Journal of Cellular Biochemistry 91:478–482 (2004)

Effect of Finasteride on Risk of Prostate Cancer: How Little we Really Know

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Abstract The Prostate Cancer Prevention Trial (PCPT) reported conclusively that finasteride prevents or delays the detection of prostate cancer. One perplexing finding was that more high-grade tumors were detected in the finasteride treated group. It is hard to put this into perspective because of the limited published data on the effects of finasteride on prostate cancer. The strong possibility exists that the increase in high-grade tumors may be due to a treatment effect, which causes intermediate grade cancers to appear to be high-grade or aggressive tumors. Confirmation of a spurious tumor grade ''inflation'' will make the conclusions of this study clearer and define the benefits of finasteride chemoprevention in a more favorable light. J. Cell. Biochem. 91: 478–482, 2004. © 2004 Wiley-Liss, Inc.

Key words: prostate cancer; finasteride; chemoprevention; Gleason grading

The Prostate Cancer Prevention Trial (PCPT) recently reported early termination of the trial demonstrating conclusively that finasteride, an inhibitor of one the two subtypes of the enzyme 5-alpha-reductase (SRDA2) which blocks the conversion of testosterone (T) to dihydrotestosterone (DHT), prevents or delays the detection of prostate cancer [Thompson et al., 2003]. Finasteride, is a drug used by millions of men to treat the symptoms associated with benign prostatic hyperplasia (BPH). The influence of finasteride on the development of prostate cancer was the primary endpoint in the report from the PCPT. The results of the study potentially represent a major turning point in the field of prostate cancer prevention.

Patients enrolled on this chemopreventive trial were required at study entry to be at low risk for the development of prostate cancer. Patients eligible for this study had no palpable nodules by digital rectal examination and a serum prostate specific antigen (PSA) level below 3 ng/ml. As the study was planned, it was powered to show a difference in treatment effect based on the assumption that the incidence of prostate cancer in the control group would be 6% over the study period of 7 years. Therefore, over 18,000 men were initially screened for entry into this protocol. Patients either received 5 mg/day of finasteride or placebo and serum PSA was monitored. All patients were asked to undergo a prostate biopsy at study closure. The first surprising finding in this study was the high percentage of men in the placebo group diagnosed with prostate cancer over the course of this study. At the time of study design, it was anticipated that in this low risk patient population, the percentage of men developing prostate cancer would be 6% but at study close, an impressive 24% of the men in the placebo group were diagnosed with prostate cancer. The second unanticipated finding was that finasteride reduced the incidence of

Grant sponsor: Specialized Program of Research Excellence for Prostate Cancer (S.P.O.R.E.) NCI (to M.A.R. and P.W.K.); Grant number: P50CA90381; Grant sponsor: Specialized Program of Research Excellence for Prostate Cancer (S.P.O.R.E.) NCI (to M.A.R.); Grant numbers: P50CA69568, R01AG21404.

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Received 27 October 2003; Accepted 28 October 2003

DOI 10.1002/jcb.10787

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prostate cancer by 25% with 18% of men treated being diagnosed with prostate cancer. The potential benefits of this finding are huge. Notwithstanding the potential for over diagnosis inherent the manner of close observation in this study including biopsies in all men at study closure at 7 years, the potential to reduce the number of cancer diagnoses, the associated "PSA anxiety," the morbidity of biopsy and consequent treatment are enormous. Nonetheless a perplexing result was found; almost 20% higher-grade prostate tumors were detected in the finasteride treated group when compared to the placebo group. This last finding is hard to put into perspective because of the limited published data on the effects of finasteride on prostate cancer.

The effects of finasteride are best characterized in the prostate tissues of men treated for lower urinary tract symptoms associated with BPH. In that setting the prostate gland is known to shrink in size due to atrophy of the benign secretory epithelium and to a lesser extent the prostatic stroma composed predominantly of smooth muscle. Some investigators have discussed a preferential decrease in size of the gland in the transition zone as compared to the peripheral zone, where BPH and prostate cancer are believed to most commonly arise, respectively [Tempany et al., 1993]. Light microscopic evaluation of the prostate gland treated with finasteride demonstrates variable atrophy of the benign secretory epithelium (Fig. 1). Depending on the degree of treatment and patient-to-patient differences, the extent of this atrophy can range from global, that is involving the majority of epithelial cells, to partial involving some glands but not all in a uniform manner. It is also worth noting that these changes are not specific to finasteride and cannot be differentiated from other causes of atrophy seen in patients without finasteride treatment [Yang et al., 1999].

