Use of 5α-reductase inhibitors for lower urinary tract symptoms and risk of prostate cancer in Swedish men: nationwide, population based case-control study

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RESEARCH

Use of 5α-reductase inhibitors for lower urinary tract symptoms and risk of prostate cancer in Swedish men: nationwide, population based case-control study

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Abstract

Objective To assess the association between 5α-reductase inhibitor (5-ARI) use in men with lower urinary tract symptoms and prostate cancer risk.

Design Nationwide, population based case-control study for men diagnosed with prostate cancer in 2007-09 within the Prostate Cancer data Base Sweden 2.0.

Setting The National Prostate Cancer Register, National Patient Register, census, and Prescribed Drug Register in Sweden, from which we obtained data on 5-ARI use before date of prostate cancer diagnosis.

Participants 26 735 cases and 133 671 matched controls; five controls per case were randomly selected from matched men in the background population. 7815 men (1499 cases and 6316 controls) had been exposed to 5-ARI. 412 men had been exposed to 5-ARI before the diagnosis of a cancer with Gleason score 8-10.

Main outcome measures Risk of prostate cancer calculated as odds ratios and 95% confidence intervals by conditional logistic regression analyses.

Results Risk of prostate cancer overall decreased with an increasing duration of exposure; men on 5-ARI treatment for more than three years had an odds ratio of 0.72 (95% confidence interval 0.59 to 0.89; P<0.001 for trend). The same pattern was seen for cancers with Gleason scores 2-6 and score 7 (both P<0.001 for trend). By contrast, the risk of tumours with Gleason scores 8-10 did not decrease with increasing exposure time to 5-ARI (for 0-1 year of exposure, odds ratio 0.96 (95% confidence interval 0.83 to 1.11); for 1-2 years, 1.07 (0.88 to 1.31); for 2-3 years, 0.96 (0.72 to 1.27); for >3 years, 1.23 (0.90 to 1.68); P=0.46 for trend).

Conclusions Men treated with 5-ARI for lower urinary tract symptoms had a decreased risk of cancer with Gleason scores 2-7, and showed no evidence of an increased risk of cancer with Gleason scores 8-10 after up to four years' treatment.

Introduction

Chemoprevention by use of 5α-reductase inhibitors (5-ARI) to decrease risk of prostate cancer has been investigated in two large randomised clinical trials. Both these trials showed a decreased risk of prostate cancer overall in men on 5-ARI—finasteride in the Prostate Cancer Prevention trial (PCPT) and dutasteride in Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial.[1 2] These 5-ARIs inhibit the conversion of testosterone to dihydrotestosterone, the most potent androgen in the prostate, and thereby decrease androgen receptor activity.[3] There was a 23-25% reduction in risk of prostate cancer at biopsy for men receiving 5-ARI, compared with men receiving placebo, in both trials. However, in both trials, there was also an increased risk of cancer with Gleason scores 8-10. Based on these findings, The US Food and Drug Administration (FDA) issued a safety announcement in 2011, stating that "5 alpha reductase inhibitors may increase the risk of a more serious form of prostate cancer."[4]

The reason for the observed increase in risk in these trials has not been conclusively elucidated, with different explanations for these associations put forward.[5-11] One theory is that the increase is real and that 5-ARI promotes prostate cancer with Gleason scores 8-10, possibly mediated through lower concentrations of 3β-Adiol and resulting in a decreased stimulation of the oestrogen β receptor.[12] Another theory is that the association is spurious and caused by detection bias, because 5-ARI facilitates the detection of small foci of tumours with Gleason scores 8-10.[4] To what degree these Gleason 8-10

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cancers are associated with progression and prostate cancer death has not been studied. However, because 5-ARIs are widely used in men with lower urinary tract symptoms due to benign prostatic hyperplasia, there is a need to further elucidate the association between 5-ARI use and high grade prostate cancer.

The aim of this study was to investigate the association between the use of 5-ARI for treating lower urinary tract symptoms due to prostatic enlargement in a clinical setting and prostate cancer risk, in particular cancer with Gleason scores 8-10.

Methods

Study design

We conducted a case-control study within the nationwide Prostate Cancer data Base Sweden 2.0, previously described in detail.[13 14]

Cases

Cases were found in the National Prostate Cancer Register, which includes more than 97% of all cases of prostate cancer in Sweden since 1998, in comparison to the Swedish Cancer Register, to which registration is mandatory and regulated by law.[15] The National Prostate Cancer Register contains information on the date of diagnosis; tumour characteristics according to the tumour, node, metastasis classification; Gleason score; serum levels of prostate specific antigen at diagnosis; and primary treatment delivered or decided within six months after diagnosis. In the Swedish Cancer Register, 28 556 men had been registered with prostate cancer in 2007-09, of whom 27 863 had been registered in the National Prostate Cancer Register and 26 735 had a Gleason score registered—that is, 93.6% of all eligible men were included in this register, and constitute our cases.

Controls

For each case of prostate cancer, a set of five matched controls was chosen. Eligible controls were all Swedish men free of prostate cancer at the end of the year of diagnosis of the index case, who lived in the same county as the case and who were born in the same year. For men diagnosed with prostate cancer at age 90 years or over, controls were only matched by year of birth, owing to the smaller available sample size of putative controls. A total of 133 671 matched controls were included in the study.

