5-Alpha Reductase Inhibitors and Prostate Cancer Mortality among Men with Regular Access to Screening and Health Care

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ABSTRACT

Background: How 5-alpha reductase inhibitor (5-ARI) use influences prostate cancer mortality is unclear. The objective of this study was to determine whether men taking 5-ARIs with regular health care access have increased prostate cancer mortality.

Methods: We undertook two analyses in the Health Professionals Follow-up Study examining 5-ARI use, determined by biennial questionnaires, and prostate cancer. A cohort analysis followed 38,037 cancer-free men for prostate cancer incidence from 1996 through January 2017 and mortality through January 2019. A case-only analysis followed 4,383 men with localized/locally advanced prostate cancer for mortality over a similar period. HRs and 95% confidence intervals (CI) were calculated for prostate cancer incidence and mortality.

Results: Men using 5-ARIs underwent more PSA testing, prostate exams and biopsies. Over 20 years of follow-up, 509 men developed lethal disease (metastases or prostate cancer death). Among men initially free from prostate cancer, 5-ARI use was not associated with developing lethal disease [HR, 1.02; 95% confidence interval (CI), 0.71–1.46], but was associated with reduced rates of overall and localized disease (HR, 0.71; 0.60–0.83). Among men diagnosed with prostate cancer, there was no association between 5-ARI use and cancer-specific (HR, 0.78; 95% CI, 0.48–1.27) or overall survival (HR, 0.88; 95% CI, 0.72–1.07).

Conclusions: Men using 5-ARIs were less likely to be diagnosed with low-risk prostate cancer, without increasing long-term risk of lethal prostate cancer or cancer-specific death after diagnosis.

Impact: Our results provide evidence that 5-ARI use is safe with respect to prostate cancer mortality in the context of regular health care access.

See related commentary by Hamilton, p. 1259

Introduction

Prostate cancer is the leading cause of cancer incidence and second leading cause of cancer mortality in men in the United States, with a lifetime risk of 11.6% for prostate cancer diagnosis and 2.4% for prostate cancer death (1). Chemoprevention has been proposed as a strategy to reduce morbidity and mortality from prostate cancer (2). 5-alpha reductase inhibitors (5-ARI) like finasteride have been suggested as such a chemopreventive agent. A common treatment for benign prostatic hyperplasia (BPH) due to their ability to reduce prostate size, 5-ARIs block the enzymatic conversion of testosterone to its biologically active form, dihydrotestosterone (3–7).

In 2003, the randomized Prostate Cancer Prevention Trial (PCPT) found finasteride reduced the risk of overall prostate cancer by almost 25%. However, the study also found a 27% increased risk of high-grade prostate cancer among men randomized to finasteride, raising concerns that a chemoprevention benefit would be offset by increased mortality (8). As a result, there has been little use of 5-ARIs for cancer prevention due to the FDA's Black Box label recommending against its use at a population level (9).

Subsequent analyses explained these PCPT results could be due to detection bias. Men in the PCPT treated with finasteride had decreased prostate volumes, which improved detection of prostate cancer by increasing the sensitivity of the PSA test and digital rectal exam and the accuracy of tumor grading on prostate biopsy (10, 11). Notably, 5-ARIs reduce serum prostate-specific antigen (PSA) concentrations by about 50% (12), highlighting the importance of regular PSA surveillance. While overall survival was similar between groups in the PCPT, concerns remained about the increased rate of high-grade tumors and the potential for increased prostate cancer mortality (13–15).

Two 2019 publications addressed whether 5-ARIs increased prostate cancer mortality with differing results. An updated PCPT analysis with a median follow-up time of 18.4 years showed no excess risk of prostate cancer mortality with finasteride use (16). In contrast, an observational study of men with prostate cancer treated at Veterans Affairs (VA) hospitals demonstrated that 5-ARI use was associated with later stage at presentation and a 39% higher risk of prostate cancer death (17).

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To address these conflicting results, we performed a prospective cohort study among 38,037 U.S. men with regular access to health care and PSA screening, and a case-only analysis of 4,383 men with prostate cancer.

Materials and Methods

Study population

The study population was nested within the Health Professionals Follow-up Study (HPFS), a prospective cohort of 51,529 U.S. male health professionals who were 40 to 75 years old at baseline in 1986 and completed a mailed baseline questionnaire. Information on age, height and weight, ancestry, medications, disease history, physical activity, lifestyle factors, and diet were gathered, with follow-up questionnaires sent biennially to update information and record health outcomes. Questionnaires began asking about PSA testing in 1994 and 5-ARI use in 1996. Men diagnosed with prostate cancer were sent prostate cancer–specific questionnaires to assess treatments, disease progression, and metastases biennially starting in 2010, and these data have been used to answer questions regarding prostate cancer epidemiology and outcomes (18–22). The research was approved by Institutional Review Boards at the Harvard T.H. Chan School of Public Health, Mass General Brigham and those of participating registries as required.

