High-Grade Prostate Cancer in the Prostate Cancer Prevention Trial: Fact or Artifact?

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Chemoprevention of prostate cancer is a laudable and desirable goal. One strategy for chemoprevention is androgen deprivation therapy with 5α-reductase inhibitors, such as finasteride and dutasteride (1, 2). The recent landmark Prostate Cancer Prevention Trial (PCPT), which used finasteride, was the first phase III clinical trial of prostate cancer prevention (1). Finasteride is the only intervention that has been shown to reduce the incidence of prostate cancer in a long-term prospective clinical trial (3). However, despite the impressive 24.8% relative reduction in the 7-year period prevalence of prostate cancer in the finasteride arm of the trial, finasteride has not been embraced in clinical practice (4). One reason is that there was a higher proportion and number of histologically high-grade carcinomas (defined as Gleason score 7–10) in the finasteride group of the PCPT compared with the placebo group. This finding raised the alarming prospect that finasteride induces, via therapeutic selection pressure, the expansion or development of a higher grade, perhaps androgen-independent, tumor cell population.

The investigation by Lucia et al. (5) in this issue of the Journal aimed to assess whether the increased prevalence of high-grade prostate cancer associated with finasteride treatment in the PCPT was a Gleason histopathologic grading artifact induced by finasteride. They report important data suggesting that finasteride does not induce histomorphologic changes in prostatic carcinoma. The evidence, albeit somewhat indirect, is convincing because, in a blinded review, three expert urologic pathologists did not detect any histopathologic differences between carcinoma in the finasteride and placebo arms using nine different histomorphologic parameters that are known to be associated with androgen deprivation therapy effects. The evidence is indirect because this was not a longitudinal test in individual patients of morphologic alterations by examining carcinoma in biopsy tissue before and after finasteride treatment. Nevertheless, these data are important because it is well established that other types of androgen deprivation therapy can induce an apparent increase in Gleason grade due to the loss of luminal glandular spaces (luminal collapse) (6) and also to the creation of single-cell infiltrates, which simulate high-grade cancer (7). Compared with other forms of androgen deprivation therapy, finasteride’s effects on the histologic appearance of prostatic carcinoma seem to be weaker or nonexistent, and this conclusion is consistent with previously published studies (8–9). As a caveat, it is possible, as the authors note, that the nine parameters may not have been the best or the only ones to define finasteride’s histomorphologic effects.

The study by Cohen et al. (10) in this issue of the Journal used two modeling methods to examine the role of detection bias (due to the effect of finasteride on reducing prostate volume) as a potential explanation for the increased number of high-grade cancers on biopsy in the finasteride group. The authors fit to the PCPT data an assumed logistic regression model for detection probability as a function of several patient characteristics, including prostate gland volume. They show that increased sampling density bias could account for the 25% increase in high-grade tumors. This explanation was previously proposed by Kulkarni et al. (11) based on an analysis of their patient population, in which there was a greater occurrence of high-grade cancer on biopsy among men with smaller prostates but an equivalent occurrence of high-grade disease in radical prostatectomy specimens. In addition, Serfling et al. (12) used modeling to quantify how cancer detection probability changes with prostate gland volume when random sextant biopsy is performed. In that study, for 30-cm³ prostates and 0.75-cm³ tumors, a decrease of 25% in prostate volume (as occurs after finasteride treatment) increased cancer detection by sextant biopsy by 23%. Although these studies collectively provide a strong suggestion that detection bias may well have played an important role in the findings of the PCPT, one must acknowledge that additional validation is necessary before categorically accepting this as the explanation (13).

Taken together, the studies by Lucia et al. (5) and Cohen et al. (10) provide substantial reassurance that the increased proportion of high-grade cancer on biopsy in PCPT is not likely to be clinically relevant. In the future, molecular testing of these PCPT tissue samples may be useful to determine whether the high-grade carcinomas seen in the finasteride arm have DNA ploidy (14) and gene expression profiles (15) similar to those of untreated high-grade carcinoma. Ultimately, analysis of radical prostatectomy specimens and long-term clinical follow-up of the finasteride-treated patients will be necessary to completely ascertain the clinical significance of the increased high-grade cancer on biopsy in the PCPT. In addition, the REDUCE (Reduction by Dutasteride of Prostate Cancer Events) trial, in which more than 8000 men with elevated prostate-specific antigen levels and one negative biopsy are randomly assigned to placebo or dutasteride for up to 4 years, during which rebiopsy is performed at 2 and 4 years, or as clinically indicated, is poised to shed additional light on this important question.
the impact of 5α-reductase inhibitors on the frequency and clinical significance of high-grade prostate cancer (16).

References


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Notes
Dr Andriele is chairman of the steering committee of the REDUCE prostate cancer prevention trial, which is sponsored by GlaxoSmithKline. Dr Grubb is an investigator for GlaxoSmithKline and is also involved in the REDUCE trial.