By use of the unique personal identity number assigned to each Swedish resident, all cases and controls were linked to several other nationwide healthcare registries and demographic databases,[16 17] and in this linkage we had no further loss of cases or controls.

Exposure to 5-ARI

Data on prescriptions for finasteride and dutasteride were extracted from the Swedish Prescribed Drug Register, which includes all prescriptions dispensed since July 2005. This register contains information on the amount and dose of each drug as well as the date of prescription and dispensing.

Sources of the covariates in the model

As of 1987, the National Patient Register collects information on inpatient care, including surgical procedures, and discharge diagnoses coded according to ICD-9 or ICD-10 (international classification of diseases, 9th or 10th revision). Using data on discharge diagnoses for the 10 years preceding the prostate cancer diagnosis of the case, we classified cases and controls into four categories of comorbidity according to the Charlson comorbidity index.[18 19] From this register, we also obtained information on the use of transurethral resection of the prostate in the study population. Since 2001, the register has collected data from outpatient consultations in specialised care with a capture rate of about 50% for prostate biopsy procedures guided by transrectal ultrasound. Therefore, we obtained information on the use of these procedures before the date of diagnosis for cases, for both cases and controls. From the Swedish Prescribed Drug Register, information on all types of α blockers used for treatment of lower urinary tract symptoms was also retrieved.

The Longitudinal Integration Database for Health Insurance and Labour Market Studies is a nationwide demographic database with information on socioeconomic factors. From this database, we obtained information on the family unit for the year of diagnosis for the case, classified as married, single with children, or single with no children. Educational level was categorised as low (≤9 years of school), middle (10-12 years), and high (≥13 years); in Sweden, these categories correspond to mandatory school, high school, and college or university, respectively.

Statistical analysis

Four separate case-control analyses were performed in this study. One analysis combined all cases and their matched controls, and the other three analyses looked at separate Gleason scores. These Gleason scores were based on the National Comprehensive Cancer Network's classification of cancers with Gleason scores 2-6, 7, and 8-10, for cases and their respective controls.[20] We used univariable and multivariable conditional logistic regression analysis to model the odds of having prostate cancer. The conditioning was made on the basis of the control's selection criteria. We adjusted the association between prostate cancer risk and 5-ARI exposure for covariates that were potential confounding factors including:

- Increased diagnostic activity driven by lower urinary tract symptoms as indicated by α blocker use; and transurethral resection of the prostate or increased levels of prostate specific antigen, as indicated by biopsies.
- Comorbidity before date of diagnosis assessed by the Charlson comorbidity index, based on discharge diagnoses in the Swedish inpatient register before the date of diagnosis for the index case
- Socioeconomic factors assessed by family status and highest level of education attained.

Results were summarised with odds ratios and 95% confidence intervals.[21] We calculated trend tests using the categories on an equidistant ordinal scale, and P values were two tailed. Exposure to 5-ARI was quantified by the number of cumulatively dispensed defined daily doses and first categorised into any use (one or more prescriptions dispensed) or no use (no prescriptions dispensed). Exposure was then separated according to the duration of defined daily doses (0-1, 1-2, 2-3, and >3 years).[22] We analysed finasteride and dutasteride, the two available 5-ARIs, combined because their outcomes were virtually the same in two clinical trials.[1 2] Because there was no reason to believe that an increasing exposure to α blockers could prevent or induce prostate cancer, exposure was divided into any use or no use in the main analysis.

Some men could have had elevated serum levels of prostate specific antigen or an abnormal digital examination, and concomitantly had lower urinary tract symptoms; therefore, they may have undergone an investigation leading to a prostate

cancer diagnosis in parallel with the initiation of 5-ARI or α blocker treatment for lower urinary tract symptoms. To avoid this potential selection bias or confounding by indication, we used a restriction period. This period was defined as the time period before prostate cancer diagnosis during which exposure to 5-ARI, α blockers, transurethral resection of the prostate, and prostate biopsies was ignored; this restriction period was also applied for corresponding controls. In addition to a six month restriction period, we performed sensitivity analyses with restriction periods of one, three, nine, and 12 months between the start of 5-ARI or α blockers use and the date of cancer diagnosis.

The number and the timing of prostate biopsy sessions in relation to date of diagnosis were divided into five categories:

- No biopsy
- One biopsy session, less than two years before diagnosis
- One biopsy session, two years or more before diagnosis
- Two or more biopsy sessions, with the first less than four years before diagnosis
- Two or more biopsy sessions, with the first four years or more before diagnosis.

The statistical analyses were performed by use of the R statistical program package (version 2.7.2).[23]

Results

Mean age at inclusion for cases (n=26 735) and controls (n=133 671) combined was 69.3 years (table 1⇓). Men who had cancers with Gleason scores 2-6 were younger (mean age 66.6 years) than those who had cancers with scores 7 (70.0 years) and 8-10 (74.0 years). Treatment with 5-ARI before diagnosis had been registered in 1499 (5.6%) cases and in 6316 (4.7%) controls. A substantially larger proportion of patients in the case group than in the control group had undergone a biopsy before the date of diagnostic biopsy (9.1% *v* 2.5%). Cases included slightly higher proportions of married men, men with high education, and men with no comorbidities than controls (table 2⇓).

