy when compared to 5-ARI users (12.6% vs. 10.6%). However, there was no significant difference between 5-ARI and alpha-blocker users in the proportion of men receiving radiation and chemotherapy. (Table 1)

Drug users after the diagnosis

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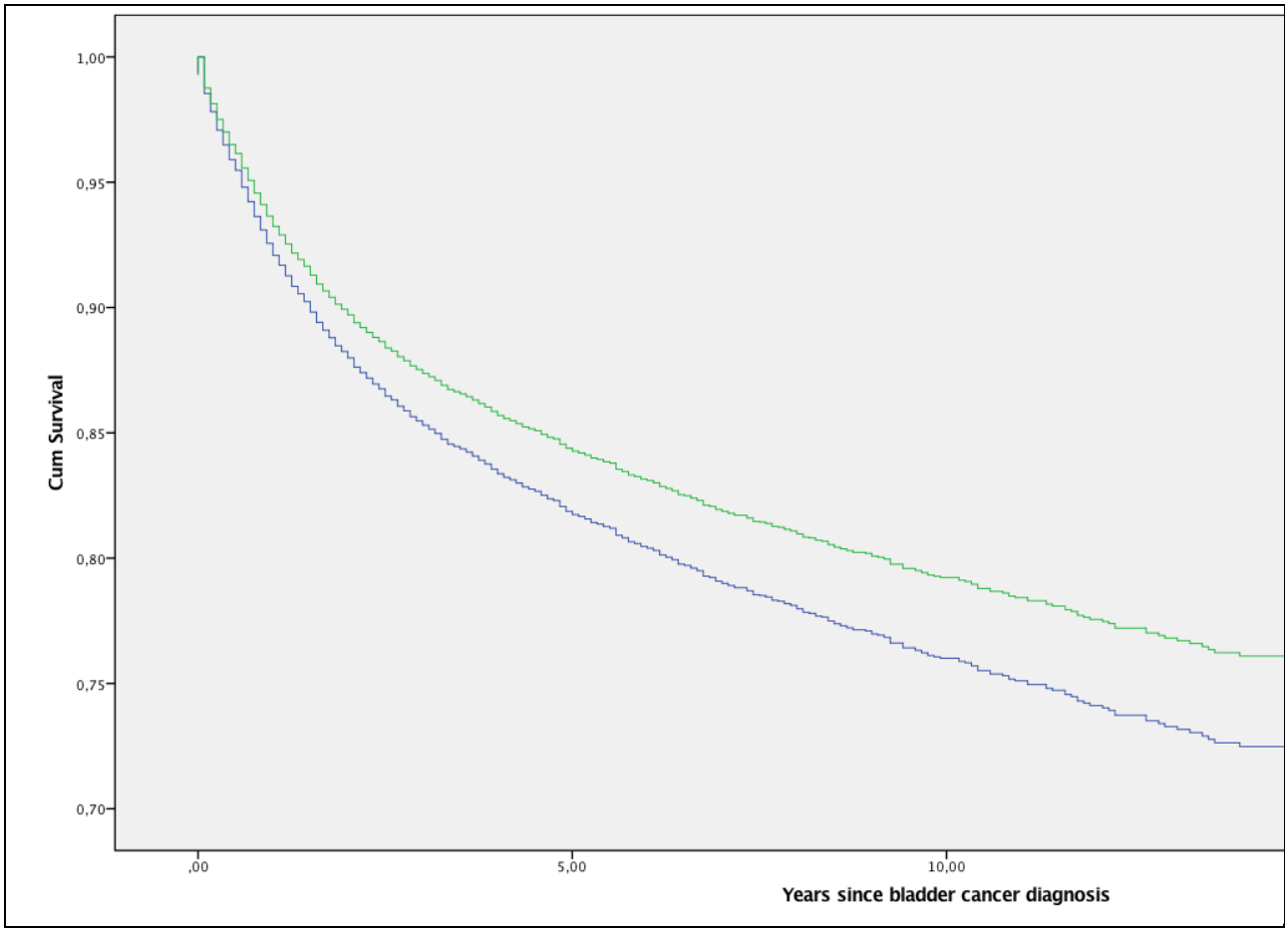
For post-diagnostic use, both 5-ARI and alpha-blocker users were nearly the same age, 5-ARI users being a year older (75 years) than alpha-blocker users. All-cause mortality was lower between 5-ARI and alpha-blocker users (45.5% and 51.2%, respectively) as was bladder cancer specific morality (14.1% and 17.9%). However, when compared to non-users, both 5-ARI and alpha-blocker users had lower all-cause and bladder cancer specific mortalities. 5-ARI users tended to have more localized tumors at diagnosis than alpha-blocker users (66.9% vs. 65.5%), whereas metastatic tumor extent was more common among alpha-blocker users (9.5% vs. 8.6%). (Table 1)

