# 5-alpha reductase inhibitors and prostate cancer mortality among men with regular access to screening and health care

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## BACKGROUND AND OBJECTIVE

- 5-alpha reductase inhibitors (5-ARIs) have been suggested as chemopreventive agents for prostate cancer
- Two 2019 publications addressed whether 5-ARIs increased prostate cancer mortality with contrasting results:
  1. A PCPT letter to the editor demonstrated no excess prostate cancer mortality with finasteride use.
  2. A study of Veterans Affairs patients with prostate cancer showed 5-ARI use was associated with later stage at diagnosis and a 39% higher risk of prostate cancer death.

**OBJECTIVE:** To address conflicting evidence, we conducted a prospective cohort study of American men with regular access to health care and screening and also studied a case-only subgroup of men with prostate cancer.

**HYPOTHESIS:** We hypothesized that 5-ARI use would not be associated with either increased risk of high-grade disease or mortality from prostate cancer.

## METHODS

**STUDY POPULATION:**

- **Full Cohort:** 38,046 men without cancer at baseline were prospectively followed in the Health Professionals Follow-up Study between 1996-2017
- **Case-Only:** 4,232 men with localized or locally advanced prostate cancer were followed over a similar period

**EXPOSURE:**

- 5-ARI use during the study period (Proscar, Propecia, Avodart)
- Exposure groups defined by use of 5-ARIs, ever versus never, as well as by duration of use (< 4 years or ≥ 4 years)

**OUTCOMES:**

- Primary outcome: development of lethal prostate cancer
- Secondary outcome: stage and grade of presentation

**STATISTICAL ANALYSIS:**

- Cox proportional hazards models were used to calculate hazard ratio (HR) and 95% confidence intervals (CI) for development of incident and lethal prostate cancer and both all-cause and cancer-specific mortality
- We adjusted for screening patterns, lifestyle factors, and concomitant medications
- Fine-Gray competing risk model used to estimate hazard ratios for prostate cancer survival.
- 5-ARI use treated as time-dependent covariate in all analyses

## RESULTS

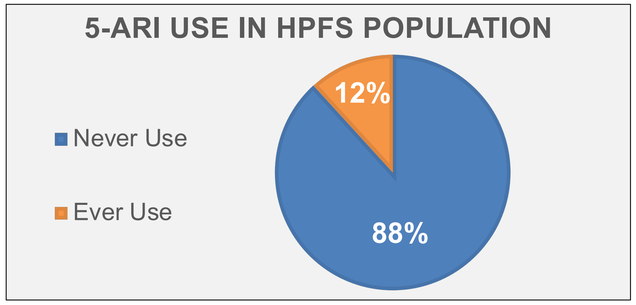


**Table 1. Age-standardized 1996 characteristics of study population by end-of-study finasteride status (n=38,046)[1]**

| | Never Use (n=33,566) | Ever Use (n=4,480) |
|---|---|---|
| **Age (years)[2]** | 62.75 (9.30) | 64.01 (8.68) |
| **Family history of prostate cancer** | 12% | 14% |
| **Had a recent PSA test** | 57% | 73% |
| **Ever had a PSA test[3]** | 94% | 100% |
| **History of prostate exam** | 69% | 78% |
| **History of prostate biopsy** | 9% | 20% |
| **Ever used alpha blockers** | 3% | 8% |
| **Current use of alpha blockers** | 3% | 8% |

[1] Values are means (SD) for continuous variables; percentages for categorical variables and are standardized to the age distribution of the study population
[2] Age value is not age-adjusted
[3] Ever had a PSA test through 2014
[4] Best guess at height from 1986, 1987, and 1988 questionnaires

**Table 2. Age-standardized characteristics of survival cohort at time of diagnosis (n=4,232)[1]**

| | Never Use (n=4,024) | Ever Use (n=208) |
|---|---|---|
| **Age at diagnosis (years)[2]** | 70.20 (7.15) | 75.08 (7.32) |
| **Follow-up time (years)** | 12.66 (5.38) | 11.92 (4.83) |
| **Ever use of alpha blockers** | 11% | 41% |
| **Family history of prostate cancer** | 18% | 17% |
| **PSA at diagnosis (ng/mL)** | 8.73 (11.90) | 9.07 (11.94) |
| **Stage at diagnosis** | | |
| **T1** | 69% | 78% |
| **T2** | 29% | 18% |
| **T3a** | 1% | 2% |
| **T3b** | 0% | 1% |
| **T4/N1** | 1% | 1% |
| **Gleason grade** | | |
| **Score ≤6** | 47% | 56% |
| **Score 7 (3+4)** | 26% | 15% |
| **Score 7 (4+3)** | 11% | 12% |
| **Score 7 (NOS)** | 2% | 1% |
| **Score 8-10** | 14% | 17% |

