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JNCI J Natl Cancer Inst (2018) 110(11): djy036

doi: 10.1093/jnci/djy036
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Risk of Prostate Cancer in Men Treated With 5α-Reductase Inhibitors—A Large Population-Based Prospective Study

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Abstract

Background: Studies have shown that 5α-reductase inhibitors (5-ARIs) decrease the risk for low-grade prostate cancer (PC), but results are conflicting concerning high-grade PCs. The objective of the present study is to evaluate the association between 5-ARI treatment for lower urinary tract symptoms and the risk for PC.
Methods: This is a population-based prospective study on all men age 40 years and older with at least one prostate-specific antigen (PSA) test in Stockholm County from January 2007 until December 2015. Data are derived from the Stockholm PSA and Biopsy Register and Prescribed Drug Register in Sweden, containing data on 5-ARI-use before diagnosis of PC. Cox proportional hazards models were used to estimate the cause-specific hazard ratios of PC for each exposure level relative to men not taking the medication.
Results: Of the 333 820 men in the cohort, 23 442 (7.0%) were exposed to 5-ARI at some time during the study period of eight years. Treatment with 5-ARI decreased the risk for overall PC, and the effect was larger with longer time of exposure (0.1 to 2 years: hazard ratio [HR] = 0.81, 95% confidence interval [CI] = 0.71 to 0.93; 2 to 4 years: HR = 0.39, 95% CI = 0.32 to 0.47; 4 to 6 years: HR = 0.40, 95% CI = 0.31 to 0.52; and 6 to 8 years: HR = 0.31, 95% CI = 0.16 to 0.60). Specifically, 5-ARI decreased the risk for PC with Gleason Scores 6 and 7 but did not statistically significantly affect the long-term risk of being diagnosed with a PC with a Gleason Score of 8 to 10 with up to eight years of treatment.
Conclusions: Treatment with 5-ARI for lower urinary tract symptoms is safe with respect to prostate cancer risk.

Finasteride and dutasteride are 5α-reductase inhibitors (5-ARIs) for treating benign enlargement of the prostate with good effect on lower urinary tract symptoms by blocking the conversion of testosterone to the more potent androgen dihydrotestosterone (1). Androgens have been known as a key driver of prostate carcinogenesis for many decades. Men with congenital deficiency of type 2 5α-reductase have undetectable prostate-specific antigen (PSA) levels and small prostates and do not develop prostate cancer (2). Two large randomized controlled trials, the Prostate Cancer Prevention Trial (PCPT) (3) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial (4), were designed to investigate the effect of finasteride (PCPT) and dutasteride (REDUCE) on prostate cancer incidence. Both trials showed a reduced risk for prostate cancer at biopsy in men treated with 5-ARI compared with men receiving placebo, 25% and 23%, respectively. However, their results also showed increased incidence of high-grade cancers (Gleason Score 8 to 10) by 0.7% and 0.5% with finasteride and dutasteride, respectively (5). In light of these results, the US Food and Drug Administration (FDA) issued a safety warning in 2011 for a potential for increased risk of high-grade prostate cancer with the use of 5-ARI (6). The recommendation resulted in some physicians changing their practice to reduce drug prescriptions of 5-ARIs for men who could benefit from their use (7). However, subesquent analyses of the PCPT data found that finasteride increased the detection rate of high-grade prostate cancer by shrinking of the prostate and thereby introduced a potential detection bias (8). Furthermore, in the 18-year follow-up of PCPT, there was no statistically significant difference in the rates of survival between the groups (9).

Received: October 31, 2017; **Revised:** January 11, 2017; **Accepted:** February 14, 2017

In current clinical practice, a large number of men are treated with 5-ARI. Given the high use of the medication and the potentially missed opportunity of treatment because of the FDA safety warning, further studies are needed to clarify the conflicting results described above. We aimed to establish if there is any alteration in prostate cancer risk for men treated in a clinical setting with 5-ARI for lower urinary tract symptoms. This analysis was done in the largest prospective population-based cohort of men representing contemporary clinical practice with respect to 5-ARI prescription patterns, PSA levels, and prostate cancer diagnostics.