The study population was restricted to men in HPFS who did not already have a cancer diagnosis (except nonmelanoma skin cancer) and completed a study questionnaire in 1996. Similarly, to the PCPT, we followed these 38,037 men prospectively for cancer incidence. We also undertook a case-only study, like the VA, by following 4,383 men with localized/locally advanced prostate cancer for cancer-specific and overall mortality.

5-ARI exposure

The primary exposure, 5-ARI use during the study period, was determined on biennial questionnaires starting in 1996 with a question about regular use of Proscar (finasteride). From 2000 to 2010, questionnaires additionally asked about Proscar and Propecia (finasteride) use (2000–2004, 2008, 2010), and also about Avodart (dutasteride) use (2012–2016). Because the medications were grouped together in questions regarding use, we could not distinguish between 5-ARI types. However, it is likely that the predominant medication during the study period was Proscar (5 mg) because of its earlier FDA approval (1992) than Propecia (1 mg; approved in 1997) or Avodart (0.5 mg; approved in 2002; ref. 23). Exposure duration was the sum of 2-year periods of use, as indicated by reporting regular use on the biennial questionnaires.

Outcomes

In the cohort analysis, the primary outcome was lethal prostate cancer, defined as development of metastatic disease or prostate cancer death. The secondary outcomes were stage and Gleason score at presentation. In the case-only analysis, the primary endpoints were progression to lethal prostate cancer and total mortality.

Grade was categorized as either Gleason 3+4 and lower, or Gleason 4+3 and higher based on surgical or biopsy reports. Analyses for Gleason score 8–10, score ≤6, score 7 (3+4), and score 7 (4+3) were also performed. Advanced cancers were tumor–node–metastasis (TNM) stage T3b/T4, N1, or M1; non-advanced cancers were TNM stage T1/T2/T3a, and N0/NX, M0/MX at diagnosis. 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 >98% (24). Cause of death was assigned by an Endpoints Committee of physicians by reviewing medical history, medical records, registry information, and death certificates.

Statistical analysis

For cohort analyses, study participants contributed person-time from the return date of the 1996 questionnaire until prostate cancer diagnosis, death, or end of follow-up (January 2017). Use of 5-ARIs (ever/never use) was the time-dependent exposure in all analyses, and was updated with each questionnaire. To avoid immortal time bias, men only contributed exposed person-time after they reported 5-ARI use on a questionnaire. For case-only survival analyses, follow-up started at time of cancer diagnosis and ended at death, development of metastases or end of follow-up (January 2019).

In cohort analyses, Cox proportional hazards models were used to estimate HRs and 95% CIs for development of all incident prostate cancer and lethal, advanced, localized, high-grade, and low-grade disease. Multivariable models included race (white, African American, Asian American, other); family history of prostate cancer in brother or father (yes/no); smoking history (never, former quit >10 years ago, former quit ≤10 years ago, current); body mass index (BMI; four categories); height (continuous); vigorous physical activity (quintiles); diabetes mellitus (yes/no); use of multivitamins, statins, alpha-blockers, digoxin (all yes/no); PSA screening (lagged by one period, yes/no); PSA screening intensity (indicator for having PSA test in 50% or more questionnaire cycles); physical exam, prostate biopsy or rectal ultrasound (all in prior 2 years, yes/no); and vasectomy (yes/no).

In case-only analyses, Cox proportional hazards models were used to estimate HRs and 95% CIs for lethal prostate cancer and all-cause mortality. Multivariable models adjusted for stage, Gleason grade, current smoking status, race, family history of prostate cancer, physical activity quintiles, BMI, and PSA at diagnosis.

All models used the questionnaire period as the timescale, were age-adjusted, and all covariates except race and height were updated with each questionnaire. Missing indicator variables were used for missing covariate information. Outcome comparisons were made between the exposure groups defined by use of 5-ARIs, ever versus never, and by cumulative duration of use, <4 years and ≥4 years. Four years was used as the cutoff as it represents use of 5-ARIs over two questionnaire periods.