There is limited data on the effect of finasteride on prostate cancer in the human. Till date most studies have concentrated on the effect in animals and tumor cell lines. Yang et al. [1999] reported on a small series of prostate needle biopsies from men treated with finasteride [Yang et al., 1999]. In this non-randomized and underpowered study there were no significant differences seen between the treatment and control groups with respect to all of the parameters examined including atrophy, Gleason grade, amount of tumor identified, or other histologic features. The study did find a trend towards higher-grade prostate cancer in the placebo group, however this was not statistically significant. The authors did express some reservations regarding how sampling was performed using multiple 18 gauge needle biopsies which may have missed the extent of the finasteride effect on the 39 biopsies from finasteride treated men. The duration of follow-up of this study was also significantly shorter than the cases studied in the PCPT.

Because finasteride lowers serum PSA levels, serum PSA could not be used as a study

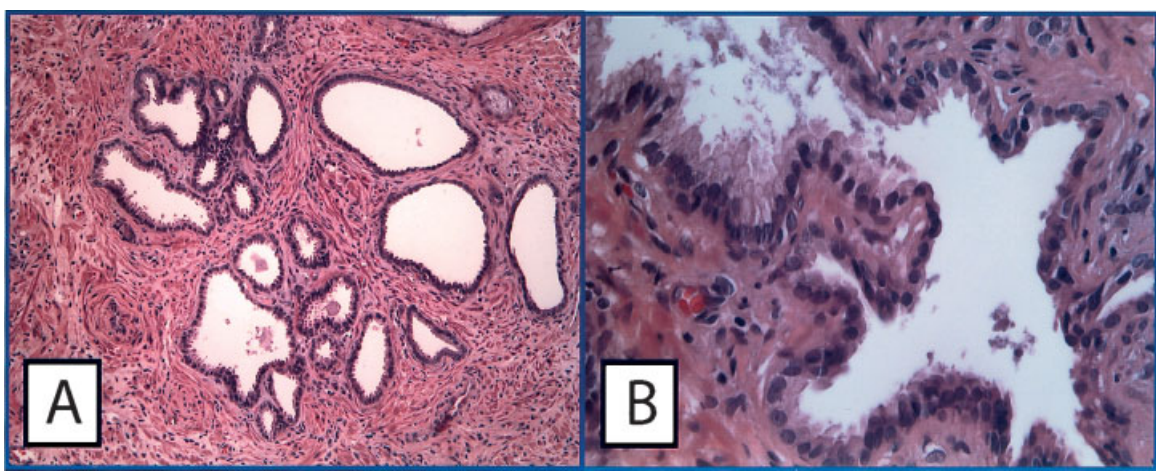

Fig. 1. The effects of finasteride on benign prostate tissue. Finasteride treatment leads to shrinkage of the benign secretory glands of the prostate (**A**). These alterations may be global involving the vast majority of the glandular tissue or may only partially affect the prostate gland (**B**). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

endpoint in the PCPT. Therefore, monitoring needed to be conducted in a different manner for the finasteride versus the placebo groups. If serum PSA was elevated, the patient underwent a transrectal ultrasound guided needle biopsy. This was described as six systematic biopsies. If the biopsy demonstrated prostate cancer, the patient was taken off from the study. If the biopsy demonstrated high-grade prostatic intraepithelial neoplasia (PIN), a repeat biopsy was recommended, as is the standard clinical practice.

The pathology for this study was first reviewed centrally and then at the study sites. Although pathologists at both the study sites and the central facility were blinded as to the treatment status of the patients, the study sites did receive the pathology report from the central pathology core. Disagreement was resolved by a referee pathologist.

The first major finding from this study was the number of prostate cancers seen after the 7-year study closed earlier than expected. A 24.8% of 4,692 men in the placebo group and 18.4% of the 4,368 men in the finasteride group were diagnosed with prostate cancer. These differences were statistically significant and unexpected as the investigators had anticipated a much lower incidence of prostate cancer diagnosed during the course of the study. It is perhaps unfortunate that men did not receive entry biopsies to rule out the presence of prostate cancer at time of enrollment.