Methods

Study Design

This is a population-based prospective study with data from the Stockholm PSA and Biopsy Register, which contains information on every PSA test (n = 4 242 978 as of January 2017) and prostate biopsy (n = 87 036) for all men in Stockholm County since 2003. Linking to the Regional Prostate Cancer Register and the Swedish National Cancer Registers contributes clinical data including tumor stage. Data on patient characteristics, civil status, and educational level were retrieved from Statistics Sweden. Exposure to 5-ARI was obtained by linking to the Swedish drug register.

Men in Stockholm County age 40 years and older were followed between January 2007 and December 2015. During this period, the men were included in the cohort one year after their first PSA test. This one-year delay was used to remove prevalent cancers detected due to the initial PSA test and to avoid potential selection bias caused by men receiving a prostate cancer diagnosis during the clinical investigation prior to 5-ARI treatment for lower urinary tract symptoms. To be included, the men had to be free of a prostate cancer diagnosis and have no records of prior 5-ARI usage. This latter requirement (incidence-based exposure) is motivated by the strong effect these drugs have on lowering the PSA level. The men were then followed until prostate cancer, death, or the end of the study, whichever came first.

Exposure and Outcome

Information on exposure to 5-ARI included prescription and expedition dates as well as package size for Finasteride (ATC code G04CB01) and Dutasteride (ATC code G04CB02). Cumulative exposure of 5-ARI was categorized as 0.1–2, 2–4, 4–6, and 6–8 years of treatment, and each subject was considered exposed after the first expedition of the medication.

Primary outcome, Gleason Score–specific prostate cancer, was collected from prostate biopsies retrieved from three pathology units in Stockholm that are performing all histologic examinations from prostate tissue in the county. Information on Gleason Score was retrieved and categorized as Gleason Score 6, 7, and 8–10.

Statistical Methods

Cox proportional hazards models were used to estimate the cause-specific hazard ratios and *P* values of prostate cancer for each exposure level relative to men not taking the medication. We censored for competing event of death and, when studying Gleason Score–specific cancers, for prostate cancer of other grades. The exposure was time dependent in the sense that each subject enters the cohort unexposed and may later change his status to exposed at the first date of expedition of the drug and that we allow for the effect of the drug to vary by years of usage.

PSA is a confounder, affected both by exposure to 5-ARI and the outcome prostate cancer. Therefore, our data are presented with two adjustments. 1) Adjusted hazard ratios were controlled for age (continuous), first-degree family history of prostate cancer (yes or no), previous negative biopsies (time-dependent covariate; yes or no), civil status (partner or single), and educational level. 2) Adjusted hazard ratios were controlled for the same variables as in (1) and, in addition, PSA before treatment with 5-ARI and interactions of PSA with age and previous negative biopsies. These two adjustments provide a lower bound (without PSA adjustment) and an upper bound (with PSA adjustment) on estimates of potential reductions in prostate cancer risk in the exposed group. There was no statistically significant violation of the proportional hazard assumption in any of the adjusted models. The assumption of proportionality was verified by a global test and also visual inspection of Schoenfeld residuals.

We also estimated cumulative incidence curves constructed from stratified Cox models (using the same adjustment as above) with separate baseline hazards for exposed and non-exposed to avoid a fixed and proportional relationship between the curves. As sensitivity analyses, we changed the one-year delay to enter the cohort after the initial PSA test to six and 18 months, and restricted age to 50 to 70 years. The analyses were performed using R and Stata (10). All 95% confidence intervals are two-sided. The cut-point for statistical significance was less than .05.

All data were stored in a secure database in accordance with ethical committee approval. A regional ethics board approved the study (Regional Ethics Testing Board, Stockholm; EPN DnR 2012/438-31/3).

Results

Of the 333 820 men in the cohort, 23 442 (7.0%) were exposed to 5-ARI at some time during the study period of eight years. Duration of exposure to 5-ARI was 0.1–2 years in 32.1% of the exposed men, 2–4 years in 26.1%, 4–6 years in 28.0%, and 6–8 years in 13.8%. Men treated with 5-ARI were older (mean age at study start = 69 vs 60 years) and had higher PSA prior to entering the cohort compared with men not treated with 5-ARI (mean = 5.0 vs 4.6 ng/mL). A previous negative prostate biopsy was more common among men treated with 5-ARI than among those who were not (16.5% vs 5.8%) (Table 1). The median time between negative biopsy and entry into the cohort was 0.47 years for non-5-ARI users and 0.43 years for 5-ARI users.

