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Do 5α-Reductase Inhibitors Alter Prostate Cancer Detection and What Are the Implications?

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Abstract

The 5α-reductase inhibitors (5-ARIs) have a number of effects on benign, hyperplastic, and malignant prostate epithelium. The extent of these effects appears to differ significantly among patients, and on average, appears less than that observed with luteinising hormone-releasing hormone (LHRH) agonist therapy. Indeed, the ''characteristic changes'' observed for hormonal therapy may not be so specific after all, if such changes can also be observed in men not receiving 5-ARIs or hormonal therapy. Although prostate specimens derived from men receiving a 5-ARI need to be interpreted with care, currently little evidence supports the original contention that use of a 5-ARI can result in significant misinterpretation of Gleason grade in those with prostate cancer. Data from the Prostate Cancer Prevention Trial (PCPT) strongly suggest that the reduction in prostate volume combined with changes in the performance of prostate-specific antigen (PSA) observed with 5-ARI treatment results in an excess detection of tumours, especially high-grade lesions, compared with untreated men. The effects of 5-ARIs on PSA appear to improve the predictive value of PSA as a diagnostic test for prostate cancer, possibly by differential suppression of PSA derived from cancerous and noncancerous tissue. New analyses, under development, are seeking to examine how this increased detection affects the reduction in risk of prostate cancer observed with 5-ARI therapy during the 7 yr of the PCPT.

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1. Introduction

It has been understood for some time that treatment with 5α-reductase inhibitors (5-ARIs) has the ability to influence prostate cancer detection. Through inhibition of dihydrotestosterone (DHT) synthesis, 5-ARIs significantly reduce androgen drive to the prostate, which in its normal, hyperplastic, or cancerous state is androgen sensitive [1,2]. Androgens, particularly DHT, are recognised as the major regulator of prostate growth and differentiation. Interfering with the actions of androgen on the prostate results in glandular atrophy causing shrinkage of the prostate and reduction of prostate-specific antigen (PSA) synthesis [3]. The use of 5-ARIs, therefore, has the potential to alter

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prostate cancer detection in three ways: through effects on prostate histology that may alter the pathologist's view of a biopsy or radical prostatectomy specimen; through a decrease in the volume of the prostate, leading to alterations in suspicion of cancer on digital rectal examination (DRE) or through altered biopsy sampling; and through a reduction in serum PSA levels, resulting in an altered performance as a marker of suspicion for prostate cancer.

Although postulated for years, more recent clinical data have produced a dramatic expansion of our knowledge of these effects and of their clinical implications. The completion of the Prostate Cancer Prevention Trial (PCPT) [4] and subsequent controversies over the incidence of tumours with high Gleason grades detected in the finasteride arm [5] have focussed considerable attention on these issues. The PCPT, sponsored by the National Cancer Institute and coordinated by the Southwest Oncology Group, evaluated the ability of finasteride to reduce the period-prevalence of prostate cancer, defined as the total number of prostate cancers diagnosed over a 7-yr period, in men taking the drug compared with placebo. Over 18,000 men were randomised to receive either finasteride (5 mg/d) or placebo and followed with annual examinations and PSA measurements. Biopsies of the prostate were obtained during the study due to abnormal examination or PSA findings (for cause) and also at the end of the study regardless of examination or PSA findings. The study observed a 24.8% reduction in prostate cancer in the finasteride group compared with placebo [4]. However, a higher proportion of tumours with a Gleason score of 7–10 were detected in the finasteride group versus the placebo group (37.0% vs. 22.2% of graded tumours; $p < 0.001$), with the majority of this difference accounted for in the for-cause biopsies (Fig. 1). This raised the concern that alteration of the androgen balance through inhibition of 5α-reductase may promote the growth of more aggressive prostate tumours [4].

An important observation that pointed to an artifactual cause for this observation, rather than a true potentiation effect, was that the proportions of high-grade tumours in the two treatment arms did not diverge with time, a trend that would be expected if finasteride did promote the development of more aggressive tumours [6]. Furthermore, if finasteride did potentiate growth of high-grade cancer, then pathologic prognostic factors associated with tumour volume and extent would be expected to be greater in the high-grade tumours in the finasteride arm of the study compared with the placebo arm. In contrast, preliminary results from the PCPT indicate that the tumours with Gleason scores 7–10 were less extensive in the finasteride arm compared with placebo for all of these features [7]. Other potential explanations for these observations therefore need to be examined.

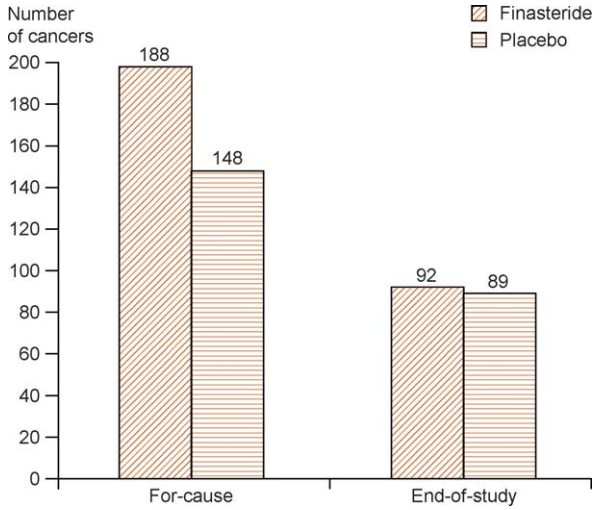

Fig. 1 – Gleason grade 7–10 tumours diagnosed in the Prostate Cancer Prevention Trial by timing of biopsy [4].

2. Histopathologic effects of 5-ARIs

For some time it has been known that treatment of benign prostatic hyperplasia (BPH) with the type-2 selective 5-ARI, finasteride, results in a reduction of prostate epithelial volume and an increase in the stromal-epithelial ratio of similar magnitude in the transitional and peripheral zones of the prostate [8]. Finasteride treatment of normal or hyperplastic prostate tissue results in atrophy and involution [9–14], smaller nuclei and nucleoli [11], increased apoptosis [12,15], decreased microvessel density [16,17], and no increase in cellular proliferation [15].

Although 5-ARIs are known to cause a number of histologic changes in normal and hyperplastic prostatic tissues, their direct effects on the morphology of prostate cancer are less clear. It is well established that luteinising hormone-releasing hormone (LHRH) agonist therapy has a profound impact on the morphology of cancer and the accuracy of Gleason grading, causing tumours of lower grade to artifactually appear high grade [18]. This has led to the consensus that Gleason grading should not be performed on tumours that have been hormonally treated [19]. However, substantive data of the effects of 5-ARIs on Gleason grading have not, until recently, become available.