The most perplexing finding was that of the men who were treated with finasteride that had prostate cancer, 37% (280/757) had high-grade cancer with Gleason scores 7–10. This was significantly higher than the 22.2% (237/1068) Gleason scores 7–10 cancers seen in the placebo group. The Gleason grading system is a purely architectural system, relying on tumor grade assignments based on how prostate tumors proliferate [Gleason, 1966, 1992]. The system also accounts for a primary growth pattern or the most common pattern and then if a second architectural pattern is observed, this is referred to as the secondary pattern. The Gleason score is then the sum of these two patterns. If only one pattern is observed, the single pattern is doubled giving a Gleason score (also known synonymously as a Gleason grade or sum). This score ranges from 2 to 10 with 2 being the lowest and 10 the highest possible score. In the finasteride trial the authors did not distinguish biopsies that had a very small amount of Gleason pattern 4 in the background of Gleason pattern 3 from the reverse. Both scenarios would lead to a score of 7 but as has been demonstrated by numerous investigators, there is a significant differences between Gleason score $3+4$ and $4+3$ even though the sum of both equal 7 [Pound et al., 1999; Stamey et al., 1999]. However, regardless of how one categorizes the Gleason scores, the fact remains that according to the study there was a significantly higher percentage of Gleason grade 7–10 prostate cancers seen in the treated group.

Nonetheless, the authors offered several explanations as to why there was an increased rate of high-grade prostate cancers identified in the treatment group. The first explanation is that finasteride produced a treatment effect. Treatment is well-characterized in men receiving androgen deprivation therapy prior to biopsy or surgery. The androgen receptor is most sensitive to DHT but can also be stimulated by T as higher concentrations [Grino et al., 1990]. Some assess DHT to be four times as potent as T [Geller and Sionit, 1992]. Antiandrogens such as flutamide or bicalutimide block the effect of androgen on the androgen receptor effectively, and LHRH analogues, Lupron and Zoladex diminish T and DHT profoundly. In the case of finasteride, serum T levels are modestly increased and intraprostatic DHT levels are diminished by as much as 80%. All in all, this would suggest that treatment-related pathologic alterations should be less dramatic in finasteride treated men than with antiandrogens or LHRH analogues. The editorial accompanying the article on the PCPT suggests that treatment effect on established prostate cancer is an unlikely scenario as the only other study looking at the effect of finasteride on prostate cancer failed to show any significant differences between the treatment and control group [Scardino, 2003]. However, even that is not clear. There is currently too little information on the potential of an androgen-treatment (Lupron-like) effect with finasteride making intermediate grade cancers appear to be high-grade tumors. The effect of finasteride may take longer to appreciate or may be highly variable due to known functional polymorphisms in SRDA2 enzyme [Jenkins et al., 1992]. Therefore, decreased stimulation of the androgen receptor over long periods of time may lead to similar alterations. Specifically, morphological changes such as

those observed in androgen treated prostate cancer including loss of glandular architecture, cytoplasmic vacuolization, and nuclear pyknosis (Fig. 2) [Reuter, 1997]. As described by Reuter [1997] and others treated carcinoma exhibits a paradoxical high Gleason score but its proliferation rate and degree of aneuploidy is less than grade-matched, untreated tumors. It is important to note that the value of the Gleason grading system is its time-honored correlation to outcome in the pretreatment scenario (i.e., prior to surgery or radiation). There is no data validating the prognostic value of Gleason grading after therapy, specifically after hormonal therapy including finasteride. Thus, grading of androgen treated prostate cancer by the conventional Gleason system may be misleading and should be avoided [Van de Voorde et al., 1994; Reuter, 1997]. Two important questions remain. Was there an androgen deprivation-like pathologic effect due to long-term finasteride treatment? Should the biopsies performed on this study have been graded using the standard Gleason system given that therapy treated tumors are not usually graded?

The second explanation offered by the author's postulates that by locally decreasing the DHT, only tumors that can grow in a low androgen environment survive. There is little data on human tumor samples to support this hypothesis. One study looking at five patients treated with finasteride for BPH but were subsequently diagnosed with prostate cancer found alterations in the androgen receptor in two of the five cases [Koivisto et al., 1999]. In one instance a mutation in the androgen receptor was seen and in the other case a modest amplification of the receptor was seen by fluorescence in situ hybridization (FISH) analysis.