In the multivariable analysis without adjustment for PSA, treatment with 5-ARI was statistically significantly associated with a decreased risk of overall prostate cancer from two years of exposure up to the end of the follow-up of eight years (0.1–2 years: HR = 1.00, 95% CI = 0.88 to 1.15, $P = .92$; 2–4 years: HR = 0.49, 95% CI = 0.41 to 0.60, $P < .001$; 4–6 years: HR = 0.53, 95% CI = 0.41 to 0.69, $P < .001$; and 6–8 years: HR = 0.42, 95% CI = 0.22 to 0.81, $P = .01$) (Table 2). In the second multivariable analysis including PSA, treatment with 5-ARI was similarly statistically significantly associated with a decreased risk of overall prostate cancer, but at all exposure levels. The effect was larger with increasing duration of 5-ARI exposure (0.1–2 years: HR = 0.81, 95%

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Table 1. Characteristics of the study cohort*

Variable	Non-5-ARI		5-ARI	
	Person-years	No. (%) (n = 329 672)	Person-years	No. (%) (n = 23 442)
Age, y				
<50	285 613	58 643 (17.8)	1317	442 (1.9)
50–59	546 074	112 227 (34.0)	11 494	3469 (14.8)
60–69	511 643	99 897 (30.3)	29 406	9500 (40.5)
70–79	196 660	40 732 (12.4)	18 796	7004 (29.9)
>80	68 153	18 135 (5.5)	5569	3027 (12.9)
Prostate-specific antigen, ng/mL				
0–1	732 687	146 990 (44.6)	8654	2816 (12.0)
1–3	626 757	125 689 (38.1)	26 369	8103 (34.6)
3–5	133 649	28 712 (8.7)	15 471	5349 (22.8)
5–10	75 311	17 807 (5.4)	11 863	4878 (20.8)
>10	34 930	9390 (2.8)	4128	2267 (9.8)
Previous negative biopsy	97 979	19 195 (5.8)	12 821	3879 (16.5)
Family history of prostate cancer	189 770	36 848 (11.1)	6597	2108 (9.0)
Educational level				
Elementary school	311 122	63 185 (19.2)	15 131	5669 (24.2)
High school	383 610	79 266 (24.0)	13 298	4616 (19.7)
Technical training school	291 922	57 747 (17.5)	13 841	4726 (20.2)
University/college	344 917	70 580 (21.4)	13 888	4618 (19.7)
Civil status				
Single	607 080	129 401 (39.3)	22 524	8556 (36.5)
Partner	998 045	199 609 (60.5)	44 005	14 857 (63.4)

*Total number of exposed and nonexposed do not sum to the total number of patients (n = 333 820) because most men on finasteride entered as unexposed. 5-ARI = 5α-reductase inhibitor.

CI = 0.71 to 0.93, P = .002; 2–4 years: HR = 0.39, 95% CI = 0.32 to 0.47, P < .001; 4–6 years: HR = 0.40, 95% CI = 0.31 to 0.52, P < .001; and 6–8 years: HR = 0.31, 95% CI = 0.16 to 0.60, P = .001) (Table 2). For cancers with Gleason Scores of 6 and 7, the same trend was seen with statistically significantly decreased risk of prostate cancer with exposure of 5-ARI from two to six years after adjustment (1) and statistically significantly decreased risk at all exposure levels when adding PSA to the adjustments.

For high-grade cancers with Gleason Scores of 8 to 10, the risk was not statistically significantly changed at any of the exposure levels after adjustments including PSA. However, in adjustment (1) (without PSA), a statistically significantly increased risk was seen after 0.1–2 years of exposure to 5-ARI (HR = 1.56, 95% CI = 1.15 to 2.12, P = .004), but no statistically significantly altered risk was seen thereafter (on the contrary, a statistically nonsignificant protective effect was seen) (Table 2). Sensitivity analyses restricted to men age 50 to 70 years did not alter these results materially.

