REVIEW ARTICLE

Do α-reductase inhibitors prevent prostate cancer?

2008 Practice Guideline from the American Society of Clinical Oncology and American Urological Association

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KEY WORDS

5-α-reductaste inhibitor, finasteride, Prostate Cancer Prevention Trial (PCPT), prostate cancer, risk reduction

ABSTRACT

As new guidelines on the use of 5-α-reductase inhibitors (5-ARIs) for prostate cancer chemoprevention produced by the American Society of Clinical Oncology (ASCO) and American Urological Association (AUA) have recently been published, the use of 5-ARIs is becoming of increasing interest. We analyzed the current evidence to support the use of 5-ARIs in the prevention of prostate cancer. We therefore compared the new guidelines of the ASCO and AUA with the current data concerning the use of 5-ARIs in the prevention of prostate cancer. At present, there is still an open debate going on whether or not it is advisable to incorporate the use of 5-ARIs as chemopreventive agents in daily practice.

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Received: August 1, 2009.
Accepted: August 1, 2009.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2009; 119 (10): 648-653

Introduction Cancer of the prostate is now recognized as one of the most important medical problems facing the male population. In Europe, prostate cancer is the most common solid neoplasm, with an incidence rate of 214 cases per 1000 men.[1] Furthermore, prostate cancer is currently the second most common cause of cancer death in men.[2] In addition, since 1985, there has been a slight increase in most countries in the number of deaths from prostate cancer.[3,4]

Since prostate cancer diagnosis is rising, the challenge to identify possible chemopreventive agents is also increasing. 5-α-receptor inhibitors (5-ARIs) may offer this possibility. Although substantial data are available on the use of 5-ARIs in other settings, primarily, treatment of benign prostatic hyperplasia and alopecia, the Prostate Cancer Prevention Trial (PCPT) is the only completed randomized trial prospectively designed to show a reduction in period-prevalence of prostate cancer.[5-10]

This review will focus on the evidence for reducing the risk of clinical prostate cancer with 5-ARIs with an emphasis on a critical appraisal of the new guidelines of the American Society of Clinical Oncology (ASCO) and American Urological Association (AUA).

5-α-reductase inhibitors and their mechanism of action in prostate cancer Testosterone is the major circulating androgen but the androgen activity is maximized only after the 5-α-reductase (5-AR) enzymes converted testosterone into dihydrotestosterone (DHT). Two forms of 5-AR exist.[11] 5-AR2 is the predominating form in benign prostate tissue. In high grade prostatic intraepithelial neoplasia and localized prostate cancer, 5-AR2 is decreased and 5-AR1 is increased. However, both are increased in advanced prostate cancer. In rat and human models in which 5-AR1 predominates, a dual 5-AR inhibition with dutasteride causes a higher decrease in cell growth than selective inhibition of 5-AR2 with finasteride alone. Recently, 5-AR3 has been discovered. It is expressed at low levels in benign prostate tissue and is highly expressed in advanced prostate cancer. Its significance is still unknown.

The evidence for using 5-ARIs for prostate cancer prevention lays in the mechanism for reducing androgen stimulation of the prostate without lowering circulating testosterone levels.[12] 5-AR inhibition within the prostate reduces DHT levels under castration level. Testosterone levels increase, but not as much as DHT in placebo-treated prostates. Therefore, 5-AR inhibition results in DHT

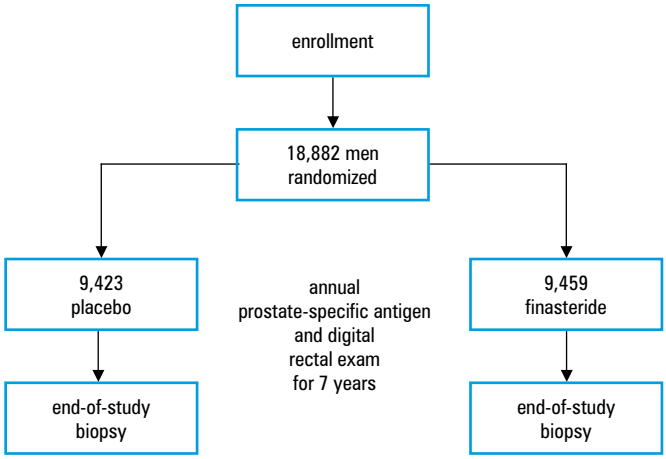


FIGURE 1 PCPT study design[5] (reprinted from Canby-Hagino E, et al. Looking back at PCPT: looking forward to new paradigms in prostate cancer screening and prevention. Eur Urol. 2007; 51: 27-33. Copyright 2007, with permission from Elsevier)

