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5α-reductase Inhibitors and Risk of High-grade or Lethal Prostate Cancer

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Abstract

Importance—5α-reductase inhibitors (5ARIs) are widely used for benign prostatic hyperplasia despite controversy regarding potential risk of high-grade prostate cancer with use. Furthermore, the effect of 5ARIs on progression and prostate cancer death remains unclear.

Objective—To determine the association between 5ARI use and development of high-grade or lethal prostate cancer.

Design, Setting, and Participants—Prospective observational study of 38,058 men followed for prostate cancer diagnosis and outcomes between 1996–2010 in the Health Professionals Follow-up Study.

Exposure—Use of 5ARIs between 1996–2010.

Main Outcome Measures—Cox proportional hazards models were used to estimate risk of prostate cancer diagnosis or development of lethal disease with 5ARI use, adjusting for possible confounders including prostate specific antigen testing.

Results—During 448,803 person-years of follow-up, we ascertained 3681 incident prostate cancer cases. Of these, 289 were lethal (metastatic or fatal), 456 were high-grade (Gleason 8–10), 1238 were Gleason grade 7, and 1600 were low-grade (Gleason 2–6). A total of 2878 (7.6%) men

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reported use of 5ARIs between 1996 and 2010. After adjusting for confounders, men who reported ever using 5ARIs over the study period had a reduced risk of overall prostate cancer (HR 0.77; 95% CI, 0.65–0.91). 5ARI users had a reduced risk of Gleason 7 (HR 0.67; 95% CI, 0.49–0.91) and low-grade (Gleason 2–6) prostate cancer (HR 0.74; 95% CI, 0.57–0.95). 5ARI use was not associated with risk of high-grade (Gleason 8–10, HR 0.97; 95% CI, 0.64–1.46) or lethal disease (HR 0.99; 95% CI, 0.58–1.69). Increased duration of use was associated with significantly lower risk of overall prostate cancer (HR for 1 year of additional use 0.95; 95% CI, 0.92–0.99), localized (HR 0.95; 95% CI, 0.90–1.00), and low-grade disease (HR 0.92; 95% CI, 0.85–0.99). There was no association for lethal, high-grade, or grade 7 disease.

Conclusions and Relevance—While 5ARI use was not associated with developing high-grade or lethal prostate cancer, they were associated with a reduction in low-grade, Gleason 7 and overall prostate cancer. Since the number of patients with high-grade or lethal prostate cancer in our cohort was limited, we cannot rule out potential risk of harm with 5ARI use.

Introduction

Prostate cancer is the second leading cause of cancer mortality in U.S. men and the most commonly diagnosed non-cutaneous malignancy.[1] North American men have a 1 in 6 lifetime risk of prostate cancer diagnosis with a median age at diagnosis of 67 years.[1] Due to the high incidence of prostate cancer and the significant personal and public costs associated with diagnosis and treatment, preventive measures would have a powerful impact on reducing associated morbidity and mortality. In addition, prostate cancer is well-suited for chemoprevention efforts due to its long latency period and multi-step pathogenesis.[2]

5α-reductase inhibitors (5ARI) have been suggested as chemopreventive agents for prostate cancer. The enzyme, 5-α reductase, facilitates conversion of testosterone to the biologically active form, dihydrotestosterone, and is important in prostate development and maintenance.[3,4] There are two primary isotypes: 5α-reductase type 1 and 5α-reductase type 2.[3,5] 5ARIs such as finasteride (type 2 inhibitor) and dutasteride (type 1 and 2 inhibitor), inhibit conversion of testosterone, resulting in lower intra-prostatic levels of dihydrotestosterone and subsequent induction of apoptosis.[3,5,6] This inhibition results in prostate size reduction and is the basis for 5ARIs being widely used by men who suffer from lower urinary tract symptoms due to benign prostatic hyperplasia.[7,8]

Two large, randomized controlled trials examined the efficacy of 5ARIs for prevention of prostate cancer and showed a 23–25% reduction in prostate cancer incidence compared to placebo.[9,10] The reduction in prostate cancer was predominantly due to decreased incidence of low-grade (Gleason ≤ 6) cancer. There was an unexpected increase in high-grade cancer (Gleason 8–10) in the treatment group.[11] Because of this, utilization of 5ARIs for chemoprevention was not endorsed. Criticisms of these trials include poor generalizability due to the high cumulative incidence of prostate cancer associated with mandated end of study biopsy, relatively short duration, and inability to evaluate the effect of 5ARIs on incidence of metastatic or fatal prostate cancer. While overall survival between groups was similar in the Prostate Cancer Prevention Trial (PCPT), implications for the increased incidence of high-grade cancer on cancer-specific survival remain unclear.[12–17]