5-ARI users had undergone less surgical procedures than alpha-blocker users (1 vs. 2). Additionally, 5-ARI users had less cystectomies (6.8% vs. 9.4%), radiation (8.4% vs. 11.5%) and chemotherapies (20.1% vs. 22.8%) than alpha-blocker users. There was no statistically significant difference between 5-ARI and alpha-blocker users in Charlson co-morbidity index. (Table 1)

Bladder cancer survival by 5-ARI and alpha-blocker use before the diagnosis

Figure 1. Bladder cancer-specific survival by 5alpha-reductase inhibitor and alpha-blocker use before bladder cancer diagnosis

a) 5-alpha-reductase inhibitors



N of men at risk	10,720	4,772	1,974	571

Compared to non-users, 5-ARI-use before bladder cancer diagnosis was associated with lowered risk of bladder cancer death in the multi-variable adjusted analysis (HR 0.85, 95% CI 0.74-0.97) (Table 2, Figure 1a). The risk decrease did not clearly depend on the annual dose but became stronger along with years of use; in stratified analysis the risk decrease was significant only after 3 years of use.

Conversely, pre-diagnostic use of alpha-blockers was not associated with bladder cancer survival (HR 1.02, 95% CI 0.92-1.14) (Table 2, Figure 1b). Again, the risk association did not depend on the annual dose or the duration of use.