As a sensitivity analysis, a Fine-Gray competing risk model estimated subdistribution HRs for prostate cancer survival. Diagnostic bias associated with PSA testing was examined by restricting the cohort to 22,424 men in who reported PSA testing between 1994 and 1996. Given the increased prostate cancer risk among men with a family history of prostate cancer, we examined the effect of 5-ARI use on prostate cancer diagnoses in this population using real-world data. In addition, the cohort analysis was repeated with alpha-blockers, another treatment for BPH, as the exposure to account for the effect of medical attention for BPH symptoms. Alpha-blocker models were adjusted for 5-ARI use.

The proportional hazards assumption was tested by comparing models with and without interaction terms between 5-ARI use and calendar time using log-likelihood tests; nonproportional hazards were not detected ($P > 0.05$). Analyses were performed using SAS version 9.4 (SAS Institute, Inc.; Cary, North Carolina).

Data availability statement

The data generated in this study are available upon request from the corresponding author.

Results

Full cohort study

Of 38,037 men, 5,099 (13.4%) men reported ever use of 5-ARIs between 1996 and 2016 (**Table 1**), with a median duration of use of 4 years. Ever users were older on average than never users (63.4 vs. 62.8 years). In addition, men who had ever used 5-ARIs were more likely to have had recent PSA screening (prevalence difference, 16%; 95% CI, 15%–18%) and were more likely to have had a prostate biopsy or rectal ultrasound prior to 1996 (prevalence difference, 11%; 95% CI, 10%–13%).

Participants contributed 628,257 person-years over the study period, during which 4,575 men developed prostate cancer and 509 developed lethal disease (**Table 2**). Among men diagnosed with prostate cancer, 83.7% presented with localized disease, and 71.8% presented with a Gleason score of 3+4 or lower. In both age-adjusted and fully adjusted models, we found no association between ever use of 5-ARIs and lethal (mHR, 1.02; 0.71–1.46), advanced (mHR, 1.02; 0.73–1.41) or high-grade prostate cancer (mHR, 1.06; 0.84–1.33). In fully adjusted models, there was a 21% reduced risk of overall prostate cancer (95% CI, 0.70–0.90), a 29% lower risk of localized disease (95% CI, 0.60–0.83), and a 38% reduced risk of low-grade disease (95% CI, 0.51–0.74). We found similar results examining duration of use (<4 and ≥4 years).

Table 1. Age-standardized characteristics of the HPFS population in 1996 by end-of-study 5-ARI status (n = 38,037).[a]

	Never use (n = 32,938)	Ever use (n = 5,099)
Age in years[b]	62.8 (9.3)	63.4 (8.6)
BMI kg/m^2	26.1 (3.6)	26.2 (3.6)
Height in centimeters	178.3 (7.0)	178.2 (6.6)
Race		
White	91%	92%
African American	1%	1%
Asian American	2%	1%
Other race	2%	2%
Unknown	5%	5%
Smoking status		
Never smoker	49%	52%
Past smoker (quit >10 years ago)	32%	34%
Past smoker (quit ≤10 years ago)	12%	10%
Current smoker	7%	4%
Family history of prostate cancer	12%	14%
Had a PSA test in the last 2 years	57%	72%
History of prostate exam	69%	78%
History of prostate biopsy	9%	19%
Vasectomy	26%	27%
Diabetes mellitus type 2	6%	5%
Medications		
Ever used alpha-blockers	3%	8%
Current statin use	8%	12%
Current digoxin use	3%	3%
Current aspirin use	42%	48%
Current acetaminophen use	6%	6%
NSAID use	4%	5%
Current multivitamin user	38%	43%
Physical activity in MET-hours/week	32.1 (31.9)	32.9 (31.6)

[a]Values are means (SD) for continuous variables; percentages for categorical variables and are standardized to the age distribution of the study population.
[b]Age value is not age-adjusted.

Case-only study

In the case-only group of 4,383 men with localized/locally-advanced prostate cancer, 235 (5.4%) men ever used 5-ARIs (Supplementary Table S1). Ever users were on average older than never users (75.1 vs. 70.3 years) and had shorter follow-up (10.4 vs. 11.8 years). Diagnostic PSA levels were approximately equal between ever and never users of 5-ARIs (8.9 vs. 8.8 ng/mL never users). Ever users also had a slightly higher percent of stage T1 cancer (77% vs. 69% never users) and a slightly higher percent of Gleason ≤6 cancer (53% vs. 47% never users).