The Food and Drug Administration (FDA) recently evaluated the potential risks and benefits of 5ARIs in prostate cancer chemoprevention.[11,18] They concluded that finasteride and dutasteride do not have a favorable risk-benefit profile for the proposed use of chemoprevention in healthy men and that the incidence of metastatic disease and prostate-cancer-specific morbidity and mortality has not been evaluated.[11]

To investigate the relationship between 5ARI use and high-grade or lethal prostate cancer, we performed a prospective cohort study among 38,000 U.S. men. We hypothesized that 5ARI use may reduce risk of developing low-grade prostate cancer, while increasing the incidence of high-grade and lethal prostate cancer. We demonstrate that while 5ARIs were associated with decreased risk of low and intermediate grade prostate cancer, they were not associated with increasing or decreasing risk of high-grade or lethal prostate cancer.

Methods

Study Population

The Health Professionals Follow-up Study (HPFS) is a prospective cohort of 51,529 United States male health professionals who were 40–75 years old at baseline in 1986. The men responded to a mailed baseline questionnaire in 1986, which collected information on age, height and weight, ancestry, medications, disease history, physical activity, lifestyle factors, and diet. Follow-up questionnaires were sent biennially from 1988–2010; information on prostate specific antigen (PSA) testing was collected beginning in 1994. From 2000, all men with prostate cancer received yearly prostate cancer-specific questionnaires to ascertain disease progression and metastases. This cohort has been used to answer questions related to epidemiology and outcomes of prostate cancer.[19–23] The HPFS is approved by the Human Subjects Committee at the Harvard School of Public Health.

We restricted the study population to men in HPFS who completed the study questionnaire in 1996 when questions on 5ARI use were first included. Men who were diagnosed with cancer (except non-melanoma skin cancer) prior to 1996 or did not complete the medication section were excluded. The remaining 38,058 men were followed prospectively for 5ARI use, cancer incidence, metastases and mortality until 2010.

Assessment of Exposure to 5α-reductase Inhibitors

The primary exposure variable was 5ARI use during the study period. The question regarding use of Proscar (finasteride) was added to the questionnaire in 1996 and repeated biennially since then. In 2004 the question was modified to include “Proscar, Propecia, and Avodart”. Finasteride is available in 5mg (Proscar) and 1mg (Propecia for male-pattern baldness) formulations and dutasteride (Avodart) is available in a 0.5mg formulation. Information on specific type or dose was not provided, but finasteride(5 mg) use likely comprised most of the exposure in this cohort due to earlier FDA approval (Proscar 1992, Propecia 1997, Avodart 2002) and Propecia typically targeting a younger population.[24] Duration of exposure was calculated by summing use across the 2-year periods encompassed by the biennial questionnaires.

Assessment of Prostate Cancer Outcomes

Development of high-grade or lethal prostate cancer during the study period were the primary outcomes. Total prostate cancer incidence was studied as a secondary outcome. Information on pathology, treatment, PSA at diagnosis, and metastases were abstracted from medical records and pathology reports. Prostate cancer was categorized as low-grade (Gleason 2–6), intermediate grade (Gleason 7) or high-grade (Gleason 8–10) based on radical prostatectomy (RP) or biopsy pathology reports. Of 3294 (89%) cases with available Gleason grade information, 58% were from biopsy and 42% from RP specimens. Among men with both biopsy and RP Gleason (n=1345), 27% (n=360) were upgraded, 4% (n=49) were downgraded, and 70% (n=936) were unchanged on final pathology. Advanced cancers were those that had spread beyond the prostate, including to the seminal vesicles, lymph nodes or bone (TNM stage T3b, T4, N1, M1), either at diagnosis or during follow-up and those that resulted in prostate cancer death. Lethal cancers were a subset of advanced cancers and included only those that caused death or metastases. Non-advanced cancers were stage T1 or T2 and N0, M0 at diagnosis and did not progress to nodal or distant metastases during follow-up. Cases with missing stage or grade information were included in the analysis for total prostate cancer but excluded from analyses for stage or grade. Deaths were obtained from next-of-kin, the postal system, and the National Death Index, with a previously reported sensitivity of greater than 98%[25], and cause of death was assigned by an Endpoints Committee of four physicians by reviewing medical history, medical records, registry information, and death certificates.