Similarly, cumulative incidence curves of the probability of prostate cancer (overall and Gleason Scores 6, 7, and 8–10) in men treated with 5-ARI compared with men not treated with 5-ARI showed large differences in the overall group and for Gleason Scores 6 and 7. There was no evident difference in men with Gleason Score 8–10 prostate cancer (Figure 1). Change of the one-year entry delay into the cohort after the initial PSA test to six or 18 months did not alter the association of overall prostate cancer risk and exposure to 5-ARI in sensitivity analyses.

Discussion

In this large population-based historical prospective study, we found a reduced risk of prostate cancer among 5-ARI users. The reduced risk was restricted to cancers with Gleason Scores 6 and 7. No statistically significantly altered long-term risk of prostate cancer with Gleason Scores of 8 to 10 was observed with up to eight years of treatment when adjusting for confounders including PSA. Our results support the use of 5-ARI in daily clinical practice and provide further evidence to the existing literature through wide generalizability compared with previous randomized trials and improved internal validity compared with existing observational studies, as well as a larger study size and longer exposure time.

This is the largest prospective study to assess the association between 5-ARI use and the risk of prostate cancer, and the number of exposed men exceeds the number in all the previous prospective trials taken together. Furthermore, our study has a long exposure time of 5-ARI compared with the existing prospective trials, adding important knowledge to the current evidence as previous research has indicated an increased effect with longer exposure to the medication (11). Additionally, our study contains data on PSA before and after treatment with 5-ARI. PSA is a key variable when evaluating the risk for prostate cancer in men on 5-ARI, as the drug affects PSA levels and PSA is highly correlated to the outcome. We have PSA values on all 333 820 men, including PSA measurements before initiation of 5-ARI exposure in the 23 442 men that were exposed to 5-ARI in our cohort. We were therefore able to control for potential confounding by PSA level before the start of medication.

The aim of our study was to evaluate the safety of 5-ARI treatment for lower urinary tract symptoms in terms of risk for prostate cancer, as opposed to prostate cancer prevention, which was studied in the PCPT and REDUCE trials. From this point of view, our study population is more representative of the population taking 5-ARI in terms of PSA levels and prostate volume compared with the PCPT trial, where all men had a PSA

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Table 2. HR for prostate cancer overall and by Gleason Score

5-ARI exposure, y	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* P‡	Adjusted† HR (95% CI)	Adjusted† P‡
Prostate cancer overall					
0	1.00 (ref)	1.00 (ref)	–	1.00 (ref)	–
0.1–2	1.70 (1.49 to 1.93)	1.00 (0.88 to 1.15)	.92	0.81 (0.71 to 0.93)	.002
2–4	0.85 (0.70 to 1.04)	0.49 (0.41 to 0.60)	<.001	0.39 (0.32 to 0.47)	<.001
4–6	0.92 (0.71 to 1.18)	0.53 (0.41 to 0.69)	<.001	0.40 (0.31 to 0.52)	<.001
6–8	0.72 (0.37 to 1.40)	0.42 (0.22 to 0.81)	.01	0.31 (0.16 to 0.60)	.001
Gleason Score 6					
0	1.00 (ref)	1.00 (ref)	–	1.00 (ref)	–
0.1–2	1.29 (1.04 to 1.59)	0.82 (0.66 to 1.02)	.07	0.67 (0.54 to 0.83)	<.001
2–4	0.64 (0.46 to 0.88)	0.39 (0.28 to 0.54)	<.001	0.32 (0.23 to 0.44)	<.001
4–6	0.76 (0.51 to 1.13)	0.47 (0.32 to 0.70)	<.001	0.37 (0.25 to 0.55)	<.001
6–8	0.81 (0.33 to 1.97)	0.50 (0.21 to 1.22)	.13	0.39 (0.16 to 0.94)	.04
Gleason Score 7					
0	1.00 (ref)	1.00 (ref)	–	1.00 (ref)	–
0.1–2	1.81 (1.48 to 2.21)	1.05 (0.85 to 1.29)	.65	0.84 (0.69 to 1.03)	.100
2–4	0.76 (0.55 to 1.04)	0.43 (0.31 to 0.59)	<.001	0.33 (0.24 to 0.46)	<.001
4–6	0.73 (0.46 to 1.15)	0.41 (0.26 to 0.65)	<.001	0.31 (0.20 to 0.49)	<.001
6–8	0.62 (0.20 to 1.94)	0.35 (0.11 to 1.10)	.07	0.26 (0.08 to 0.81)	.02
Gleason Score 8–10					
0	1.00 (ref)	1.00 (ref)	–	1.00 (ref)	–
0.1–2	3.22 (2.39 to 4.35)	1.56 (1.15 to 2.12)	.004	1.25 (0.92 to 1.70)	.15
2–4	2.20 (1.51 to 3.21)	1.03 (0.70 to 1.50)	.89	0.79 (0.54 to 1.16)	.23
4–6	2.47 (1.49 to 4.10)	1.14 (0.69 to 1.91)	.60	0.85 (0.51 to 1.41)	.53
6–8	0.71 (0.10 to 5.09)	0.33 (0.05 to 2.36)	.27	0.23 (0.03 to 1.68)	.15