being replaced in the prostate with lower concentrations of a less potent androgen.[13] There is also some evidence that testosterone, by promoting cellular differentiation, may suppress tumor growth when testosterone conversion to DHT is blocked.[14] This additional mechanism by which 5-ARIs may prevent growth of prostate cancer is still being investigated.

5-ARIs must have a dual effect: they must play a role in preventing new cancers from forming but also must control the growth of existing prostate. The PCPT provides the best evidence for the concept of 5-AR inhibition in prostate cancer prevention.[15]

The Prostate Cancer Prevention Trial: design and findings The PCPT has been the first prospective randomized clinical trial of prostate cancer prevention.[16] FIGURE 1 shows the PCPT study design. It was conceived in 1992 and activated in 1993 shortly after the US Food and Drug Administration approved finasteride. The PCPT was the first large-scale population-based trial to test a chemopreventive strategy against prostate cancer. This prospective randomized, blinded, and placebo-controlled trial tested the hypothesis that finasteride, which selectively inhibits type 2 5-AR, would lower intraprostatic DHT levels and thereby prevent prostate cancer. At the start, 18,882 men aged ≥55 years with a normal digital rectal examination (DRE) and serum prostate-specific antigen (PSA) level of <3.0 ng/ml were randomly assigned to treatment with 5 mg finasteride daily or placebo for 7 years. Prostate biopsies were performed for cause (abnormal prostate examination or PSA >4.0 ng/ml) and at the end of 7 years. The trial was stopped 15 months early by an independent data and safety monitoring committee, after achieving the primary endpoint of a 25% risk reduction on the finasteride arm, and sensitivity analysis indicating that additional biopsies would not change the outcome.

Probably the greatest challenge to this study was the fact that finasteride affected serum PSA measurement. At the time the study was initiated, it was known that finasteride reduced PSA by approximately 50%.[17] Without controlling for this reduction and using a prostate cancer incidence endpoint, a reduction in prostate cancers detected would be noted but this would be merely due to the fall in PSA. To control for this detection bias, two steps were taken.

First, a procedure of PSA indexing was performed. On an annual basis, all men in the placebo group with a PSA level >4.0 ng/ml were advised to consider a prostate biopsy. The fraction of the total placebo group >4.0 ng/ml was calculated. Then, the PSA cut-off point in the finasteride group was adjusted so that the same highest fraction of men in the treatment group received a recommendation for biopsy. Practically, a doubling of PSA was initially used to correct for the first 3 years, but due to a continued fall in PSA in the finasteride group, the PSA in this group was multiplied by 2.3 in subsequent years to ensure the same number of biopsies in the two study groups for the remainder of each subject's years on study. Despite this correction for PSA, other biases could exist. For example, finasteride reduces the prostate volume, which may alter the gland texture and manipulate abnormal DREs. This led to a second design characteristic of the PCPT: an end-of-study prostate biopsy. This biopsy was planned in all individuals not previously diagnosed with prostate cancer who reached the 7-year mark on study.[18]

The initial PCPT results Thompson et al. published their findings in 2003.[5] The study was closed early, based on the recommendations of an independent data and safety monitoring committee, because there was convincing evidence that the primary study objective was achieved. There was a 24.8% reduction in period prevalence of the disease, and sensitivity analysis indicated that additional biopsies would not change the findings. The major findings of the PCPT include the following[5,6,18]:

1 A 24.8% reduction of prostate cancer in the finasterid group. The prevalence of prostate cancer was 18.4% in the group taking finasteride compared with 24.4% in the placebo group.