Statistical Analysis

Each subject contributed person-time from questionnaire return in 1996 until prostate cancer diagnosis, death or study conclusion in January 2010. Incidence rates and incidence rate ratios for prostate cancer were calculated for 5ARI ever users versus 5ARI never users. In all analyses, 5ARI use was treated as a time-dependent covariate and was updated in each questionnaire cycle.

Cox proportional hazards models using age as the time scale were used to estimate the hazard ratio of prostate cancer for 5ARI users compared to never users. All models were stratified by age and time period to control as finely as possible for confounding by age, calendar time and any possible two-way interactions between these two time scales. To adjust for potential confounding, multivariable models also included smoking history (never, former quit >10 years ago, former quit <10 years ago, current), race (White, African-American, Asian-American, other), family history of prostate cancer in brother or father (yes/no), vigorous physical activity (quintiles), body mass index (six categories), height (quartiles), diabetes mellitus (yes/no), PSA testing (yes/no in prior questionnaire cycle), intensity of PSA testing (variable indicating men who had testing in >50% of time periods), physical examinations (yes/no in prior two years), prostate biopsy or rectal ultrasound (yes/no in prior two years), vasectomy, and use of other medications (statins, digoxin, alpha-blockers, saw palmetto, aspirin, NSAIDs, multivitamins; all yes/no). All covariates except race and height were updated in each questionnaire cycle. We used missing indicator variables for missing covariate information. As 5ARI use may influence carcinogenesis over

time, we analyzed use of 5ARIs as ever vs. never as well as by duration of use, < 4 years and > 4 years. Duration of use was also analyzed as a continuous variable.

To investigate possible diagnostic bias associated with PSA testing, we repeated the primary analysis restricted to those men who reported PSA testing between 1994–1996. To account for the effect of lower urinary tract symptoms from benign prostatic hyperplasia leading to medical attention, PSA testing, digital rectal examinations and prostate biopsy, we repeated the analysis using alpha-blockers, an alternate medication for treatment of BPH, as the exposure variable.

95% confidence intervals were calculated and *P*-values were two-sided with statistical significance set at $p<0.05$.

We tested the proportional hazards assumption by comparing models with and without interaction terms between 5ARI use and age using log-likelihood tests. The assumption was met for all outcomes ($p>0.05$). Analyses were performed using SAS version 9.2 (SAS Institute, Inc.; Cary, NC).

Results

During fourteen years (448,803 person-years) of follow-up, 3,681 men in the cohort were diagnosed with prostate cancer. Of these, 289 were lethal (metastatic or fatal), 456 were high-grade (Gleason 8–10), 1238 were Gleason grade 7, and 1600 were low-grade (Gleason 2–6). Stage was missing in 8% of ever and never users. Grade was missing in 12% and 11% of ever and never users, respectively. Ever use of 5ARIs was reported by 2878 men (7.6%) between 1996 and 2010. 5ARI users were more likely to be older, have had a PSA test, digital rectal exam (DRE), and prostate biopsy/rectal ultrasound. Men who had ever used 5ARIs were also more likely to be on an alpha-blocker, statin, or take multivitamins than those who never used 5ARIs (Table 1). The overall mortality per 100,000 person-years was 1746 among 5ARI never users and 1567 among ever users.

High-grade and Lethal Prostate Cancer

We found no significant association between 5ARI use and high-grade (HR 0.97; 95% CI, 0.64–1.46) or lethal (HR 0.99; 95% CI, 0.58–1.69) disease after multivariate adjustment, including physical exam, PSA testing, and prostate biopsy/rectal ultrasound (Table 2). When the definition of high-grade was expanded to included Gleason 4+3=7 prostate cancer, there was no associated increased risk with 5ARI use (HR=1.07; 95% CI, 0.79–1.45). Including locally-advanced disease (TNM stage T3b, T4), commonly a precursor of lethal disease, again revealed no associated increased risk (HR=0.80; 95% CI, 0.51–1.23).