*Adjusted for age, family history, previous biopsies, civil status, and educational level. 5-ARI = 5α-reductase inhibitor; CI = confidence interval; HR = hazard ratio.
†Adjusted for prostate-specific antigen, age, family history, previous biopsies, civil status, educational level, and interactions.
‡Cox proportional hazards models were used to estimate the cause-specific hazard ratios and *P* values; 95% confidence intervals are two-sided.

of less than 3 ng/mL and were free of lower urinary tract symptoms, and the REDUCE trials, where all men had a previous negative biopsy and a PSA of 2.5–10 ng/mL. Clinical practice has changed in these last 10 years, with an increase in the number of biopsy cores and modifications to the Gleason Score (12). Compared with PCPT and REDEEM, our data are more recent and representative of contemporary clinical practice (13). Furthermore, both the PCPT and REDUCE have been criticized for possible overdetection of cancers because all men were offered an end-of-study biopsy. In the PCPT, 61% of the cancers were detected at the end-of-study biopsy, and in REDUCE 88%. This led to detection of many small and clinically insignificant cancers, and the generalizability of these results can be questioned. In contrast, the majority of biopsies in our cohort were performed because of a clinical indication such as an elevated PSA or abnormal digital rectal exam, resulting in a larger proportion of clinically significant cancers compared with the PCPT and REDUCE trials.

Two limitations of our study compared with the PCPT and REDUCE trials are the observational design, leading to systematic differences between men who were treated with 5-ARI, and that there was no standardized, predefined indication for prostate biopsy used in the study. The 5-ARI group could have increased diagnostic activity driven by lower urinary tract symptoms and thus more contact with the health care system. To address this problem, we adjusted for factors influencing how often a man chooses to seek care, such as age, PSA level, previous negative biopsy, civil status, and educational level. Furthermore, an initially higher PSA could also lead to increased diagnostic activity. By using a restriction period of 12 months in our analysis, we reduced the risk that men with prevalent cancers were included in the analysis, which could lead to a falsely increased risk after a short exposure to 5-ARI. The time of exposure after a negative biopsy is a period where incidence of cancer would be expected to be lower. A sensitivity analysis was performed with censoring of all men with a negative biopsy for one year, and the results did not change the overall interpretation of the data.

We lacked data on side effects of 5-ARI treatment, such as urinary and sexual symptoms, and data on prostate volume, which is negatively associated with both 5-ARI treatment and prostate cancer risk. Data on 5ARI exposure included prescription and expedition dates. However, this does not guarantee that the individual took the medication, and the analysis is thus based on an intention-to-treat basis. Furthermore, there is a possibility of loss to follow-up in the data because individuals could have moved outside of Stockholm County during the study period.

