



# The continuing debate of 5-alpha reductase inhibitors and prostate cancer risk

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Finasteride and dutasteride are 5-alpha reductase inhibitors (5-ARIs) which have been shown to improve symptoms of benign prostatic hyperplasia (BPH) and reduce the risk of urinary retention and BPH-related surgeries (1,2). These medications inhibit the conversion of testosterone to the more potent androgen dihydrotestosterone. Given that androgens are known to influence the development of prostate cancer (PCa), it was proposed that 5-ARIs could additionally serve as chemoprotective agents and reduce the prevalence of PCa in the general population (3).

This hypothesis was subsequently tested in two randomized controlled trials (RCTs) in the early 2000s. Indeed, the Prostate Cancer Prevention Trial (PCPT) and Reduction by Dutasteride of Prostate Cancer Events (REDUCE) demonstrated that the use of 5-ARIs were associated with decreased incidence of overall PCa by approximately 25% (4,5). Notably, however, this risk reduction was confined to low grade cancers, while the incidence of high-grade PCa (Gleason score 8–10) was slightly but significantly increased in patients treated with 5-ARIs.

These observations led to additional scrutiny of both 5-ARI medications and the trials that aimed to explore them, and the safety of 5-ARIs remains a topic of widespread debate. Several groups have proposed various mechanisms to explain the findings of the PCPT and REDUCE trials. Some authors have postulated that 5-ARIs, rather than biologically inducing high-grade tumors, actually increase the detection of high-grade cancers by shrinking the prostate, improving whole gland sampling, and selectively inhibiting low-grade tumors, all of which introduce detection biases (6–8). Furthermore, large observational studies have shown findings

contradictory to the PCPT and REDUCE trials—that exposure to 5-ARI does not significantly change the risk of high-grade PCa incidence (9,10). In 2011, after considering the relevant data, the US Food and Drug Administration (FDA) ultimately modified the labels of 5-ARIs to include the observation of increased high-grade prostate cancers in relevant clinical trials (11,12). Repeat analysis by the FDA also revealed a less substantial reduction in the relative risk of PCa (14%; 95% CI, 4–23%) than the 25% reported when considering only for-cause biopsies—those that would be performed in standard clinical practice.

Acknowledging the widespread prevalence of BPH and PCa, the clinical effectiveness of 5-ARIs in treating BPH, and the concerning nature of these data, the safety of these medications remains an area of active study. In the current article, Wallerstedt *et al.* (13) aimed to further explore PCa risk in men treated with 5-ARIs. Using several national Swedish and Stockholm registries (with available prostate-specific antigen (PSA) testing, biopsy results, clinical and oncologic data, and drug use information), the authors performed a large, population-based prospective analysis (N=333,820 in total cohort; N=23,442 with some 5-ARI exposure) investigating 5-ARI use and Gleason score-specific PCa incidence in men  $\geq$ 40 years old during an 8-year study period. Inclusion was limited to men with no prior 5-ARI exposure nor previous PCa diagnosis. Importantly, PSA before 5-ARI treatment was available for all patients and was included in a separate multi-variate model to account for the effects of 5-ARI use and PCa itself on PSA levels. Cumulative exposure to 5-ARI was categorized into 2-year intervals to

allow for analysis based on exposure level.

In summary, their findings demonstrated a significantly reduced risk of overall PCa with 5-ARI treatment, and this effect became larger with increasing duration of 5-ARI exposure [HR 0.81 at 0.1–2 years (0.71–0.93); HR 0.31 at 6–8 years (0.16–0.60)]. When broken down into Gleason score-specific analyses, the protective effect of 5-ARI exposure remained for Gleason score 6 and 7 prostate tumors. At the same time, the authors observed no significant differences in the incidence of Gleason score 8–10 cancers based on 5-ARI exposure—findings contradictory to the PCPT and REDUCE trials. The authors concluded that 5-ARI use should be supported in clinical practice given its safety with regards to low- and high-grade PCa risk.

Although this is not the first observational study to challenge the findings of the PCPT and REDUCE trials with respect to high-grade PCa risk, the current study does represent the largest cohort to date. Additionally, adjustment for PSA level prior to 5-ARI exposure was a unique addition to their analysis that was lacking in previous observational studies (9,10). While the PCPT only included men with a PSA level less than 3 and AUA symptom score less than 20 and REDUCE trial had a PSA cutoff of 2.5–10 along with a single negative prior prostate biopsy, the current study made no such inclusion limitations for PSA levels or lower urinary tract symptoms. Thus, one could argue that the current study is more broadly generalizable to the larger population of men who are candidates for BPH treatment with 5-ARI.

At the same time, there are limitations of these data, which the authors acknowledge, including the lack of standardized indications for biopsy and the inability to confirm that medications were taken as prescribed. Furthermore, 5-ARI users were older, had higher PSA values, and were more likely to have had a previous negative biopsy than non-users. While the authors attempted to control for relevant factors in various sensitivity analyses, these limitations underscore precisely why observational data represent a lower standard of evidence. For example, the absence of data describing indications for biopsy is particularly problematic. Indeed, the literature describes that corrected PSA values in the 5-ARI population require multiplication by a factor of two or greater (14) and that any increase in PSA during treatment is associated with an approximate 6-fold increase in the risk of high-grade disease (15). In the absence of data describing indications for biopsy, however, it is quite possible that a failure to detect more high-grade disease simply reflects a failure to perform timely and appropriate biopsy during follow-up. In fact, recent data from the region suggest that

abnormal PSA values have not been appropriately explored in many cases (16).

Despite conflicting data regarding the incidence of high-grade PCa, the question remains whether or not these differences translate to impact long-term oncologic and survival outcomes. Longer-term data from the PCPT showed that 15-year overall survival rates were not significantly different between the finasteride group (78.0%) and the placebo group (78.2%) (17). Furthermore, Pinsky and colleagues demonstrated that the projected PCa mortality rates from the treatment arms of both PCPT and REDUCE trials were not greater than the placebo arms (18). The Finnish Prostate Cancer Screening Trial (which did not show a difference in incidence of high-grade tumors with finasteride use) similarly found that 5-ARI use was not associated with an increased risk of PCa-specific mortality (19). While reassuring, these analyses do not provide the definitive evidence desired when considering intervention in otherwise healthy patients.

The utility of 5-ARIs in treating BPH and lower urinary tract symptoms is clear and well-established. The role of these medications as a chemopreventive drug is decidedly less clear, as 5-ARI use appears to decrease the diagnosis of low-grade, clinically insignificant cancers, while potentially yielding a small increase in the risk of high-grade cancers. Acknowledging the quality and nature of these data, 5-ARIs remain a reasonable and effective option for the treatment of BPH. Patients and physicians need to understand, however, the importance of PSA monitoring in men taking 5-ARIs and how these medications impact thresholds for biopsy as compared to the general population.

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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