Overall and Low-Grade Prostate Cancer

The age-adjusted hazard ratio of overall prostate cancer for ever-use of 5ARIs compared with never-use was 1.05 (95% CI, 0.89–1.23). After multivariate adjustment, we observed a 23% lower risk of overall prostate cancer for men who had ever used 5ARIs (HR 0.77; 95% CI 0.65–0.91) (Table 2). There was also a significantly decreased risk of intermediate

(Gleason grade 7) (HR 0.67; 95% CI, 0.49–0.91), and low-grade (Gleason 2–6) prostate cancer (HR 0.74; 95% CI, 0.57–0.95).

Duration of 5α-reductase Inhibitor Use

We observed a statistically significant reduction in overall, localized, Gleason grade 7 and Gleason grade 2–6 prostate cancer when comparing 5ARI users of less than four years to those who reported never using 5ARIs. Hazard ratio estimates were similar, but not statistically significant, for users of four or more years compared to never users. The hazard ratio of all types of prostate cancer did not appear to vary by duration of 5ARI use of four or more years; however, the number of long-term users was low (Table 3).

When analyzed as a continuous variable, increased duration of use was associated with significantly lower risk of overall prostate cancer (HR for 1 year of additional use 0.95; 95% CI, 0.92–0.99), localized (HR 0.95; 95% CI, 0.90–1.00), and low-grade disease (HR 0.92; 95% CI, 0.85–0.99). There was no association for lethal, high-grade, or grade 7 disease.

Sensitivity Analyses

To evaluate the impact of PSA screening we also conducted the analysis among only men who underwent PSA testing in 1996. This revealed very similar results to the primary analysis. In this subgroup, we found no association with high-grade or lethal disease; however, use of 5ARIs remained significantly associated with a reduced risk of overall disease, localized, low and intermediate grade disease (Table 4).

To evaluate the possibility that differences in diagnostic intensity (physician visits, PSA testing, prostate biopsy) between 5ARI users and non-users might affect our results (beyond adjusting for these variables), we repeated the analysis using alpha-blocker use as the primary exposure variable, as the patient population and symptomatology were assumed to be similar (Table 5). While 5ARI use was significantly associated with a reduced risk of overall prostate cancer (HR 0.77; 95% CI, 0.65–0.91), alpha-blocker use was not significantly associated with risk (HR, including 5ARI use, 0.93; 95% CI, 0.83–1.03). High-grade or lethal prostate cancer was not significantly associated with use of either 5ARIs or alpha-blockers.

Discussion

Investigating the role of 5ARIs in the development of lethal prostate cancer is a critical endpoint to understanding the potential harms and implications of 5ARI use. In this prospective cohort study, 5ARI use was not associated with increased or decreased risk of high-grade or lethal prostate cancer. However, the number of patients with high-grade or lethal prostate cancer in our cohort was limited, leading to wide confidence intervals in our analyses. Therefore, we cannot definitively rule out potential risk of harm with 5ARI use. We found that 5ARI use was associated with significantly decreased risk of overall, low-grade, and Gleason 7 prostate cancer. Notably, our results showed a 23% reduction in overall prostate cancer, quite similar to the previously published findings of two randomized trials studying the effect of 5ARIs on prostate cancer incidence.[9,10] The reduced risk of

Gleason 7 disease with 5ARI treatment is a novel finding not observed in these trials and may be due to general upgrading of biopsy pathology over the study period.

It was initially reported in the REDUCE trial that there was no increase in high-grade cancer. However, subsequent pathologic reassessment by the FDA detected an absolute increase of 0.5% in incidence of high-grade (Gleason 8–10) cancer with dutasteride use.[11] Similarly, the FDA review reported an absolute increase of 0.7% in incidence of high-grade (Gleason 8–10) cancer with finasteride use in the PCPT.[10,11] As a result, use of 5ARIs for chemoprevention of prostate cancer has not been widely embraced.

In our study, while we found similar reduction in overall prostate cancer as the PCPT and REDUCE trials, we found no increased risk of high-grade disease. There remained a decreased risk of overall disease and no increased risk of high-grade prostate cancer in a PSA-screened subset. Potential explanations for the discrepant findings could be mandated prostate biopsies increasing the likelihood of cancer detection, or insufficient statistical power or follow-up in our cohort. It is theorized that prostate cancer reduction with 5ARI use is due to detection bias as users typically have lower PSA levels and are therefore, less likely to undergo biopsy. However, 5ARI users in our study were more likely to have had PSA testing (99% vs. 93%) or prostate biopsy (24% vs. 9%) than non-users. Therefore detection bias does not explain the lower risk of localized and low-grade disease observed.