b) alpha-blockers

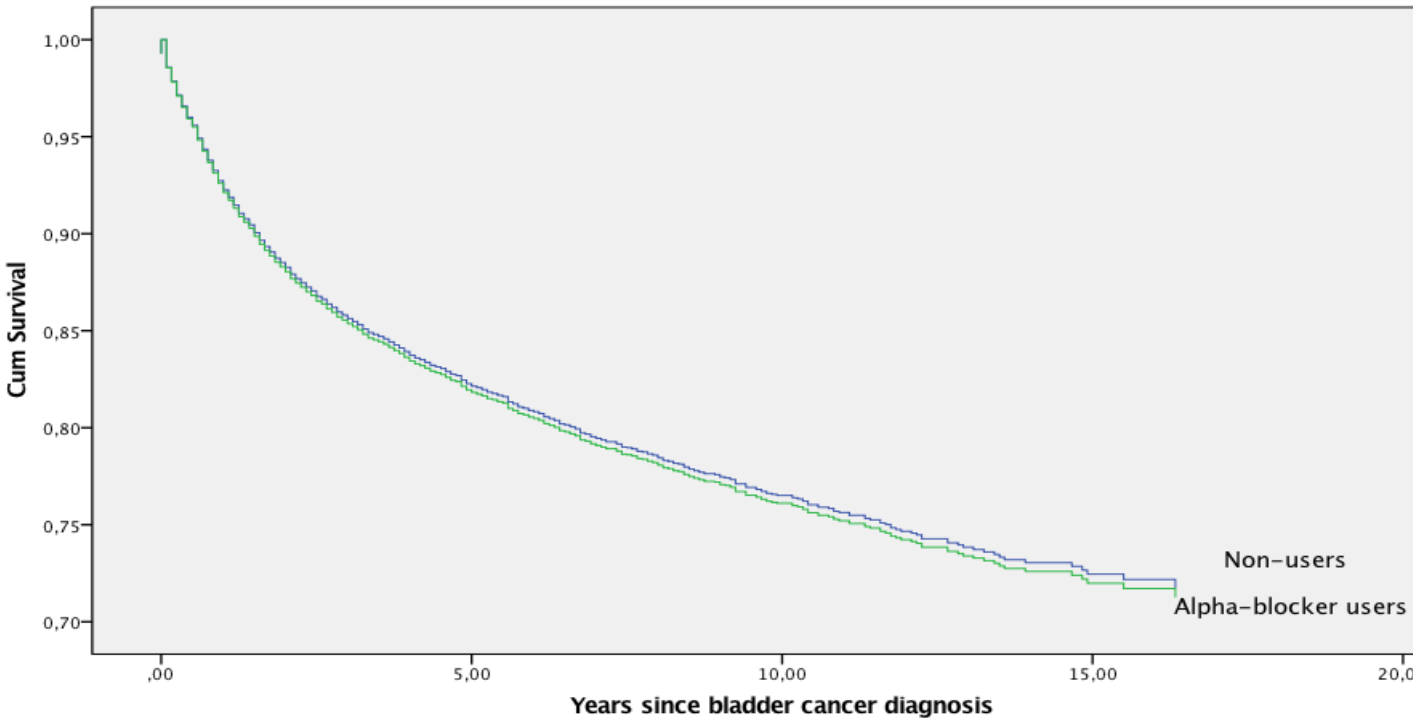


TABLE 2. Risk of bladder cancer death by use of 5-ARIs and alpha-blockers before and after the diagnosis. Study population of 10,720 Finnish men diagnosed with bladder cancer during 1997-2012.

Pre-diagnostic use							
	5-ARI users				Alpha-blocker users		
Medication use	N of participants/deaths	HR (95% CI)$_{age\ adjusted}$	HR (95% CI) mutlivariable adjusted		N of participants/deaths	HR (95% CI)$_{age\ adjusted}$	HR (95% CI) mutlivariable adjusted
Non-users		Ref	Ref			Ref	Ref

Any use	1328/288	0.89 (0.78-1.02)	0.85 (0.74-0.97)		2353/514	0.94 (0.85-1.05)	1.02 (0.92-1.14)
Intensity of use:		Median 228 doses/year			Median 135 doses/year		
Median or below	664/152	0.96 (0.81-1,148)	0.87 (0.73-1.04)		1173/236	0.87 (0.76-1.00)	0.92 (0.80-1.06)
Above median	664/136	0.82 (0.68-0.98)	0.82 (0.69-0.99)		1180/278	1.03 (0.90-1.18)	1.14 (0.99-1.30)
Duration of use:		Median 2 years				Median 2 years	
Median or below	741/177	1.01 (0.86-1.19)	0.92 (0.78-1.08)		1414/316	0.97 (0.86-1.10)	1.01 (0.89-1.14)
Above median	587/111	0.75 (0.62-0.92)	0.76 (0.62-0.93)		939/198	0.90 (0.77-1.06)	1.05 (0.89-1.23)

Post-diagnostic use							
	5-ARI users				Alpha-blocker users		
Medication use	N of participants/deaths	HR (95% CI)$_{age\ adjusted}$	HR (95% CI) mutlivariable adjusted		N of participants/deaths	HR (95% CI)$_{age\ adjusted}$	HR (95% CI) mutlivariable adjusted
Non-users		Ref	Ref			Ref	Ref
Any use	1880/266	0.73 (0.64-0.83)	0.78 (0.68-0.89)		4250/761	0.93 (0.85-1.02)	0.96 (0.88-1.06)
Intensity of use:		Median 225 doses/year				Median 145 doses/year	
Median or below	943/172	0.98 (0.83-1.15)	0.93 (0.79-1.09)		2126/463	1.09 (0.98-1.21)	1.04 (0.94-1.16)
Above median	937/94	0.51 (0.41-0.63)	0.61 (0.50-0.75)		2124/298	0.76 (0.66-0.86)	0.86 (0.76-0.98)
Duration of use:		Median 2 years				Median 1 year	
Median or below	1281/232	0.745 (0.65-0.86)	0.78 (0.68-0.90)		2176/512	0.92 (0.83-1.02)	0.92 (0.83-1.01)

Above median	599/34	0.61 (0.43-0.87)	0.73 (0.51-1.04)		2074/249	0.96 (0.82-1.12)	1.13 (0.97-1.32)

Bladder cancer survival by 5-ARI and alpha-blocker use after the diagnosis

The use of 5-ARIs after bladder cancer diagnosis was associated with decreased risk of cancer-specific death in the multi-variable adjusted analysis (HR 0.77, 95% CI 0.68-0.88) (Table 2). Also for post-diagnostic use the risk decrease was dose-dependent, in inverse correlation with yearly dose of 5-ARI use.