[1] Values are means (SD) for continuous variables; percentages for categorical variables and are standardized to the age distribution of the study population
[2] Value is not age-adjusted

**Table 3. Association between ever use of finasteride and various prostate cancer outcomes in 38,046 men who were initially cancer-free in HPFS (588,579 person-years)**

| | Number of Events | Adjusted Hazard Ratio[1] | 95% CI |
|---|---|---|---|
| **All Incident Prostate Cancer** | 4403 | 0.76 | 0.66, 0.88 |
| **Lethal[2]** | 482 | 1.04 | 0.71, 1.50 |
| **Stage at diagnosis** | | | |
| **Advanced[3]** | 600 | 1.03 | 0.73, 1.45 |
| **Localized[4]** | 3220 | 0.69 | 0.58, 0.81 |
| **Gleason grade** | | | |
| **High-grade (4+3 and above)** | 1068 | 1.02 | 0.79, 1.31 |
| **Score 8-10** | 617 | 1.05 | 0.76, 1.45 |
| **Score 7 (4+3)** | 451 | 0.98 | 0.66, 1.47 |
| **Low-grade (3+4 and below)** | 2776 | 0.60 | 0.49, 0.72 |
| **Score 7 (3+4)** | 1014 | 0.39 | 0.26, 0.58 |
| **Score ≤6** | 1762 | 0.72 | 0.57, 0.90 |

[1] adjusted for smoking status; race; family history of prostate cancer; vigorous activity levels; BMI; height; diabetes; PSA testing intensity; multivitamin, statin, current alpha blocker, digoxin, aspirin and NSAID use; vasectomy, prostate exam and biopsy.
[2] defined as death from prostate cancer or metastases over follow-up
[3] defined as T3b or T4, N1, or M1
[4] defined as T1, T2 or T3a, N0 and M0

**Table 4. Association of finasteride use and lethal prostate cancer and total mortality in men with localized prostate cancer at diagnosis (n=4,232)**

| | Age-adjusted HR (95% CI) | Model 1 adjusted HR (95% CI)[1] | Model 2 adjusted HR (95% CI)[2] |
|---|---|---|---|
| **Lethal prostate cancer[3] (n=302)** | | | |
| **Ever use of finasteride** | 1.03 (0.64, 1.67) | 0.72 (0.44, 1.17) | 0.76 (0.46, 1.26) |
| **≥ 4 years of use** | 0.63 (0.26, 1.53) | 0.46 (0.19, 1.11) | 0.47 (0.19, 1.16) |
| **< 4 years of use** | 1.36 (0.78, 2.37) | 1.08 (0.61, 1.90) | 1.11 (0.63, 1.98) |
| **Total mortality[4] (n=1726)** | | | |
| **Ever use of finasteride** | 0.92 (0.75, 1.13) | 0.83 (0.67, 1.02) | 0.84 (0.68, 1.04) |
| **≥ 4 years of use** | 0.91 (0.67, 1.24) | 0.78 (0.57, 1.07) | 0.79 (0.58, 1.08) |
| **< 4 years of use** | 0.93 (0.71, 1.22) | 0.87 (0.66, 1.15) | 0.90 (0.68, 1.18) |

1 adjusted for stage at diagnosis, Gleason grade, and age at diagnosis
2 adjusted for everything in model 1 and BMI, family history of prostate cancer, PSA at diagnosis, activity level, and race
3 defined as prostate cancer death or distant metastases over follow-up
4 defined as death from any cause or distant prostate cancer metastases

## SUMMARY & FUTURE GOALS

- Our results align with those of the PCPT, showing that 5-ARI use is not associated with increased risk of high-grade or lethal prostate cancer
- The Fine-Gray competing risk model and a sensitivity analysis limiting the study population to men with PSA screening in the 1996 questionnaire cycle yielded similar results
- 5-ARI users demonstrated a reduction in development of low-grade and localized disease, and no significant change in developing high-grade or advanced disease
- 5-ARI use is safe with respect to prostate cancer mortality, which alleviates concerns in settings of 5-ARI use for BPH and alopecia
- The benefit of 5-ARIs reducing the risk of only localized or low-grade cancer should be weighed against the quality of life issues associated with 5-ARI use