Prostate cancer risk in univariable analysis

In the univariable analysis (table 3⇓), the odds ratio of having prostate cancer was 0.90 (95% confidence interval 0.73 to 1.10) for men exposed to 5-ARI for three years or more. The risk of diagnosis fell for cancers with Gleason scores 2-6 (0.70 (0.53 to 0.93)), but increased slightly for cancers with Gleason scores 8-10 (1.36 (0.99 to 1.85)).

Prostate cancer risk in multivariable analysis

In the multivariable analysis (table 4⇓), all exposure times to 5-ARI combined were associated with a decreased risk of prostate cancer (overall, odds ratio 0.89 (95% confidence interval 0.84 to 0.94); with Gleason scores 2-6, 0.88 (0.80 to 0.96); with Gleason score 7, 0.85 (0.77 to 0.94)). However, the risk was unchanged for cancer with Gleason scores 8-10 (1.01 (0.90 to 1.13)). There was a decrease in risk with an increasing duration of 5-ARI exposure for all cancers combined in men receiving 5-ARI treatment for more than three years (0.72 (0.59 to 0.89); P<0.001 for trend; table 4). The same pattern was seen for risk of cancer with Gleason scores 2-6 (P<0.001 for trend) and 7 (P<0.001 for trend). By contrast, the risk of tumours with Gleason scores 8-10 did not decrease with increasing exposure time (for 0-1 year, odds ratio 0.96 (95% confidence interval 0.83 to 1.11); for 1-2 years, 1.07 (0.88 to 1.31); for 2-3 years, 0.96 (0.72 to 1.27); for >3 years, 1.23 (0.90 to 1.68); P=0.46 for trend; table 4). Men using α blockers had an increased risk of prostate cancer (1.33 (1.27 to 1.39)); this risk was highest for tumours with Gleason scores 2-6 (1.60 (1.50 to 1.71)) and lowest for those with Gleason scores 8-10 (1.06 (0.96 to 1.18)).

Risk estimates for the other risk factors in the multivariable analyses were similar to those in the univariable analyses. During the first year of 5-ARI exposure, an increasing duration of the restriction period was associated with a decreasing risk of prostate cancer (fig 1⇓). However, the duration of the restriction period did not alter the association between an increased duration of exposure to 5-ARI and a decreasing overall prostate cancer risk. The pattern for α blocker exposure was different, with an increased risk to be diagnosed with prostate cancer overall. This raised risk was most pronounced for cancer with Gleason scores 2-6, less obvious for cancer with Gleason score 7, and not seen for cancer with Gleason scores 8-10 (fig 2⇓).

Discussion

In this nationwide, population based, case-control study, increasing duration of exposure to 5-ARI was associated with a decreased risk of prostate cancer overall, and this decrease was restricted to cancers with Gleason scores 2-6 and 7. There was no significant association in risk of cancers with Gleason scores 8-10. Our data, together with previous studies, suggest that the net balance between benefit and harm for 5-ARI use is favourable in men with lower urinary tract symptoms based on prostatic enlargement.

Strengths and limitations of the study

Our study had some limitations owing to its observational design. There was no predefined indication or protocol for the performance of prostate biopsies in our study, we had no data on serum levels of prostate specific antigen or digital rectal examinations including prostate size at the start of 5-ARI exposure, data from routine histopathological assessment were used for Gleason classification, and our follow-up time was restricted to a maximum of four years. Furthermore, confounding by indication was a concern because we could not assume that men were free of prostate cancer when 5-ARI was initiated. However, by use of a restriction period, we reduced the risk that men with prevalent cancer were included in the analysis and classified as exposed to 5-ARI, thereby creating a falsely increased risk after a short exposure to 5-ARI. We further adjusted our risk estimates for covariates that were potential confounders related to an increased diagnostic activity of prostatic diseases by including them in the multivariable models.

Strengths of our study design included its large size; 412 men had been exposed to 5-ARI before the diagnosis of a cancer with Gleason scores 8-10. By comparison, cancer with Gleason scores 8-10 was diagnosed in 90 and 29 men in the case groups in the PCPT and REDUCE trials, respectively.[1 2] Another strength was that we had detailed and complete information on exposure assessed in daily doses for finasteride, dutasteride, and α blockers by use of data from the Prescribed Drug Register before the date of diagnosis. We also had access to comprehensive information on risk factors for prostate cancer, including diagnostic intensity in terms of prostate biopsy sessions, transurethral resection of the prostate, comorbidity, and socioeconomic factors. The duration of the restriction period did not alter the association between 5-ARI exposure and risk of prostate cancer in men who had been exposed to 5-ARI for more than one year. The use of a restriction period decreased the selection mechanisms for men in the cases group who had

undiagnosed clinical prostate cancer and who received 5-ARI for a short period of time in parallel with a diagnostic investigation leading to a diagnosis.

