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Revisiting 5α-reductase inhibitors and the risk of prostate cancer

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Abstract

The role of 5α-reductase inhibitors (5-ARI) in prostate cancer chemoprevention remains a controversy, as cancer prevention trials with 5-ARIs have shown a decreased incidence of low-grade prostate cancer but a potential increased risk in high-grade disease. Recent studies have shed light on the long-term safety of 5-ARIs in terms of influencing prostate cancer risk.

Androgen ablation therapy has been the cornerstone of initial treatment for metastatic prostate cancer for decades, based on Huggins and Hodges' 1941 finding that androgens drive prostate carcinogenesis[1]. In the early 1990s, it was hypothesized that inhibition of 5α-reductase (5-AR), the enzyme that lowers intraprostatic dihydrotestosterone levels, could prevent prostate cancer. Inhibiting 5-AR was an attractive target for prostate cancer chemoprevention, and two large randomized, placebo-controlled cancer prevention trials were initiated to evaluate the effect of the FDA-approved 5-AR inhibitors (5-ARIs), finasteride and dutasteride: the Prostate Cancer Prevention Trial (PCPT) with finasteride[2] and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial[3]. Both trials were positive for reducing the risk of prostate cancer, but only for low-grade disease. In the PCPT study, 7 years of finasteride therapy reduced the prevalence of prostate cancer by 24.8%[2] and in the REDUCE trial, dutasteride treatment was associated with a relative risk reduction of 22.8% over 4 years[3]. However, both trials demonstrated a potential increased risk of high-grade disease. The FDA conducted a pathological reassessment of the trial data and detected an absolute increase of 0.7% and 0.5% in the incidence of high-grade cancers (Gleason score 8–10) with finasteride and dutasteride, respectively[4]. Because of this concerning finding, the FDA not only recommended against approval of 5-ARIs for the chemoprevention of prostate cancer but also modified both drug labels to include the observation that these drugs might increase the risk of developing high-grade prostate cancer[1]. The evidence at the time was inadequate to determine the effects of the drugs on prostate cancer-specific morbidity and mortality.

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Author contributions

Both authors researched data for the article, made substantial contributions to discussion of content, and wrote, reviewed, and edited the manuscript before submission.

Competing interests

The authors declare no competing interests.

However, two recently published epidemiology studies have revisited the prostate-cancer-preventive properties of these agents and bring into question the original concerns regarding the increased incidence of high-grade disease. Unger and colleagues[5] investigated whether the protective effects of finasteride lasted after drug discontinuation and extended the median follow-up duration to 16 years. They linked the Medicare claims database with the PCPT clinical records beyond the 7-year follow-up point specified in the original study protocol to better understand the cancer outcomes. At the 16-year follow-up point, men treated with finasteride had a 21.1% decreased risk of prostate cancer compared with placebo, with no increased risk of prostate cancer for those who received finasteride suggesting that a relatively short treatment duration of 7 years with finasteride could reduce prostate cancer diagnoses in the long term'. In the second study, Wallerstedt and co-workers" investigated the safety of 5-ARI treatment for lower urinary tract symptoms in terms of the associated risk of prostate cancer. Using the registry in Sweden, they evaluated 23,442 men who were exposed to finasteride or dutasteride for any length of time during the 8-year study period. Treatment with 5-ARIs reduced the overall risk of developing prostate cancer, and the effect was larger with longer drug exposure (0.1–2 years HR = 0.81 versus 6–8 years HR = 0.31). More importantly, 5-ARI treatment did not affect the long-term risk of high-grade cancer diagnosis with up to 8 years of treatment, demonstrating the safety of 5-ARIs with respect to prostate-cancer risk. Findings from the two new studies provide reassurance that 5-ARIs do not promote the development of prostate cancer.

These results raise the question of whether the safety warning on the labels of both 5-ARIs with respect to the increased risk of high-grade prostate cancer is still warranted. Subsequent analyses of the PCPT trial offered various explanations for the increase in high-grade cancers, including detection bias owing to the reduction of prostatic volume and increased sensitivity of PSA testing[7], or that the excess high-grade cancers detected in PCPT and REDUCE could be related to the study designs. Additionally, long-term data from the PCPT trial further demonstrated no increased mortality among finasteride users after 18 years of follow-up monitoring[8], and two separate studies also reinforce these results by showing that 5-ARI use is unlikely to increase prostate cancer mortality in men receiving these drugs to treat benign prostatic hyperplasia[9,10].

The safety warnings on 5-ARI labels have changed clinical practice, especially among urologists, reducing prescriptions of 5-ARIs for men who could benefit from their use. In fact, some prominent urologists have even extrapolated these data to suggest that the only thing that 5-ARIs can do is prevent you from knowing that you might have lethal cancer until it is too late to cure. However, the published data contradict this argument and suggest that 5-ARIs are safe in terms of prostate cancer risk and mortality, and the new research findings from Unger and colleagues[5] and Wallerstadt and co-workers[6] suggest there might be true long-term benefits of 5-ARIs in preventing prostate cancer. What remains to be addressed is whether the safety warning should be removed from 5-ARI labels, as the benefits of 5-ARI therapy might far out-weigh any potential risks related to prostate cancer incidence.

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