High-Grade Prostate Cancer and the Prostate Cancer Prevention Trial

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Prostate cancer remains a major public health challenge worldwide and has defied efforts to develop effective and acceptable therapy for its control. This reality provides a strong rationale for focusing on prevention. In the Prostate Cancer Prevention Trial (PCPT), the 5α-reductase inhibitor finasteride reduced the prevalence of prostate cancer by 24.8% (versus placebo) in 18,882 men randomized to treatment with that agent (1). Despite this definitive evidence of risk reduction, finasteride has generally not been accepted clinically. The reports by Lucia and colleagues (2) and Redman and colleagues (3) in this issue of the journal do much to address the paradox that one of the most successful findings of prevention trials has not resulted in widespread acceptance. This failure to apply finasteride is not attributable to toxicity such as sexual side effects but rather to a concern over high-grade prostate cancer and a lack of confidence in the importance of the clinical observations (4, 5). Is this reluctance to apply finasteride justified? Do recent PCPT publications, including two in this issue of the journal, provide sufficient data to alter the recommendations and guide future prevention research?

The challenge of finasteride application hinges on three central questions that we will address:

1. Does finasteride preferentially suppress cancers with no lethal potential, and therefore is it an unnecessary intervention?
2. Does finasteride accelerate adaptation that leads to early progression of prostate cancer to a lethal phenotype?
3. Do we now have sufficient evidence about the efficacy and safety of finasteride to change the perspective of physicians and overcome the reluctance to use it?

Regarding question 1, the prevalence of low-grade prostate cancers detected by screening influences the perspective of physicians. Does this context surround the initial report of the PCPT (which screened annually with digital rectal examination and serum prostate-specific antigen) with the concern that 5α-reductase inhibition prevented exclusively cancers with no lethal potential? To see value in finasteride even if this concern were valid, one must accept the basic assumption that the diagnosis of prostate cancer confers risk to a patient's quality and duration of life. Given present practice, reducing the frequency of diagnosed cancer will spare individuals the consequences of being labeled a "cancer patient" and reduce both unnecessary concern and the morbidity that accompanies therapy. Furthermore, Lucia and colleagues showed that a substantial portion of the cancers prevented by finasteride (primarily Gleason score ≤6 cancers) were clinically significant according to well-studied biopsy criteria (2).

Lucia and colleagues (6) built on the previously reported pathologic analyses with a more thorough and complete study. The results of their present effort show that the frequency of cancer remained reduced and that there was no increase in clinically significant cancer in the treated patients by current morphologic criteria. The volume of finasteride-treated tumors of all grades was lower than that of placebo-treated tumors. Furthermore, as shown in the previous analyses of Thompson and colleagues (7–9), the initially reported differences in high-grade disease may have been attributable to a detection bias in the treatment arm owing to changes in prostate and cancer volume and improved sensitivity of serum prostate-specific antigen concentration and digital rectal examination. Taken together, these data provide convincing evidence that the reduced frequency of detected cancer is clinically significant. In addition, these studies provide a plausible explanation for the initially reported results involving high-grade disease.

Regarding question 2, in the initially reported PCPT results, the increased incidence of the "higher-grade-appearing tumor" following finasteride chemoprevention therapy raised the specter of accelerated adaptation of the cancer, resulting in earlier-than-anticipated lethal progression and potential harm to a subset of patients. To address this concern, Redman et al. conducted analyses. The first of these analyses convincingly showed that the detection bias induced by finasteride increased the sensitivity of serum prostate-specific antigen and digital rectal examination but had relatively little effect on the overall results of the PCPT. The effect of bias on high-grade disease detection was addressed in the extrapolated rates of high-grade prostate cancer in the men who underwent radical prostatectomies (~25% of the total number of men who had biopsy-detected cancer) to the entire population of men with prostate cancer in the PCPT. This analysis showed that the true rate of high-grade prostate cancer in the finasteride-treated men (6.0%) was 27% lower than the rate in the placebo-treated men (8.2%). Thus, Redman and colleagues were able to conclude that there was no statistically significant increase in high-grade cancer, in contrast to the previously reported result. Another report in this issue of the journal supports this conclusion (10).

However, because these results are based on a small number of events, our ability to reach this conclusion with confidence is limited. We are comforted by the analysis of the traditional criteria of tumor lethality, as reported by Lucia et al. Their observation that the volume of detected cancers, irrespective of grade, was less in finasteride-treated patients than in controls is in line with the conclusion of Redman.
et al. The results of these analyses effectively eliminate the concern that finasteride caused an increase in aggressive cancers within the study period.

Regarding question 3, should this new evidence from Lucia et al. and Redman et al. give physicians the confidence to use the 5α-reductase inhibitor finasteride for the prevention of prostate cancer? The effect of finasteride in reducing the frequency of detected meaningful cancer and the paucity of evidence of irreversible toxicity induced by the drug support the authors’ conclusions that finasteride is a safe and effective prevention option that should be offered to men at risk for prostate cancer.

It is important now to build on the PCPT in developing more effective preventive agents alone or in combinations, which will require progress in the following areas: (a) understanding of the mechanism(s) underlying prostate cancer progression and response to finasteride, (b) characterization of human prostate cancer founded on an improved understanding of its biology, (c) proposals for and testing individualized risk reduction strategies based on our understanding of the underlying biology of prostate carcinogenesis, (d) identification of candidate surrogate markers that can overcome clinical heterogeneity, (e) integrating biological insights with the derived surrogate markers to develop efficient studies that will shorten the time and expense required to test new interventions, and (f) trials designed to optimize the duration of therapy with respect to both preventive activity and expected and unexpected side effects. Based on the advances reported for finasteride in this issue of the journal, we conclude that the promise of prostate cancer prevention is a reality and that the findings of the PCPT provide the impetus and foundation for the further studies suggested here.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References