At the end of follow-up, 320 men in the case-only cohort developed lethal prostate cancer (**Table 3**). In the fully adjusted multivariable model, there was no association between ever using 5-ARIs and total mortality (mHR, 0.88; 0.72–1.07) or lethal prostate cancer (mHR, 0.78; 0.48–1.27). Findings were similar stratifying by duration of use.

Sensitivity analyses

In the 22,424 men with PSA screening in 1996, we found that results were similar to the primary analyses (**Fig. 1A**; Supplementary Table S2). There was a reduced risk of overall, localized and low-grade prostate cancer among ever users of 5-ARI in multivariable models, and no significant association between 5-ARI use and lethal, advanced, or high-grade disease.

In 4,824 men with a family history of prostate cancer, we found 5-ARI use reduced risk of all prostate cancer by 27%, localized disease by 33%, and low-grade disease by 42% without increasing risk of lethal disease (**Fig. 1B**; Supplementary Table S2).

The alpha-blocker cohort analysis showed that the 5-ARI results were likely not influenced by diagnostic intensity, as alpha-blocker use was not appreciably associated with a decreased risk of overall, localized, or low-grade prostate cancer (Supplementary Table S3). Furthermore, there was an inverse association between alpha-blocker use and developing high-grade prostate cancer.

In the case-only cohort, a Fine-Gray competing risk model, which models a world free from death from other causes (Supplementary Table S4), showed no association between ever using 5-ARIs and developing lethal prostate cancer (sHR, 0.81; 0.49–1.33).

Discussion

We found no increased risk of lethal prostate cancer among cancer-free men using 5-ARIs nor an increased risk of death or progression to lethal disease in 5-ARI users with localized/locally advanced cancer at diagnosis. Our findings align with the PCPT cohort analysis, which found no excess risk of prostate cancer death. In addition, we found 5-ARI users had a lower risk of low-grade and localized prostate cancer. We found no significant association between use of 5-ARIs and risk of high-grade or advanced disease. Men on 5-ARIs had greater screening and interactions with the health care system, as evidenced by higher prevalence of PSA screening (prevalence difference, 16%; 95% CI, 15%–18%), prostate exams (10%, 8–11), and prostate biopsies (11%, 10–13), which could have influenced our results.

To understand the relationship between 5-ARIs and prostate cancer mortality, findings from the PCPT and VA studies must be considered in the context of their strengths and limitations. The PCPT was a randomized study design, which reduces bias due to confounding; however, all PCPT participants received a planned prostate biopsy by the end of follow-up. This is a major difference from observational data and it could lead to earlier detection regardless of 5-ARI use. The VA study found men on 5-ARIs had delayed diagnostic biopsy, were more likely to present with high-grade disease, had higher PSA values, and

Table 2. Association between 5-ARI use (ever use and duration of use) and prostate cancer outcomes in 38,037 men who were initially cancer-free in HPFS (628,257 person-years), 1996–2017.

		Ever use of 5-ARIs			< 4 Years of 5-ARI use		≥ 4 Years of 5-ARI use	
	Total events	Number of events	Age-adjusted HR (95% CI)	Adjusted HR[a] (95% CI)	Number of Events	Adjusted HR[a] (95% CI)	Number of events	Adjusted HR[a] (95% CI)
All Incident prostate cancer	4,575	253	1.03 (0.90–1.17)	0.79 (0.70–0.90)	154	0.76 (0.65–0.90)	99	0.85 (0.69–1.04)
Lethal prostate cancer[b]	509	34	1.08 (0.76–1.54)	1.02 (0.71–1.46)	22	1.03 (0.66–1.59)	12	1.01 (0.56–1.81)
Stage at diagnosis								
Advanced[c]	648	42	1.12 (0.81–1.53)	1.02 (0.73–1.41)	25	0.94 (0.62–1.42)	17	1.17 (0.71–1.91)
Localized[d]	3,324	170	0.96 (0.82–1.13)	0.71 (0.60–0.83)	104	0.69 (0.56–0.84)	66	0.74 (0.58–0.95)
Gleason score								
High-grade (4+3 and above)	1,126	84	1.24 (0.99–1.56)	1.06 (0.84–1.33)	45	0.92 (0.67–1.24)	39	1.30 (0.93–1.80)
Score 8–10	657	53	1.27 (0.95–1.69)	1.11 (0.82–1.49)	29	0.98 (0.67–1.43)	24	1.32 (0.86–2.01)
Score 7 (4+3)	469	31	1.20 (0.82–1.73)	0.99 (0.68–1.45)	16	0.83 (0.50–1.37)	15	1.27 (0.75–2.16)
Low-grade (3+4 and below)	2,865	122	0.86 (0.72–1.03)	0.62 (0.51–0.74)	80	0.63 (0.51–0.79)	42	0.59 (0.43–0.80)
Score 7 (3+4)	1,057	33	0.57 (0.40–0.81)	0.45 (0.31–0.63)	20	0.43 (0.28–0.68)	13	0.47 (0.27–0.81)
Score ≤6	1,808	89	1.06 (0.85–1.31)	0.73 (0.58–0.90)	60	0.75 (0.58–0.98)	29	0.68 (0.46–0.98)