A third explanation suggests that by killing off the low-grade tumor cells, the high-grade tumor cells are free to expand. Prostate cancer is known to be one of the slowest growing tumors and therefore, this phenomena would be favored the longer the treatment time interval. Morgentaler et al. [1996] reported on men with low T levels seeking androgen replacement therapy [Morgentaler et al., 1996]. Fourteen percent of 77 patients were diagnosed with either Gleason grade 6 or 7 prostate cancer. In this small study, the low T levels did not lead to a high percentage of high-grade tumors in this cohort.

The side effects of treatment and impact on quality of life also need to be taken into consideration when evaluating the full impact of this study. The effect of finasteride on urinary symptomatology might be anticipated, the finasteride treated group reported fewer urinary symptoms over the course of the trial; nearly twice as many men underwent a transurethral resection of the prostate due to lower urinary

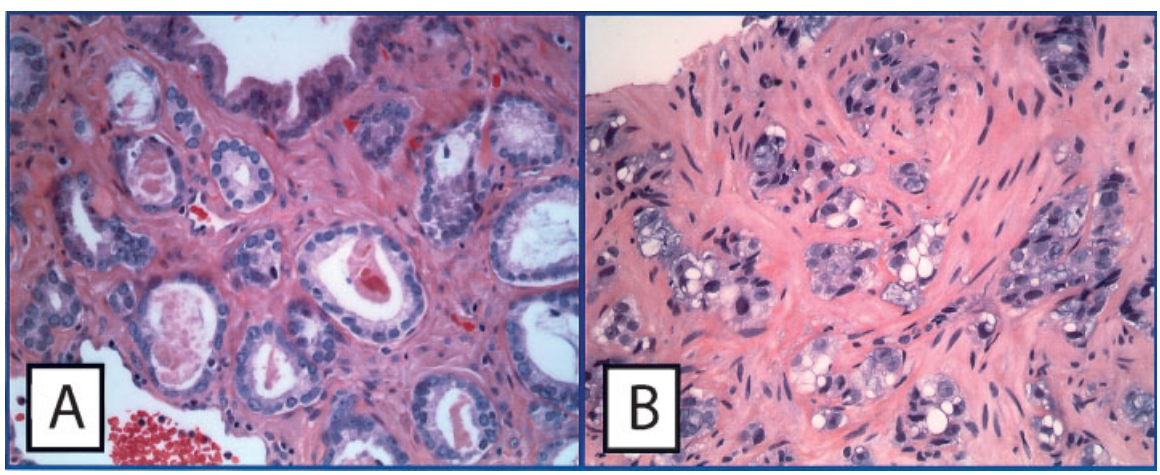

Fig. 2. The effects of androgen deprivation therapy on prostate cancer. Intermediate prostate cancer is characterized by small to intermediate sized glands, which infiltrate between benign glands. Untreated prostate cancer usually demonstrates abundant cytoplasm (**A**). Androgen deprivation therapy, even for a relatively short course (i.e., 3 months), can lead to a dramatic shrinkage of gland size, vacuolization, and a decrease in nuclear size (pyknosis) (**B**). These changes can be variable and lead to spurious up grading of prostate tumors if the pathologist is unaware of this therapy-related effect. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

symptoms in the placebo group as compared to the finasteride treated group with 1.9% (180/9,457) and 1.0% (96/9,423) requiring surgery, respectively. A more difficult area to evaluate is quality of life. Decreases in sexual potency, libido, and ejaculate volume were reported more frequently in the finasteride treated group when compared to the placebo group, however the high incidence of these effects on the placebo arm reflect both the aging process and the difficulty in assessing these parameters accurately.

If finasteride treatment does cause high-grade tumors, men on finasteride will need to weigh this risk. The organizers of this study (South Western Oncology Group and the National Cancer Institute) should assemble a panel of prostate cancer pathologist to review these samples to determine the long-term effect of finasteride on prostate cancer grading.

There is reason for great excitement in the reporting of a 24% decrease in prostate cancer diagnosed in the finasteride treated group, however further study is needed to comprehend the observation that the finasteride increases the incidence of high-grade tumors and diminishes parameters of sexual function. Nonetheless, while it is critical to see over the course of time, if the reduced incidence of prostate cancer is also associated with a drop in cancer specific mortality, the sheer profound decrease in incidence afforded by finasteride and the consequent reduction in cancer diagnoses, the associated "PSA anxiety," the morbidity of biopsy and consequent treatment justify careful consideration of its use in healthy men over the age of 55.

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