Again, use of alpha-blockers did not relate to bladder cancer survival (HR 0.98, 95% CI 0.90-1.07) (Table 2). However, in high-dose (more than 210mg in total) use alpha-blockers were also associated with lowered bladder cancer mortality compared to non-users. Nevertheless, 5-ARI users had greater risk reduction than alpha-blocker users especially after multivariable adjustment.

Lag-time analyses

Decreased risk of bladder cancer death became statistically non-significant within three years' lag time, although the risk estimate was lowered even with time lag of five years (Table 3).

TABLE 3. Long-term association between 5-ARI use and risk of bladder cancer death. Study population of 10,720 Finnish men diagnosed with bladder cancer during 1997-2012.

	Lag time:			
	None	1 yr	3 yrs	5 yrs

	HR (95% CI) multivariable adjusted	HR (95% CI) mutlivariable adjusted	HR (95% CI) mutlivariable adjusted	HR (95% CI) mutlivariable adjusted
5-ARI use				
None	Ref	Ref	Ref	Ref
Any	0.78 (0.68-0.89)	0.75 (0.65-0.86)	0.86 (0.73-1.01)	0.87 (0.71-1.05)

The association between 5-ARI and alpha-blocker use and number of TURBs

Among endoscopically treated patients both 5-ARI and alpha-blocker use were associated with a lower risk of having multiple TURB procedures after bladder cancer diagnosis compared to the non-users (Table 4). The association was statistically significant only among alpha-blocker users, but similar risk estimates were observed also in 5-ARI users.

TABLE 4. Risk of having multiple TURBs after diagnosis by 5-ARI and alpha-blocker use.

Risk of having multiple TURB:s after diagnosis by 5-ARI and alpha-blocker use					
	5-ARIs			alpha-blockers	
Number of TURBs	OR (95% CI) age adjusted	OR (95% CI) mutlivariable adjusted		OR (95% CI) age adjusted	OR (95% CI) mutlivariable adjusted
2 or more	0.89 (0.74-1.07)	0.89 (0.74-1.07)		0.84 (0.73-0.98)	0.84 (0.72-0.97)
5 or more	0.82 (0.59-1.16)	0.82 (0.58-1.16)		0.70 (0.54-0.92)	0.70 (0.54-0.91)

DISCUSSION

Men who use 5-ARIs had a lower risk for bladder cancer death compared to the non-users. This risk difference was not observed among the alpha-blocker users, even after adjustment for co-morbidities and other background variables. Indications for use of these drug groups overlap, but only 5-ARIs affect androgen metabolism. Thus our results support role of androgens in bladder cancer progression.

This is the first study that clarifies the association between use of 5ARIs targeting androgen metabolism and bladder cancer survival. In a prior study the use of 5-ARIs was associated with a lowered risk for bladder cancer.[5] These findings have been subsequently supported by a case-control study reporting lowered risk of bladder cancer in Taiwanese men using finasteride and a cohort study demonstrating decreased bladder cancer risk among men using 5-ARIs or androgen deprivation therapy for prostate cancer in a cohort of 228 Japanese men.[7,11] The results of our study are in line with the previous studies regarding potential beneficial effects of 5-ARI use in men with bladder cancer. However, to our knowledge this is the first study to suggest beneficial effects of 5-ARI use and role of androgens in bladder cancer progression. Interestingly, also androgen deprivation therapy for prostate cancer has been linked to lowered risk of BCa recurrence further supporting the role of androgens in BCa.[12]

The risk association with bladder cancer death among 5-ARI users depended on annual dose and cumulative duration of use. This suggests a causal association. However, non-causal explanations must be considered as well.

The indication for 5-ARI use in our study is symptomatic benign prostatic hyperplasia. Our data did not cover 5-ARI usage for male pattern baldness. Men with lower urinary tract symptoms (LUTS) undergo urological examination more often than men without such symptoms. Therefore, bladder tumors could be detected earlier and at more curable phase in such men, generating lead time bias. This bias was evaluated by analyzing also alpha-blockers, drug group with similar indications for use, thus affected by the same bias, but with a completely different mechanism of action. The risk decrease was observed only in 5-ARI users, strongly suggesting that lead time bias does not explain the observed risk difference. Further, lead time bias would presumably mean less TURBs required in 5-ARI and alpha-blocker users compared to non-users. A significantly lower risk of undergoing multiple TURBs was observed only in alpha-blocker users compared to non-users, again arguing against lead time bias in 5-ARI users.