Comparison with other studies

Our observational study differed in several important aspects from previous clinical trials,[1 2] and one important difference was the inclusion criteria and the clinical setting in which the studies were undertaken. In our study, 5-ARI was used because of lower urinary tract symptoms, most likely caused by benign prostatic hyperplasia, and we had little means other than introducing a restriction period to exclude prevalent cancers. In the PCPT trial, inclusion criteria included a normal digital rectal examination and a prostate specific antigen concentration lower 3 ng/mL; in the REDUCE trial, eligible men had a prostate specific antigen concentration of 2.5-10 ng/ mL and one negative prostate biopsy session.[1 2] In these trials, the majority of cancers were detected at the end of study since biopsies were preplanned for all participants (61% in PCPT and 88% in REDUCE), which led to the detection of many small and probably insignificant cancers. This endpoint cancer on biopsy at the end of the study has caused concern, and some authors have questioned the generalisability of the results from these trials.[24] Although we had no registration on the indication for biopsy, the vast majority of biopsies in our study were performed for cause—that is, a clinical indication such as elevated serum levels of prostate specific antigen or an abnormal digital rectal examination—and therefore, a much larger proportion of cancers were clinically significant in our study than in the PCPT and REDUCE trials.

The clinical setting in our study was similar to that in the combination of avodart and tamsulosin (CombAT) study, in which men with moderate to severe benign prostatic hyperplasia were randomised to dutasteride, tamsulosin, or a combination of both, and risk for prostate cancer was investigated.[25] In CombAT, biopsies were undertaken for cause—that is, for an abnormal result from an digital rectal examination or increased serum levels of prostate specific antigen. Dutasteride, alone or in combination with tamsulosin, was associated with a 40% relative risk reduction of prostate cancer diagnosis compared with tamsulosin monotherapy. The risk decreased for cancers with all Gleason scores, including scores 8-10—in contrast to our study and the PCPT and REDUCE trials. However, there were only 24 cancers with scores 8-10, out of a total of 134 prostate cancers in CombAT.

In the recent trial on reduction by dutasteride of clinical progression events in expectant management (REDEEM), men with low risk prostate cancers on active surveillance were randomised to dutasteride or placebo.[26] After three years, 54 (38%) of 144 men in the dutasteride group (hazard ratio 0.62 (95% confidence interval 0.43 to 0.89), P=0.009), and 70 (48%) of 145 controls had had prostate cancer progression (defined as progression on prostate biopsy or start of treatment for prostate cancer).

In an observational cohort study performed within the Finnish prostate cancer screening trial, overall incidence of prostate cancer was non-significantly decreased in finasteride users (hazard ratio 0.87 (95% confidence interval 0.63 to 1.19)), compared with non-users.[27] Risk of cancer with Gleason scores 2-6 was significantly decreased among finasteride users (0.59 (0.38 to 0.91)), whereas risk of cancer with scores 7-10 was non-significantly increased (1.33 (0.77 to 2.30)). By contrast with our observations, overall risk of prostate cancer was not increased significantly among α blocker users in the Finnish study. Our interpretation of the increased risk of prostate cancer in men on α blockers is that men with lower urinary tract symptoms have a higher probability of undergoing a prostate specific antigen test and eventually a prostate biopsy, and thereby have an increased risk of a prostate cancer diagnosis, previously described in a Danish nationwide cohort study.[28] Globally, data from our study— together with data from the PCPT, REDUCE, CombAT, REDEEM, and Finnish studies—indicate that the association between 5-ARI exposure and risk of low grade prostate cancer is different from that to high grade cancer.[1 2 25-27] In all these studies, a decreased risk of cancer with Gleason scores 2-6 for men receiving 5-ARI was observed, but the association has been less consistent for cancer with Gleason scores 8-10. Both the PCPT and REDUCE trials reported an increased risk of cancer with Gleason scores 8-10, whereas our study and the CombAT study did not observe a significant increase of Gleason score 8-10 cancers in men receiving 5-ARI treatment for lower urinary tract symptoms. Treatment with 5-ARI for men with lower urinary tract symptoms due to prostatic enlargement provides symptom relief and a decreased risk of surgical procedures.[29 30] With these benefits in mind and the lack of serious side-effects, the net balance seems favourable for men with lower urinary tract symptoms treated with 5-ARI.

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Contributors: DR, HG, LH, and PS designed the study, analysed and interpreted the data, and drafted the manuscript. LM and AB-A contributed to the study design, analysis, and interpretation of the data. All authors made substantial contributions to drafts of the manuscript, had full access to all data (including statistical reports and tables) in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. DR and PS are guarantors.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study was approved by the research ethics board at Umeå University Hospital (2011-53-31M).

Data sharing: No additional data available.