It has been proposed that the increased risk of high-grade disease found in the randomized trials might be due to prostate size reduction leading to better biopsy sampling and higher likelihood of cancer detection (i.e. reducing the volume of benign prostate tissue with 5ARI therapy).[26,27] Others have suggested that sensitivity of PSA as a biomarker is improved with 5ARI therapy, which may have led to higher rates of high-grade prostate cancers in the PCPT and REDUCE trials. [28,29] Among patients in the PCPT who underwent prostatectomy, the finasteride-associated increase in high-grade disease (Gleason ≥7) at biopsy (42.7% finasteride versus 25.4% placebo, P<.001) was diminished at prostatectomy (46.4% finasteride versus 38.6% placebo, P = .10).[27] However, no post-hoc analyses conducted to date have been able to definitively prove that 5ARIs do not increase high-grade cancer.

5ARIs are commonly used to reduce symptoms and consequences of benign prostatic hyperplasia.[8,9] Reassuringly, long-term follow-up from the PCPT found no significant difference in the rates of overall survival between finasteride and placebo; however, prostate cancer-specific survival could not be assessed. It is possible that a difference in cancer-specific survival could exist and be overshadowed by deaths from other causes, given the prolonged natural history of prostate cancer, a finding documented in other trials.[30] Our results support findings from other studies that show 5ARI users do not appear to be at increased risk of high-grade or lethal prostate cancer.[14,16] 5ARIs seem to predominantly protect against Gleason 6 prostate cancer with minimal influence on Gleason 8–10 disease. This may represent inherently different biology between low and high-grade prostate cancer and potentially, a role for 5ARI treatment in active surveillance. [31–33]

Strengths of this study include the prospective nature of the cohort, large sample size, prolonged follow-up, high degree of subject response, PSA data, and detailed long-term prostate cancer-specific outcomes. In particular, the ability to study lethal prostate cancer is a powerful and unique aspect. There are limitations of this observational study. There was limited central pathologic review of Gleason score (11%). This may result in misclassification of cases by grade, particularly Gleason 7. It is unlikely, however, that there would be significant discrepancy in assignment of Gleason 8–10 as pathologic criteria for this diagnosis is subject to less interobserver variation. Medication history was reported biennially, which may introduce random error into calculation of exposure duration. Survey data was self-reported but, due to study subjects being knowledgeable and committed, remains high-quality. The HPFS consists predominantly of white men (91% Caucasian) and thus may limit generalizability of study findings. Finally, our study does not take into account that variable degrees of prostatic 5ARI expression may have an effect on efficacy of 5ARIs.[5]

Conclusions

We found that while 5ARIs were associated with significantly reduced risk of low and intermediate grade prostate cancer, they were not associated with increased or decreased risk of high-grade or lethal prostate cancer. However, the number of patients with high-grade or lethal prostate cancer was limited, leading to wide confidence intervals in our analyses, therefore, we cannot definitively exclude potential risk of harm with 5ARI use.

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Abbreviations

REDUCE	Reduction by Dutasteride of Prostate Cancer Events
PCPT	Prostate Cancer Prevention Trial
HPFS	Health Professionals Follow-up Study

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Table 1

Age-standardized characteristics of study population in 1996 by 5α-reductase inhibitor use throughout study period.

	5α-reductase inhibitor Never Users	5α-reductase inhibitor Ever Users
	(n=35180)	(n=2878)
Age in years*	62.6(9.2)	66.1(8.6)
Body mass index, kg/m2	26.1(3.6)	26.2(3.6)
Race (%)		
Caucasian	91	92
African American	1	1
Asian	2	1
Other race	2	1
Missing	5	4
Smoking Status (%)		
Current	7	4
Never smoker	41	44
Family history of prostate cancer (%)	13	14
PSA test in prior 2 years (1994–1996) (%)	58	76
Ever had a PSA test up to 2008 (%)	93	99
Digital rectal exam in prior 2 years (%)	69	80
Prostate biopsy or ultrasound in prior 2 years (%)	9	24
Vasectomy (%)	26	26
Diabetes (%)	6	6
Current alpha-blocker use (%)	3	10
Current statin use (%)	9	13
Current digoxin use (%)	3	3
Current aspirin use (%)	42	50
Current acetaminophen use (%)	6	7
Other current NSAID use (%)	4	5
Current multivitamin user (%)	38	45
Vigorous activity (% in highest quintile)	17	18
Case characteristics by use at diagnosis	n=3521	n=160
Age at diagnosis*	70.3(7.6)	75.4(6.9)
PSA at diagnosis	15.2(144.2)	9.6(11.3)
Lethal cases (%) **	9	8
Advanced cases (%)**	17	14
Localized cases (%)**	77	78
Gleason grade categories (%):		
Gleason 8–10	14	15
Gleason 7	38	30