2 Increased high-risk prostate cancer in the finasterid group. The Gleason grade 7–10 cancers was 6.4% in the finasteride group compared with 5.1% placebo group.

3 Finasteride reduced the risk for prostate cancer, independently of the screening status. The risk reduction in prostate cancer was apparent both for men undergoing biopsy for cause (abnormal prostate examination or elevated PSA) and for men undergoing end-of-study biopsy.

4 Urinary symptoms and treatments were more common with placebo. The incidence of acute urinary retention was decreased by about ⅓ in the finasteride arm (risk ratio [RR] 0.67; absolute rates, 6.3 vs. 4.2%). Consistent with this observation, the incidence of transurethral resection of the prostate was 1.9% in the placebo arm and 1.0% in the finasteride arm, a statistically

significant decrease in the risk for surgical interventions.

5 Sexual side-effects were more common with finasteride. These included decreased libido, decreased ejaculate volume, and gynecomastia. The sexual dysfunction associated with finasteride decreased over time, although it remained statistically significant.

6 Finasteride was associated with 24% smaller prostate volumes, compared with the placebo arm.

The prevalence of prostate cancer among men without clinical suspicion for prostate cancer was unexpectedly high. The study design assumed a 6% prevalence based on estimates by Cooner for expected prevalence of prostate cancer in clinical urology practice.[19,20] This estimate was deliberately conservative to reduce the risk of under-powering the study. The incidence of prostate cancer detected on the basis of an abnormal prostate examination or elevated PSA at 7 year was 6%, suggesting that a substantial fraction of prostate cancers detected by the PCPT might never develop important clinical manifestations. This "over-detection" of prostate cancer may be even more pronounced among men treated with finasteride, due to relative over-sampling of their smaller glands by needle biopsy.[18]

Concerns about finasteride and high-risk prostate cancer The PCPT revealed a higher prevalence of Gleason grade 7–10 cancers in the finasteride group, which raised numerous concerns. For all biopsies evaluated in the PCPT, Gleason scores of 7, 8, 9 or 10 were noted in 280 of 757 (37%) men treated with finasteride, and in 237 of 1068 (22.2%) men treated with placebo. Among "for cause" biopsies, high-grade disease was reported in 188 of 393 (47.8%) men on finasteride and in 148 of 504 (29.4%) of men on placebo. Overall, a higher grade disease was found in 6.4% of men treated with finasteride compared with only 5.1% of men treated with placebo.[9]

The possibility that finasteride changed histology in a high risk pattern or that the Gleason score after finasterid could not be used at all raised a number of questions. Subsequent analyses found that finasteride biases toward improved prostate cancer detection and accuracy in prostate cancer grading at biopsy. Fortunately, we have some answers at present as listed below.

Finasteride does not increase the risk of high-grade prostate cancer Redman et al. recently published a bias-adapted model approach that finasteride does not increase the risk of high-grade prostate cancer. This analysis used the PCPT data that included 3-month longer collection of endpoints than in the original report with observed prostate cancer rates of 22.9% (4.8% with high grade, placebo) vs. 16.6% (5.8% with high grade, finasteride). Based on these updated results, the bias-adjusted prostate cancer rates are estimated to be 21.1% (4.2% high grade, placebo) and 14.7% (4.8% high grade, finasteride), a 30% risk reduction in prostate cancer and a nonsignificant 14% increase in high-grade cancer with finasteride. Moreover, high-grade prostate cancer estimations, based on an analysis that incorporated grading information from radical prostatectomies in 500 subjects diagnosed with cancer, were incorporated. The resulting estimates were high-grade cancer rates of 8.2% (placebo) vs. 6.0% (finasteride), a 27% risk reduction with finasteride. Finally, Redman et al. examined the impact of biopsy sensitivity on the relative risk of high-grade prostate cancer and found that differential sensitivity of biopsy between the treatment arms may have a significant impact on risk ratio estimates. These collective results suggest that the observed, unadjusted higher risk of high-grade disease with finasteride seems to have been due to facilitated diagnosis resulting primarily from increased biopsy sensitivity with finasteride.[21]