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What is known on this topic

Several studies have shown that 5α-reductase inhibitors decrease the risk of prostate cancer with Gleason scores 2-7

However, the effect of 5α-reductase inhibitors on the risk of cancers with Gleason scores 8-10 is uncertain

What this study adds

Men receiving up to four years' treatment of 5α-reductase inhibitors for lower urinary tract symptoms showed no evidence of an increased risk of prostate cancer with Gleason scores 8-10

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Tables

Table 1| Covariate exposure before date of prostate cancer diagnosis for cases and matched controls, according to date of diagnosis for index case

	Gleason score of cancer							
	Overall		2-6		7		8-10	
	Cases (n=26 735)	Controls (n=133 671)	Cases (n=11 985)	Controls (n=59 838)	Cases (n=9285)	Controls (n=46 425)	Cases (n=5482)	Controls (n=27 408)
Age (years)								
Mean (standard deviation)	69.3 (9.1)	69.3 (9.1)	66.6 (8.2)	66.6 (8.2)	70.0 (8.9)	70.0 (8.9)	74.0 (9.1)	74.0 (9.1)
5-ARI								
No treatment	25 236 (94.4)	127 355 (95.3)	11 357 (94.9)	57 619 (96.3)	8809 (94.9)	44 156 (95.1)	5070 (92.5)	25 580 (93.3)
Treatment received (exposure period)								
Combined*	1499 (5.6)	6316 (4.7)	611 (5.1)	2219 (3.7)	476 (5.1)	2269 (4.9)	412 (7.5)	1828 (6.7)
0-1 year	950 (3.6)	3548 (2.7)	447 (3.7)	1325 (2.2)	293 (3.2)	1249 (2.7)	210 (3.8)	974 (3.6)
1-2 years	304 (1.1)	1443 (1.1)	105 (0.9)	491 (0.8)	92 (1.0)	510 (1.1)	107 (2.0)	442 (1.6)
2-3 years	151 (0.6)	791 (0.6)	47 (0.4)	233 (0.4)	52 (0.6)	304 (0.7)	52 (0.9)	254 (0.9)
>3 years	94 (0.4)	534 (0.4)	12 (0.1)	170 (0.3)	39 (0.4)	206 (0.4)	43 (0.8)	158 (0.6)
α blockers								
No treatment	24 321 (91.0)	125 649 (94.0)	10 734 (89.7)	56 655 (94.7)	8545 (92.0)	43 535 (93.8)	5042 (92.0)	25 459 (92.9)
Treatment received	2414 (9.0)	8022 (6.0)	1234 (10.3)	3183 (5.3)	740 (8.0)	2890 (6.2)	440 (8.0)	1949 (7.1)
Previous prostate biopsy†								
No previous biopsy	24 284 (90.8)	130 423 (97.6)	10 568 (88.3)	58 463 (97.7)	8572 (92.3)	45 308 (97.6)	5144 (93.8)	26 652 (97.2)
Previous biopsy undertaken‡								
1 biopsy, <2 years	921 (3.4)	880 (0.7)	571 (4.8)	415 (0.7)	250 (2.7)	288 (0.6)	100 (1.8)	177 (0.6)
1 biopsy, ≥2 years	732 (2.7)	1610 (1.2)	375 (3.1)	645 (1.1)	223 (2.4)	562 (1.2)	134 (2.4)	403 (1.5)
≥2 biopsies, <4 years	497 (1.9)	370 (0.3)	297 (2.5)	167 (0.3)	142 (1.5)	121 (0.3)	58 (1.1)	82 (0.3)
≥2 biopsies, ≥4 years	301 (1.1)	388 (0.3)	157 (1.3)	148 (0.2)	98 (1.1)	146 (0.3)	46 (0.8)	94 (0.3)
Transurethral resection of the prostate								
No resection	25 742 (96.3)	128 056 (95.8)	11 603 (97.0)	57 887 (96.7)	8939 (96.3)	44 399 (95.6)	5200 (94.9)	25 770 (94.0)
Resection conducted	993 (3.7)	5615 (4.2)	365 (3.0)	1951 (3.3)	346 (3.7)	2026 (4.4)	282 (5.1)	1638 (6.0)

Data are number or number (%) of individuals unless stated otherwise.

*All exposure times combined.

†Prostate biopsy sessions performed before the diagnostic biopsy session for the case and corresponding date for the control.

‡Biopsies undertaken within specified period before diagnosis.

Table 2| **Socioeconomic factors and comorbidity for cases and matched controls**

	Gleason score of cancer							
	Overall		2-6		7		8-10	
	Cases (n=26 735)	Controls (n=133 671)	Cases (n=11 985)	Controls (n=59 838)	Cases (n=9285)	Controls (n=46 425)	Cases (n=5482)	Controls (n=27 408)
Family status								
Married	18 596 (69.6)	88 399 (66.1)	8620 (72.0)	40 232 (67.2)	6373 (68.6)	30 672 (66.1)	3603 (65.7)	17 495 (63.8)
Single, with children	5706 (21.3)	29 539 (22.1)	2349 (19.6)	12 677 (21.2)	2062 (22.2)	10 195 (22.0)	1295 (23.6)	6667 (24.3)
Single, no children	2433 (9.1)	15 733 (11.8)	999 (8.3)	6929 (11.6)	850 (9.2)	5558 (12.0)	584 (10.7)	3246 (11.8)
Highest attained level of education								
High	6189 (23.1)	28 189 (21.1)	3101 (25.9)	13 702 (22.9)	2105 (22.7)	9626 (20.7)	983 (17.9)	4861 (17.7)
Middle	10 097 (37.8)	49 846 (37.3)	4756 (39.7)	23 128 (38.7)	3470 (37.4)	17 157 (37.0)	1871 (34.1)	9561 (34.9)
Low or missing data	10 449 (39.1)	55 636 (41.6)	4111 (34.3)	23 008 (38.5)	3710 (40.0)	19 642 (42.3)	2628 (47.9)	12 986 (47.4)
Charlson comorbidity index								
0	17 929 (67.1)	87 616 (65.5)	8542 (71.4)	41 830 (69.9)	6235 (67.2)	29 852 (64.3)	3152 (57.5)	15 934 (58.1)
1	4562 (17.1)	23 027 (17.2)	1839 (15.4)	9495 (15.9)	1624 (17.5)	8226 (17.7)	1099 (20.0)	5306 (19.4)
2	2471 (9.2)	12 496 (9.3)	987 (8.2)	4792 (8.0)	823 (8.9)	4481 (9.7)	661 (12.1)	3223 (11.8)
≥3	1773 (6.6)	10 532 (7.9)	600 (5.0)	3721 (6.2)	603 (6.5)	3866 (8.3)	570 (10.4)	2945 (10.7)