Another possible non-causal explanation could be more efficient treatment of bladder cancer in men using 5-ARIs. Such men could be presumed to be more generally fit and more often suitable for cystectomy. However, 5-ARI users were less often managed with cystectomy which further argues against healthy user bias.

The strength of our study is the ability to compare bladder cancer survival between 5-ARI users and alpha-blocker users. Alpha-blockers and 5-ARIs have completely different mechanisms of action, yet they are used often with similar indications and therefore these comparisons allowed evaluation the impact of selection bias between users and non-users. Interestingly, the survival benefit was observed only among men using 5-ARIs, supporting a causal association.

The data for the study was collected from nation-wide databases that provided us accurate information on drug purchases and bladder cancer deaths. The exact drug use history enabled us to evaluate

separately medication use before and after bladder cancer diagnosis and to evaluate the dose- and time-related dependence on the risk of bladder cancer death, as well as simultaneous use of 5ARIs and alpha-blockers.

Finasteride treatment of androgenetic alopecia was not recorded by SII, causing bias towards the null. However, this does not interfere with our conclusion of improved BCa survival among 5-ARI users**.** As our study is a retrospective comparison and 5-ARI use was not randomized, confounding due to background factors, such as socioeconomic inequality**,** could have affected observed survival differences. Information on intravesical therapies was not available in the national database. On the other hand, the lack of data concerned the alpha-blocker group as well, thus not affecting comparisons between 5-ARI users and alpha-blocker users. We had no information on the participants' lifestyle-related risk factors, such as tobacco smoking, nutrition or physical activity, that may have an impact on the prognosis of cancer. These factors may differ between drug users and non-users. However, the bias caused by life style choices is not related to the amount of drug used, therefore the dose-dependent risk trends seen for 5-ARI use are likely related to the direct effect of 5-ARIs on bladder cancer progression.

CONCLUSIONS

This is the first study estimating the role of 5-ARI use in the prognosis of bladder cancer. 5-ARI users have better disease-specific survival after bladder cancer diagnosis when compared to non-users. Similar risk associations were not observed in users of alpha-blockers. Our study supports the role of androgens in the progression of bladder cancer. If confirmed in further studies, 5-alpha-reductase inhibition may prove to be a viable strategy to improve bladder cancer outcomes

CONFLICTS OF INTEREST

Dr Tammela reports grants from Expert Responsibility Area of the Tampere University Hospital, during the conduct of the study; personal fees from Astellas, Bayer and Roche, outside the submitted work

Dr. Murtola reports grants from Finnish Cultural Foundation, grants from Expert Responsibility Area of the Tampere University Hospital, during the conduct of the study; personal fees from Astellas, personal fees from Janssen, other from Astellas, other from Bayer, outside the submitted work

Other authors have nothing do disclose

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Supplement table 1. Explanations of procedure codes.	
Procedure codes	Explanation
KCC00	Cystectomy
KCC10	cystoprostatectomy
KCC20	Cystroprostatectomy plus removal of urethra
KCD02	TURB (transurethral resection of bladder tumor)
KCD05	Endoscopic removal of bladder tumor
KCD32	Endoscopic laser ablation of bladder tumor

Supplement table 2. Risk for BCa death by tumor extent. Multivariable adjusted analysis.			
Pre-diagnostic use	Localized	Metastatic	Unknown
5-ARIs	0.98 (0.79-1.21)	0.86 (0.69-1.07)	0.62 (0.45-0.85)
Alpha-blockers	1.09 (0.92-1.29)	0.89 (0.76-1.04)	0.99 (0.79-1.24)
Post-diagnostic use			
5-ARIs	0.74 (0.60-0.91)	1.02 (0.82-1.26)	0.61 (0.45-0.83)
Alpha-blockers	1.07 (0.93-1.23)	0.89 (0.76-1.04)	0.89 (0.74-1.08)