Finasterid does not induce significant histological changes in the prostate Studies lead by Yang et al. showed that finasteride does not induce significant histological changes in the prostate.[22] Moreover, the greater incidence of high risk prostate cancer in the finasteride group was not due to a histological artefact as originally thought.[22] The Gleason grade has also since been proven to be a valid prognostic predictor in men on finasteride.[23] Men with prostate cancer and low testosterone levels have higher Gleason grades and worse outcomes than men with prostate cancer and normal testosterone levels.[24] Similarly, there was the possibility that finasteride may have been selected for high-grade tumors by the suppression of low grade tumors. The issue of accuracy in determining the true Gleason grade in a biopsy has also been questioned. Unfortunately, errors in the predicted biopsy Gleason score are common, due to inter-observer variability.[25]

A finasteride-induced prostatic volume decrease may contribute to an increased high-risk prostate cancer detection Eliott et al. retrospectively analyzed a database of 1304 men who had been referred

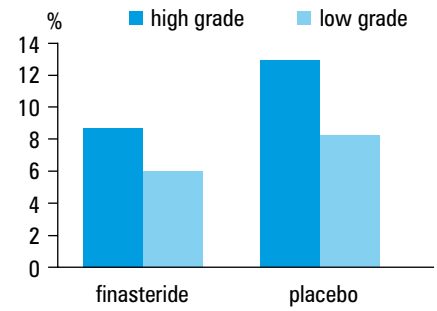
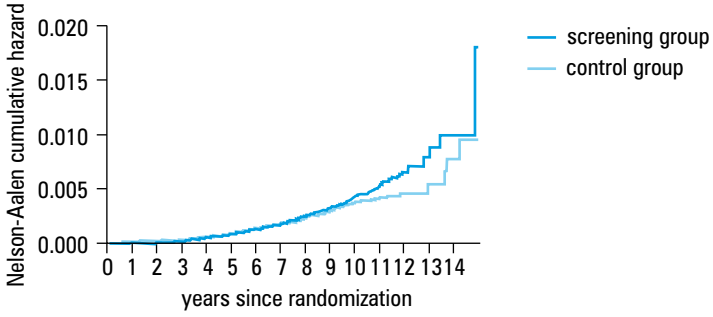


FIGURE 2 Estimated numbers of subjects with low-grade and high-grade cancer in the Prostate Chemoprevention Trial using prostectomy data; among patients on finasteride, 8.7% and 6% developed low-grade and high-grade cancer, respectively, compared with 12.9% and 8.2% for these on placebo.[26]



number of patients at risk

screening group	65,078	58,002	20,288
control group	80,101	73,531	23,758

FIGURE 3 Cumulative risk of death from prostate cancer. As of December 31, 2006, with an avarage follow-up time of 8.8 years, there were 214 prostate-cancer deaths in the screening group and 326 in the control group. Deaths that were associated with interventions were categorized as being due to prostate cancer. The adjusted rate ratio for death from prostate cancer in the screening group was 0.80 (95% CI, 0.65–0.98; p = 0.04). The Nelsen-Aalen method was used for the calculation of cumulative hazard. (from Schröder FH, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. 2009; 360: 1320–1328. Copyright (c) 2009 Massachusetts Medical Society. All rights reserved.)

for initial biopsy after an abnormal digital rectal exam or a PSA 4–10 ng/ml, the same conditions as in the PCPT, except that none were on finasteride. Nearly 500 of them were eventually diagnosed with prostate cancer, 247 of which had an aggressive, high-grade disease. The team found that the smaller the prostate, the more likely a biopsy would result in a diagnosis of high-grade cancer, and the more likely a high PSA level would predict the disease. In men with prostates between 20 cm^3 and 29.9 cm^3, for example, the diagnostic rate for one level of high-grade cancer was 29.7%. For men with prostates larger than 80 cm^3, it was only 6.5%. The authors therefore conclude that a decrease in prostate volume over time and the resultant change in PSA performance characteristics may have contributed a bias toward detection of high-grade disease in the finasteride arm of the PCPT. The relative high-grade prostate cancer proportions are depicted in FIGURE 2.[26]