[a]Adjusted for age, smoking status, race, family history of prostate cancer, vigorous activity levels, BMI, height, diabetes, PSA testing intensity, multivitamin use, statin use, current alpha-blocker use, digoxin use, vasectomy, prostate exam and biopsy, aspirin and NSAID use.
[b]Defined as death from prostate cancer or metastases over follow-up.
[c]Defined as T3b or T4, N1, or M1.
[d]Defined as T1, T2 or T3a, N0/NX and M0/MX.

had higher prostate cancer mortality. It is possible that, in the observational VA study, 5-ARI-related PSA suppression was not properly accounted for in screening, and so men presented with higher risk disease. In HPFS, 5-ARI users had similar unadjusted PSA levels at diagnosis to 5-ARI never users (8.9 vs. 8.8 ng/mL) and also had more interactions with health care providers including screening and biopsy. Therefore, it is possible their diagnoses were not delayed, leading to no difference in stage or grade at presentation, and ultimately no difference in mortality.

Our findings for a reduction of overall and low grade cancers are like those from both PCPT and REDUCE (25), a randomized, double-blind trial comparing dutasteride with placebo in prostate cancer incidence. The reduction in less aggressive tumors without an increase in high-grade cancers has several implications. Early diagnosis due to PSA screening has led to over-detection of cancers, particularly low-grade disease. Patients with cancer that is not clinically significant could have an improved quality of life by saving money on health care costs and avoiding side effects that accompany unnecessary treatment and testing.

An observational study in Sweden examined 5-ARIs and prostate cancer among 89,000 participants, specifically examining prostate cancer mortality differences between users and nonusers in the same Gleason Grade Groups (26). Similar to our findings, there was no evidence of increased mortality associated with 5-ARIs in men with high or low Gleason scores. In contrast to our study, the Swedish study found a higher proportion of high-grade cases among 5-ARI users compared with nonusers, but this could be due to differences in clinical presentation and follow-up of our study populations, or the length of follow-up.

Despite evidence in favor of 5-ARIs for chemoprevention, it is important to consider potential side effects of 5-ARIs. Some prior studies have shown increased risks of depression (27, 28); however, a study on psychologic adverse events in patients treated with finasteride suggested the association between depression and suicidality and

Table 3. Association between 5-ARI use and lethal prostate cancer and total mortality in men with localized or locally advanced prostate cancer at diagnosis (n = 4,383), 1996–2019.

	Number of events	Age-adjusted HR (95% CI)	Model 1 adjusted HR (95% CI)[a]	Model 2 adjusted HR (95% CI)[b]
Lethal prostate cancer[c]	320			
Ever use of 5-ARIs	19	1.03 (0.65–1.65)	0.73 (0.45–1.18)	0.78 (0.48–1.27)
<4 years of use	13	1.30 (0.74–2.26)	1.05 (0.60–1.85)	1.11 (0.63–1.96)
≥4 years of use	6	0.71 (0.32–1.61)	0.44 (0.19–0.99)	0.46 (0.20–1.06)
Total mortality (including lethal prostate cancer)[d]	1,899			
Ever use of 5-ARIs	107	0.96 (0.79–1.17)	0.87 (0.71–1.06)	0.88 (0.72–1.07)
<4 years of use	57	0.91 (0.70–1.18)	0.85 (0.65–1.11)	0.85 (0.65–1.11)
≥4 years of use	50	1.03 (0.78–1.37)	0.89 (0.67–1.19)	0.91 (0.69–1.22)

[a]Adjusted for stage at diagnosis, Gleason grade, and age at diagnosis.
[b]Adjusted for everything in model 1 and BMI, family history of prostate cancer, PSA at diagnosis, activity level, smoking status at diagnosis, and race.
[C]Defined as prostate cancer death or distant metastases over follow-up.
[d]Defined as death from any cause or distant prostate cancer metastases.