Our results of a reduced risk for low-grade prostate cancers among 5-ARI users are in line with the results from the randomized trials PCPT and REDUCE (3,4). The results of PCPT and REDUCE also showed an increase of high-grade cancers in 5-ARI users. In our data, this effect was only observed without PSA adjustment in the first exposure level of 0–2 years with 5-ARI (HR = 1.6, 95% CI = 1.2 to 2.1). No statistically significantly altered risk was seen thereafter. Rather, a statistically nonsignificant protective effect was seen after exposure of 2–8 years. Subsequent analyses of the PCPT trial showed that finasteride improves the sensitivity of PSA testing and prostate biopsy for the detection of high-grade prostate cancer through shrinking

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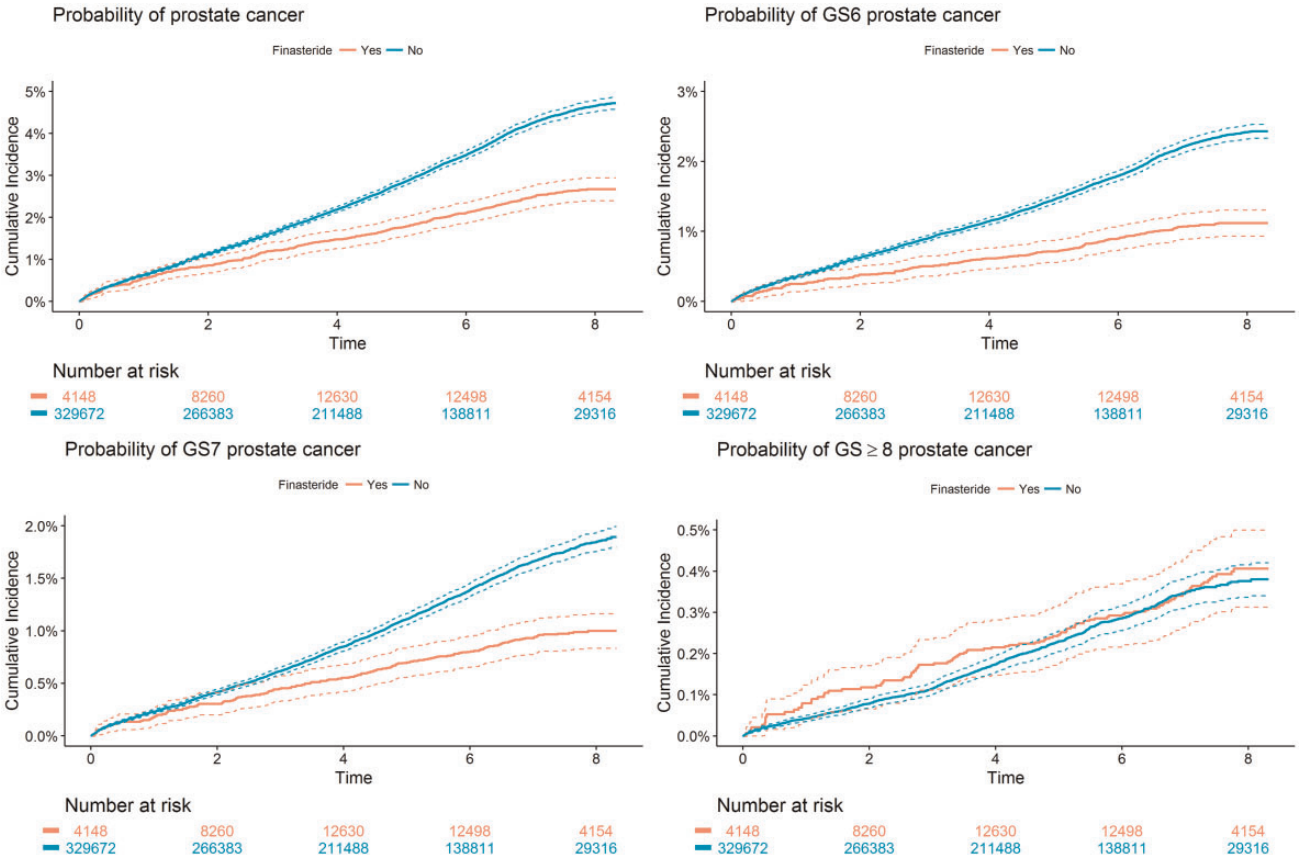