	5α-reductase inhibitor Never Users	5α-reductase inhibitor Ever Users
	(n=35180)	(n=2878)
Gleason 2–6	48	55

Values are means (SD) or percentages and are standardized to the age distribution of the study population in 1996. Case characteristics are standardized to the age distribution of the cases.

PSA = prostate specific antigen; NSAID = non-steroidal anti-inflammatory drug.

* Value is not age adjusted.

** Lethal PCa: prostate cancer death or bone metastases. Advanced: Lethal or Stage T3b or T4 or N1 or M1, or spread to lymph nodes or other metastases during follow-up. Localized: T1 or T2 and N0/M0 at diagnosis with no spread to lymph nodes or other metastases or death during follow-up

Table 2

Hazard ratio of prostate cancer by 5α-reductase inhibitor use among 38, 058 male health professionals, 1996–2010.

	Ever (versus never*) Use of 5α-reductase inhibitor			
	N Cases unexposed/exposed	Age-adjusted HR	Fully-adjusted HR§	P-value
Total Prostate Cancer	3521/160	1.05 (0.89–1.23)	0.77 (0.65–0.91)	0.002
Lethal	274/15	1.09 (0.64–1.84)	0.99(0.58–1.69)	0.96
Advanced	551/22	0.99 (0.64–1.52)	0.80 (0.51–1.23)	0.30
Organ-confined	2513/115	1.04 (0.86–1.26)	0.74 (0.61–0.90)	0.002
Gleason Grade 8–10	430/26	1.16 (0.78–1.73)	0.97 (0.64–1.46)	0.88
Gleason Grade ≥ 4+3	749/49	1.32 (0.98–1.76)	1.07 (0.79–1.45)	0.65
Gleason Grade 7	1193/45	0.87 (0.65–1.18)	0.67 (0.49–0.91)	0.01
Gleason Grade 2–6	1534/66	1.10 (0.86–1.41)	0.74 (0.57–0.95)	0.02

Follow-up: 448,803 person-years.

§Hazard ratio (HR) adjusted for: age, time period, smoking history, race, family history of prostate cancer, vigorous physical activity, body mass index, height, diabetes mellitus, history and intensity of prostate specific antigen testing, history of physical examinations, history of prostate biopsy or rectal ultrasound, vasectomy, and medication use (statins, digoxin, alpha-blockers, saw palmetto, aspirin, non-steroidal anti-inflammatory drugs, multivitamins).

*Reference group is men who never used 5α-reductase inhibitors.

Advanced: TNM stage T3b, T4, N1, M1 or fatal.

Lethal: Metastatic or fatal disease.

Table 3

Hazard ratio of prostate cancer by duration of 5α-reductase inhibitor use among 38,058 male health professionals, 1996–2010.

	Never Use*		Ever Use, < 4 years		Ever Use, 4+ years	
	N Cases	HR (reference)	N Cases	Fully-adjusted HR§	N Cases	Fully-adjusted HR§
Total Prostate Cancer	3521	1.00	106	0.75 (0.62–0.92)	54	0.81 (0.61–1.06)
Lethal	273	1.00	11	1.02 (0.55–1.88)	4	0.92 (0.34–2.49)
Advanced	551	1.00	14	0.73 (0.42–1.25)	8	0.95 (0.47–1.93)
Organ-confined	2513	1.00	76	0.73 (0.58–0.92)	39	0.77 (0.56–1.06)
Gleason Grade 8–10	430	1.00	15	0.83 (0.49–1.40)	11	1.26 (0.68–2.32)
Gleason Grade ≥ 4+3	749	1.00	29	0.95 (0.65–1.39)	20	1.33 (0.84–2.09)
Gleason Grade 7	1193	1.00	28	0.62 (0.42–0.91)	17	0.76 (0.47–1.24)
Gleason Grade 2–6	1534	1.00	46	0.75 (0.56–1.01)	20	0.71 (0.45–1.11)

Follow-up: 448,803 person-years.