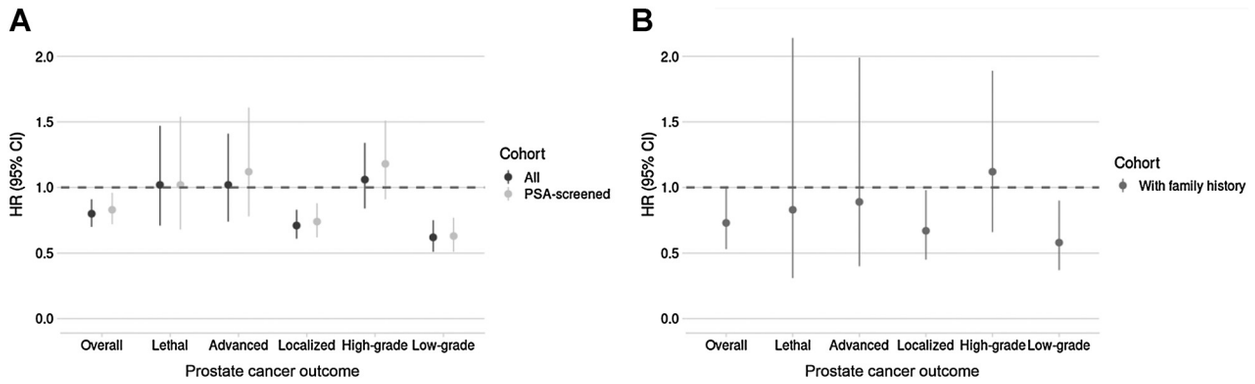

Figure 1.
HRs and 95% CIs for the association between ever use of 5-ARIs and prostate cancer outcomes. **A,** HRs and 95% CIs for all 38,037 men in the study population and the subset of 22,424 men who had PSA screening at baseline. **B,** HRs and 95% CIs for 4,824 men who have a family history of prostate cancer in their father or brother. (Note: High-grade is Gleason score 4+3 and higher; low-grade is Gleason score 3+4 and lower.)

finasteride was likely due to reporting bias (29). Sexual dysfunction and other symptoms have been noted with mixed evidence (30, 31). Still, the reduction in overall and low-risk prostate cancer may be useful in select populations (32–35).

Strengths of this study include its prospective nature, large sample size and number of events, and long-term and complete follow-up for two decades. Biennial questionnaires captured time-varying exposure and covariate data and had >90% participant response. Information on PSA screening and health care interactions allowed us to assess the potential for diagnostic bias and to interpret findings in the context of regular access to health care. Furthermore, this study avoids the issue of prevalent use because FDA approval for Proscar occurred shortly before the start of the study. The results of this study should be interpreted in the context of its limitations. Although survey findings were self-reported, they remain high quality due to the study participants being health professionals and high participation rates across the study. The generalizability may be limited by the fact that the cohort consists predominantly of non-Hispanic white men, and it would be important to address this hypothesis in a multiracial/ethnic setting.

Taken together, our results and the 2019 PCPT and VA studies emphasize the importance of real-world data in framing the benefits and risks associated with 5-ARIs. Our results contribute evidence that 5-ARI use is safe with respect to prostate cancer mortality, in concert with proper health care follow-up. Physicians must be aware that adjustment of PSA level is required for patients on 5-ARIs and that persistent increase in PSA levels of these patients should prompt close follow-up (9). This should alleviate concerns in settings of 5-ARI use for BPH and alopecia and encourage further discussion on 5-ARIs for chemoprevention. The benefit of 5-ARIs reducing the risk of low-risk cancers, particularly among populations at high-risk for prostate cancer, should be weighed against its potential side effects.

Authors' Disclosures

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Disclaimer

The authors assume full responsibility for analyses and interpretation of these data.

Authors' Contributions

J.B. Vaselkiv: Formal analysis, writing–original draft, writing–review and editing. **C. Ceraolo:** Conceptualization, writing–original draft. **K.M. Wilson:** Conceptualization, formal analysis, writing–review and editing. **C.H. Pernar:** Writing–review and editing. **E.M. Rencsok:** Writing–review and editing. **K.H. Stopsack:** Writing–review and editing. **S.T. Grob:** Project administration, writing–review and editing. **A. Plym:** Writing–review and editing. **E.L. Giovannucci:** Writing–review and editing. **A.F. Olumi:** Writing–review and editing. **A.S. Kibel:** Writing–review and editing. **M.A. Preston:** Conceptualization, writing–review and editing. **L.A. Mucci:** Conceptualization, supervision, funding acquisition, writing–review and editing.

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