Figure 1. Cumulative incidence curves of the probability of prostate cancer in men treated with 5α-reductase inhibitors and men not treated with 5α-reductase inhibitors. Adjusted for prostate-specific antigen, age, family history, previous negative biopsies, civil status, and educational level.

of the prostate (8,14). It is reasonable that the increased risk for high-grade prostate cancer we observed for the first exposure level is explained by this hypothesis. These detected cancers within two years from start of exposure are likely to be prevalent cancers independent of the 5-ARI medication, especially given that we know that these high-risk cancers develop over a long period. However, other hypotheses that could explain the increase in high-grade cancers have also been presented (15–18). Additionally, the long-term results from the PCPT trial reinforce these results, showing no increased mortality rate among finasteride users after 18 years of follow-up (9). Furthermore, a retrospective study by Wallner et al. evaluating 25 388 men treated with 5-ARI was not associated with an increased risk of prostate cancer–specific mortality compared with men treated with alpha-adrenergic blockers (19).

In an observational cohort study within the Finnish Prostate Cancer Screening Trial (ERSPC), results showed no statistically significantly affected overall prostate cancer incidence in finasteride users compared with nonusers (HR = 0.87, 95% CI = 0.63 to 1.19) (20). However, incidence of Gleason 2–6 tumors was decreased among finasteride users (HR = 0.59, 95% CI = 0.38 to 0.91), but the incidence of Gleason 7–10 tumors was unchanged. In 2013, Robinson et al. published a nationwide, population-based case–control study within the Prostate Cancer data Base Sweden 2.0 (PCBaSe). They evaluated 1499 cases and 6316 matched controls who had been exposed to 5-ARI to assess the association between 5-ARI use and prostate cancer risk (11). Their results showed a decreased risk for overall prostate cancer, which increased with duration of exposure of 5-ARI. The risk was restricted to cancers with Gleason Scores 6 to 7, and there was no statistically significant association in risk of cancers with Gleason Scores 8–10. A limitation shared by the ERSPC and PCBaSe studies is the lack of data on PSA. It is likely that the finasteride users had markedly higher PSA levels prior to being prescribed the drug, which potentially would bias the results in favor of higher risk for finasteride users.

In summary, previous evidence and our results indicate that 5-ARI exposure is associated with a reduced risk of low-grade prostate cancer with Gleason Score 6. Our results also showed a reduced risk for prostate cancer with Gleason Score 7, which is in line with previous observational studies, however, not the two RCTs. The results are contradictory concerning high-grade prostate cancer with Gleason Score 8–10, where our results adjusted for PSA showed no increased risk for high-grade prostate cancer in men receiving 5-ARI, while the two randomized trials PCPT and REDUCE showed a small increased risk. However, our results are in line with the previous contemporary observational studies (11,20).

Our results showed that men treated with 5-ARI had a reduced risk of being diagnosed with prostate cancers with Gleason Scores 6 and 7, but showed no statistically significantly altered long-term risk of being diagnosed with prostate cancer with Gleason Scores of 8–10 up to eight years of treatment. Overall, together with the benefits of symptom relief and a decreased risk of surgical procedures, treatment with 5-ARI for lower urinary tract symptoms seems beneficial and safe with respect to prostate cancer risk (21,22).

Funding

This study was supported by grants from the Strategic Research Programme on Cancer (StratCan), Karolinska Institutet, Stiftelsen Johanna Hagstrand och Sigfrid Linners Minne, the Swedish Research Council, the Swedish Cancer Society, and FORTE.

Notes

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The funders had no role in the design of the study; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication.

Anna Wallerstedt was involved in the design of the study, data abstraction, data analysis, data interpretation, and drafting the manuscript. Peter Strom was involved in the design of the study, data abstraction, data analysis, and data interpretation and made substantial contributions to drafts of the manuscript. Henrik Gronberg and Tobias Nordstrom were involved in the design of the study and data interpretation and made substantial contributions to drafts of the manuscript. Martin Eklund is the guarantor and was involved in the design of the study, data abstraction, data analysis, and data interpretation and made substantial contributions to drafts of the manuscript. Men in Stockholm County contributed with the clinical information that made this study possible.