§Hazard ratio (HR) adjusted for: age, time period, smoking history, race, family history of prostate cancer, vigorous physical activity, body mass index, height, diabetes mellitus, history and intensity of prostate specific antigen testing, history of physical examinations, history of prostate biopsy or rectal ultrasound, vasectomy, and medication use (statins, digoxin, alpha-blockers, saw palmetto, aspirin, non-steroidal anti-inflammatory drugs, NSAIDs, multivitamins).

*Reference group is men who never used 5α-reductase inhibitors.

Advanced disease: TNM stage T3b, T4, N1, M1, or fatal.

Lethal disease: Metastatic or fatal disease.

Table 4

Hazard ratio of prostate cancer in relation to 5α-reductase inhibitor use among male health professionals who underwent PSA screening in 1996.

	Ever (versus never*) Use of 5α-reductase inhibitors			
	N Cases unexposed/exposed	**Age-adjusted HR**	**Fully-adjusted HR§**	**P-value**
Total Prostate Cancer	2381/141	1.01 (0.85–1.20)	0.81 (0.68–0.96)	0.01
Lethal	162/15	1.36 (0.80–2.33)	1.17 (0.67–2.02)	0.58
Advanced	334/22	1.19 (0.77–1.84)	0.99 (0.63–1.54)	0.96
Organ-confined	1755/100	0.96 (0.79–1.18)	0.76 (0.61–0.93)	0.01
Gleason Grade 8–10	262/25	1.38 (0.91–2.09)	1.14 (0.74–1.74)	0.56
Gleason Grade ≥ 4+3	479/44	1.39 (1.01–1.90)	1.17 (0.85–1.62)	0.33
Gleason Grade 7	810/38	0.78 (0.56–1.08)	0.65 (0.47–0.91)	0.01
Gleason Grade 2–6	1087/56	0.98 (0.78–1.28)	0.73 (0.56–0.96)	0.03

Follow-up: 265,424 person-years.

§Hazard ratio (HR) adjusted for: age, time period, smoking history, race, family history of prostate cancer, vigorous physical activity, body mass index, height, diabetes mellitus, history and intensity of prostate specific antigen testing, history of physical examinations, history of prostate biopsy or rectal ultrasound, vasectomy, and medication use (statins, digoxin, alpha-blockers, saw palmetto, aspirin, non-steroidal anti-inflammatory drugs, multivitamins).

*Reference group is men who never used 5α-reductase inhibitors.

Advanced disease: TNM stage T3b, T4, N1, M1, or fatal.

Lethal disease: Metastatic or fatal disease.

Table 5

Hazard ratio of prostate cancer by alpha-blocker use among 38,058 male health professionals, 1996–2010.

	Ever (versus never*) Use of Alpha-blockers			
	N Cases unexposed/exposed	Age-adjusted HR	Fully-adjusted HR§	P-value
Total Prostate Cancer	3247/434	1.12 (1.01–1.23)	0.93 (0.83–1.03)	0.15
Lethal	262/27	0.84 (0.56–1.25)	0.78 (0.52–1.19)	0.25
Advanced	517/56	0.99 (0.74–1.30)	0.88 (0.66–1.17)	0.38
Organ-confined	2306/322	1.14 (1.01–1.29)	0.93 (0.82–1.05)	0.23
Gleason Grade 8–10	401/55	1.00 (0.75–1.33)	0.88 (0.66–1.19)	0.41
Gleason Grade ≥ 4+3	708/90	0.94 (0.75–1.18)	0.79 (0.63–1.00)	0.05
Gleason Grade 7	1111/127	0.95 (0.78–1.14)	0.80 (0.66–0.97)	0.02
Gleason Grade 2–6	1401/199	1.28 (1.10–1.49)	1.01 (0.87–1.18)	0.87

Follow-up: 448,803 person-years.

§Hazard ratio (HR) adjusted for: age, time period, smoking history, race, family history of prostate cancer, vigorous physical activity, body mass index, height, diabetes mellitus, history and intensity of prostate specific antigen testing, history of physical examinations, history of prostate biopsy or rectal ultrasound, vasectomy, and medication use (statins, digoxin, 5α-reductase inhibitors, saw palmetto, aspirin, non-steroidal anti-inflammatory drugs, multivitamins).

*Reference group is men who never used alpha-blockers.

Advanced disease: TNM stage T3b, T4, N1, M1, or fatal.

Lethal disease: Metastatic or fatal disease.