Data are number or number (%) of individuals unless stated otherwise.

Table 3| **Risk of prostate cancer diagnosis in univariable analysis (men exposed to each factor v men not exposed)**

	Risk of diagnosis, by Gleason score of cancer (odds ratio (95% CI))			
	Overall	**2-6**	**7**	**8-10**
5-ARI				
No treatment (reference)	1.00	1.00	1.00	1.00
Treatment received (exposure period)				
0-1 year	1.32 (1.23 to 1.41)	1.40 (1.30 to 1.51)	1.16 (1.03 to 1.31)	1.08 (0.94 to 1.25)
1-2 years	1.06 (0.95 to 1.19)	1.00 (0.87 to 1.15)	0.91 (0.74 to 1.12)	1.21 (0.99 to 1.47)
2-3 years	0.97 (0.83 to 1.14)	0.94 (0.77 to 1.15)	0.87 (0.66 to 1.15)	1.04 (0.79 to 1.38)
>3 years	0.90 (0.73 to 1.10)	0.70 (0.53 to 0.93)	0.95 (0.69 to 1.32)	1.36 (0.99 to 1.85)
α blockers				
No treatment	1.00	1.00	1.00	1.00
Treatment received	1.50 (1.44 to 1.57)	1.93 (1.81 to 2.05)	1.28 (1.19 to 1.39)	1.13 (1.02 to 1.25)
Previous prostate biopsy*				
No previous biopsy (reference)	1.00	1.00	1.00	1.00
Previous biopsy undertaken†				
1 biopsy, <2 years	4.18 (3.91 to 4.47)	5.19 (4.75 to 5.67)	3.70 (3.24 to 4.22)	2.66 (2.15 to 3.29)
1 biopsy, ≥2 years	2.24 (2.08 to 2.42)	2.86 (2.57 to 3.18)	1.98 (1.73 to 2.28)	1.66 (1.39 to 1.99)
≥2 biopsies, <4 years	4.93 (4.50 to 5.40)	6.04 (5.35 to 6.83)	4.63 (3.88 to 5.53)	3.10 (2.35 to 4.09)
≥2 biopsies, ≥4 years	3.41 (3.04 to 3.83)	4.46 (3.78 to 5.27)	3.07 (2.49 to 3.78)	2.37 (1.74 to 3.22)
Transurethral resection of the prostate				
No resection (reference)	1.00	1.00	1.00	1.00
Resection conducted	0.89 (0.83 to 0.95)	0.94 (0.84 to 1.04)	0.86 (0.77 to 0.96)	0.86 (0.76 to 0.97)
Family status				
Married (reference)	1.00	1.00	1.00	1.00
Single, with children	0.92 (0.90 to 0.95)	0.87 (0.83 to 0.91)	0.97 (0.92 to 1.02)	0.95 (0.89 to 1.01)
Single, no children	0.75 (0.72 to 0.78)	0.69 (0.64 to 0.74)	0.75 (0.70 to 0.81)	0.88 (0.80 to 0.96)
Highest attained level of education				
High (reference)	1.00	1.00	1.00	1.00
Middle	0.93 (0.90 to 0.96)	0.91 (0.87 to 0.95)	0.93 (0.88 to 0.98)	0.97 (0.90 to 1.05)
Low or missing data	0.86 (0.83 to 0.89)	0.79 (0.75 to 0.83)	0.86 (0.82 to 0.91)	1.00 (0.93 to 1.08)
Charlson comorbidity index				
0 (reference)	1.00	1.00	1.00	1.00
1	0.96 (0.93 to 1.00)	0.95 (0.90 to 1.00)	0.94 (0.89 to 0.99)	1.05 (0.97 to 1.12)
2	0.96 (0.92 to 1.00)	1.00 (0.93 to 1.07)	0.87 (0.81 to 0.94)	1.04 (0.95 to 1.13)
≥3	0.83 (0.79 to 0.87)	0.79 (0.73 to 0.86)	0.75 (0.68 to 0.81)	0.98 (0.90 to 1.08)

*Prostate biopsy sessions performed before the diagnostic biopsy session for the case and corresponding date for the control.
†Biopsies undertaken within specified period before diagnosis.