Anna Wallerstedt affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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References

1. Nacusi LP, Tindall DJ. Targeting 5alpha-reductase for prostate cancer prevention and treatment. *Nat Rev Urol*. 2011;8(7):378–384.
2. Imperato-McGinley J, Gautier T, Zirinsky K, et al. Prostate visualization studies in males homozygous and heterozygous for 5 alpha-reductase deficiency. *J Clin Endocrinol Metab*. 1992;75(4):1022–1026.
3. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med*. 2003;349(3):215–224.
4. Andriole GL, Bostwick DG, Brawley OW, et al. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med*. 2010;362(13):1192–1202.
5. Theoret MR, Ning YM, Zhang JJ, et al. The risks and benefits of 5alpha-reductase inhibitors for prostate-cancer prevention. *N Engl J Med*. 2011;365(2):97–99.
6. US Food and Drug Administration. FDA Drug Safety Communication: 5-alpha reductase inhibitors (5-ARIs) may increase the risk of a more serious form of prostate cancer. 2011. http://www.fda.gov/Drugs/DrugSafety/ucm258314.htm.
7. Kjaerulff TM, Ersboll AK, Green A, et al. Patterns of finasteride use in the male populations of four Nordic countries: A cross-national drug utilization study. *Scand J Urol*. 2016;50(3):220–227.
8. Thompson IM, Chi C, Ankerst DP, et al. Effect of finasteride on the sensitivity of PSA for detecting prostate cancer. *J Natl Cancer Inst*. 2006;98(16):1128–1133.
9. Thompson IM Jr, Goodman PJ, Tangen CM, et al. Long-term survival of participants in the prostate cancer prevention trial. *N Engl J Med*. 2013;369(7):603–610.
10. R Development Core Team. *R: A Language and Environment For Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2008. http://www.R-project.org.
11. Robinson D, Garmo H, Bill-Axelson A, et al. Use of 5alpha-reductase inhibitors for lower urinary tract symptoms and risk of prostate cancer in Swedish men: Nationwide, population based case-control study. *BMJ*. 2013;346:f3406.
12. Epstein JI, Allsbrook WC Jr, Amin MB, et al. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *Am J Surg Pathol*. 2005;29(9):1228–1242.
13. Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of grading patterns and proposal for a new grading system. *Am J Surg Pathol*. 2016;40(2):244–252.
14. Lucia MS, Epstein JI, Goodman PJ, et al. Finasteride and high-grade prostate cancer in the Prostate Cancer Prevention Trial. *J Natl Cancer Inst*. 2007;99(18):1375–1383.
15. Pinsky P, Parnes H, Ford L. Estimating rates of true high-grade disease in the prostate cancer prevention trial. *Cancer Prev Res (Phila)*. 2008;1(3):182–186.
16. Figg WD, Thompson IM. Effect of 5alpha-reductase inhibitor use on mortality from prostate cancer. *JAMA Oncol*. 2015;1(3):321–322.
17. Cohen YC, Liu KS, Heyden NL, et al. Detection bias due to the effect of finasteride on prostate volume: A modeling approach for analysis of the Prostate Cancer Prevention Trial. *J Natl Cancer Inst*. 2007;99(18):1366–1374.
18. Redman MW, Tangen CM, Goodman PJ, et al. Finasteride does not increase the risk of high-grade prostate cancer: A bias-adjusted modeling approach. *Cancer Prev Res (Phila)*. 2008;1(3):174–181.
19. Wallner LP, DiBello JR, Li BH, et al. 5-alpha reductase inhibitors and the risk of prostate cancer mortality in men treated for benign prostatic hyperplasia. *Mayo Clin Proc*. 2016;91(12):1717–1726.
20. Murtola TJ, Tammela TL, Maattanen L, et al. Prostate cancer incidence among finasteride and alpha-blocker users in the Finnish Prostate Cancer Screening Trial. *Br J Cancer*. 2009;101(5):843–848.
21. McConnell JD, Bruskewitz R, Walsh P, et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. *N Engl J Med*. 1998;338(9):557–563.
22. McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med*. 2003;349(25):2387–2398.