Table 4| **Risk of prostate cancer diagnosis in multivariate analysis (men exposed to each factor v men not exposed, adjusted for each factor)**

	Risk of diagnosis, by Gleason score of cancer (odds ratio (95% CI))			
	Overall	**2-6**	**7**	**8-10**
5-ARI				
No treatment (reference)	1.00	1.00	1.00	1.00
Treatment received (exposure period)				
Combined*	0.89 (0.84 to 0.94)	0.88 (0.80 to 0.96)	0.85 (0.77 to 0.94)	1.01 (0.90 to 1.13)
0-1 year	0.96 (0.90 to 1.03)	1.04 (0.93 to 1.15)	0.92 (0.81 to 1.04)	0.96 (0.83 to 1.11)
1-2 years	0.81 (0.72 to 0.91)	0.70 (0.57 to 0.86)	0.76 (0.62 to 0.95)	1.07 (0.88 to 1.31)
2-3 years	0.77 (0.65 to 0.90)	0.67 (0.50 to 0.90)	0.73 (0.55 to 0.97)	0.96 (0.72 to 1.27)
>3 years	0.72 (0.59 to 0.89)	0.27 (0.15 to 0.48)	0.79 (0.57 to 1.10)	1.23 (0.90 to 1.68)
P for trend	<0.001	<0.001	<0.001	0.46
α blockers				
No treatment (reference)	1.00	1.00	1.00	1.00
Treatment received	1.33 (1.27 to 1.39)	1.60 (1.50 to 1.71)	1.19 (1.10 to 1.29)	1.06 (0.96 to 1.18)
Previous prostate biopsy†				
No previous biopsy (reference)	1.00	1.00	1.00	1.00
Previous biopsy undertaken‡				
1 biopsy, <2 years	4.01 (3.74 to 4.29)	4.71 (4.31 to 5.16)	3.65 (3.19 to 4.18)	2.69 (2.17 to 3.33)
1 biopsy, ≥2 years	2.30 (2.13 to 2.48)	2.84 (2.55 to 3.17)	2.10 (1.83 to 2.42)	1.70 (1.42 to 2.04)
≥2 biopsies, <4 years	4.76 (4.34 to 5.23)	5.75 (5.08 to 6.51)	4.51 (3.77 to 5.39)	3.11 (2.35 to 4.11)
≥2 biopsies, ≥4 years	3.46 (3.07 to 3.89)	4.36 (3.69 to 5.16)	3.19 (2.59 to 3.94)	2.40 (1.76 to 3.28)
Transurethral resection of the prostate				
No resection (reference)	1.00	1.00	1.00	1.00
Resection conducted	0.75 (0.71 to 0.81)	0.72 (0.64 to 0.80)	0.76 (0.68 to 0.85)	0.80 (0.71 to 0.91)
Family status				
Married (reference)	1.00	1.00	1.00	1.00
Single, with children	0.94 (0.91 to 0.97)	0.89 (0.85 to 0.93)	0.99 (0.94 to 1.04)	0.95 (0.89 to 1.01)
Single, no children	0.78 (0.74 to 0.81)	0.72 (0.68 to 0.77)	0.78 (0.72 to 0.83)	0.89 (0.81 to 0.97)
Highest attained level of education				
High (reference)	1.00	1.00	1.00	1.00
Middle	0.95 (0.92 to 0.98)	0.94 (0.89 to 0.98)	0.94 (0.89 to 1.00)	0.98 (0.91 to 1.07)
Low or missing data	0.89 (0.87 to 0.92)	0.84 (0.80 to 0.88)	0.89 (0.84 to 0.94)	1.02 (0.95 to 1.11)
Charlson comorbidity index				
0 (reference)	1.00	1.00	1.00	1.00
1	0.98 (0.94 to 1.01)	0.97 (0.92 to 1.02)	0.94 (0.89 to 1.00)	1.05 (0.98 to 1.13)
2	0.98 (0.93 to 1.02)	1.02 (0.95 to 1.09)	0.89 (0.82 to 0.96)	1.05 (0.96 to 1.14)
≥3	0.84 (0.80 to 0.89)	0.82 (0.76 to 0.90)	0.76 (0.70 to 0.83)	0.99 (0.90 to 1.09)

*All exposure times combined.

†Prostate biopsy sessions performed before the diagnostic biopsy session for the case and corresponding date for the control.

‡Biopsies undertaken within specified period before diagnosis.

Figures

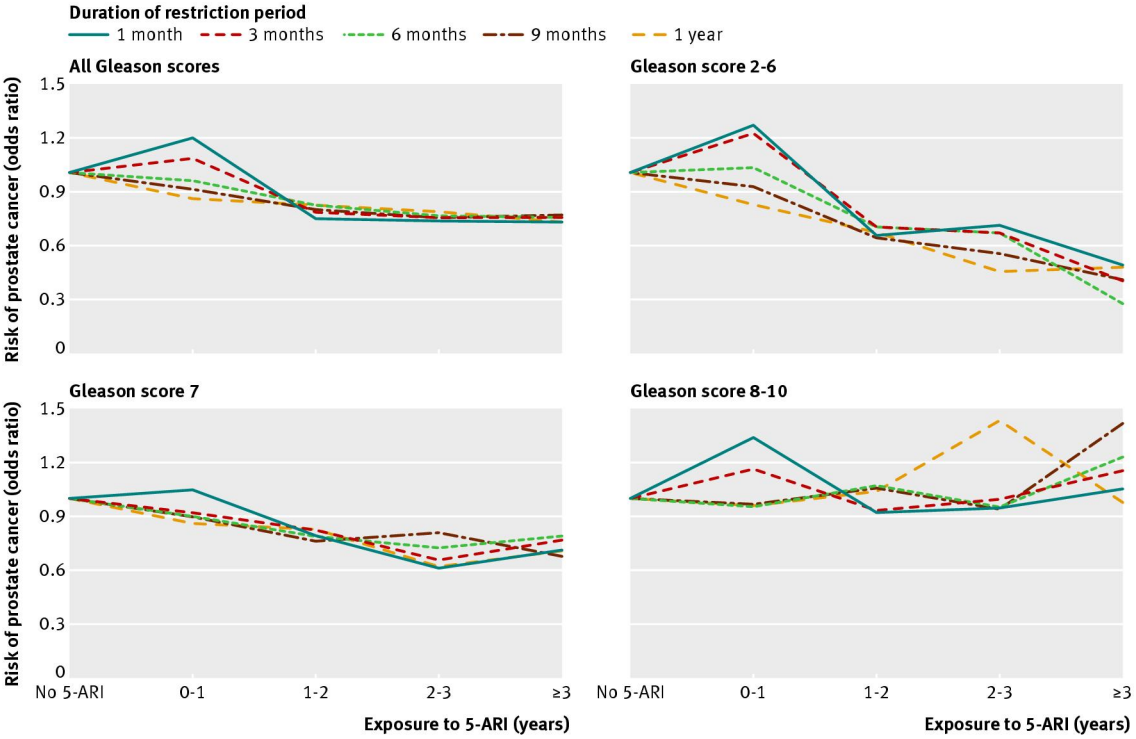

Fig 1 Risk of prostate cancer according to time of exposure to 5-ARI and duration of restriction period. Odds ratios from multivariable model include prescription of α blockers, transurethral resection of the prostate, prostate biopsies, composition of household, education, and comorbidity

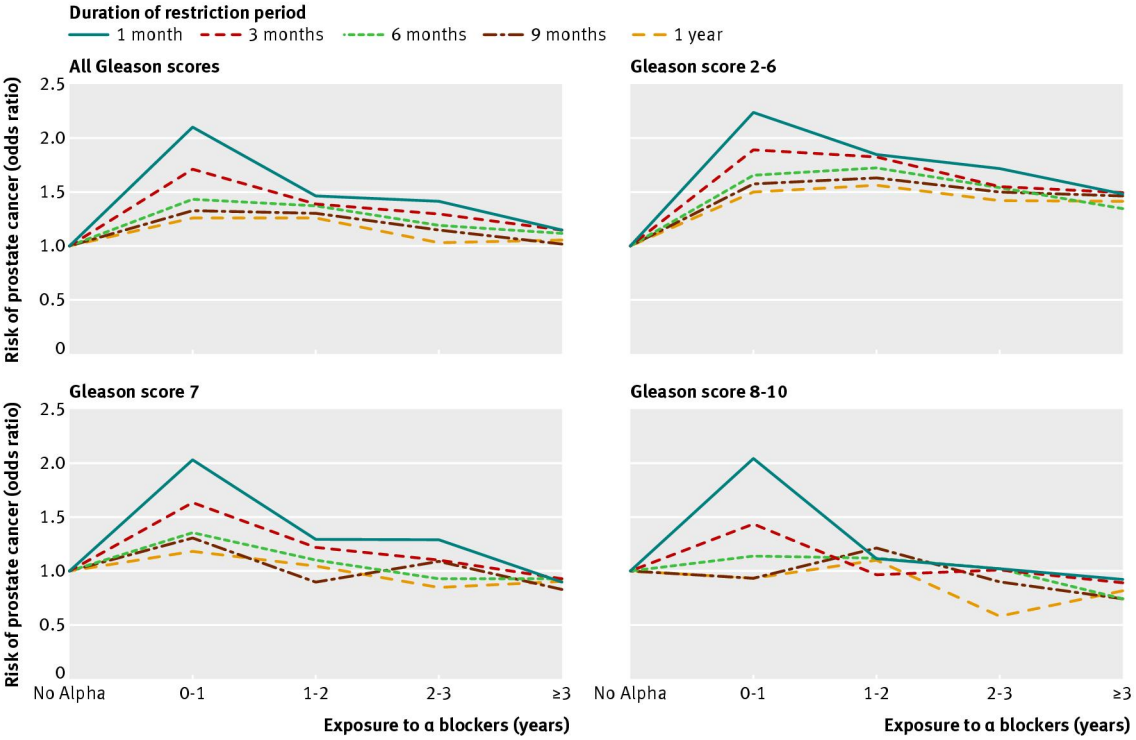

Fig 2 Risk of prostate cancer according to time of exposure to α blockers and duration of restriction period. Odds ratios from multivariable model including prescription of 5-ARI, transurethral resection of the prostate, prostate biopsies, composition of household, education, and comorbidity