The prostate cancer prevention benefits of finasteride and the AUA and ASCO guidelines Based on a systematic review of 15 randomized clinical trials, the ASCO Health Services Committee, ASCO Cancer Prevention Committee, and the AUA Practice Guidelines Committee jointly convened a panel of experts, who developed evidence-based recommendations on the use of 5-ARIs for prostate cancer chemoprevention. The guidelines for physicians are summarized below.[5]

1 Inform the man who is considering a 5-ARI that these agents reduce the incidence of prostate cancer, and be sure to be clear that these agents do not reduce the risk of prostate cancer to zero.

2 Discuss the elevated rate of high-grade cancer observed in the PCPT and inform men of the potential explanations.

3 Make it known to men that no information on the long-term effects of 5-ARIs on prostate cancer incidence exists beyond approximately 7 years, and that whether or not a 5-ARI reduces prostate cancer mortality or increases life expectancy remains unknown.

4 Inform men of possible but reversible sexual adverse effects.

5 Inform men of the likely improvement in lower urinary tract symptoms.

So far, the European Association of Urology did not formulate similar guidelines for the prevention of prostate cancer.[4]

Discussion 5-ARIs, which are already used in benign prostate conditions, may play an increasing role in prostate cancer prevention. Moreover, the overlap between benign prostate hyperplasia and prostate cancer may allow a more unified approach to managing these conditions, with 5-ARIs playing a central role.[27] It is clear that 5-ARIs will become increasingly more popular in daily practice.

For an agent to be effective in chemoprevention, it should fulfill several criteria including improved survival, cost-effectiveness, and low morbidity.[28] Studies on benign prostatic hyperplasia demonstrated that side effects are moderate. But the real aim of chemoprevention is to improve survival, and detection rate by prostate biopsy is a surrogate endpoint that has never been validated. Moreover, recent studies from Kaplan et al. seem to confirm that finasterid suppresses especially the more indolent cancers and therefore may be of limited survival benefit. On the other hand, it might be useful to use the drug to determine just how aggressive a particular tumor is. If the patient takes finasteride and has rapidly decreasing PSA levels, he may have a low-risk prostate cancer, treated by "watchful waiting". But with rising PSA levels, a more aggressive treatment may be necessary. However, because these changes in PSA may vary across men, and within individual men over time, a specific cut-off point to trigger a biopsy for men taking a 5-ARI cannot be recommended. This again is an appeal for new prospective randomized trials.[5-29]

Some scientists opposing a routine prevention policy, due to its high costs and low absolute risk reduction figures. In 2005, an economic analysis co-authored by Thompson suggested that "... finasteride is associated with substantial financial costs, and ...even under favorable assumptions, finasteride is likely to have a limited impact on prostate cancer mortality".[30] Drug price and efficacy in preventing cancer play major roles in determining the risk-benefit ratio, and cost-effectiveness must be carefully evaluated prior to mass adoption.[28,30]

Concerning overall prostate cancer survival, prevention and cost-effectiveness, we must not underestimate the importance of the recent randomized controlled trial published by Schröder, who showed a 20% reduction in mortality for

PSA-based screening, although there is a high risk of overdiagnosis. These data coming from 182,000 patients are significantly more relevant than actual 5-ARI outcomes. The cumulative risk of death from prostate cancer is depicted in FIGURE 3.[31] On the other hand, Andriole et al. found no significant difference in the incidence of death per 10,000 person-years in the screening group (2.0% or 50 deaths) compared with 1.7% (44 deaths) in the control group (RR 1.13; 95% CI, 0.75–1.70). After 7 to 10 years of follow-up, the rates were consistent in the 76,693 enrolled patients. The debate continues.[32]

As the AUA and ASCO guidelines stipulate, it is recommended to inform of actual 5-ARI data and to discuss them. This is why asymptomatic men with a low and regularly screened PSA <3.0 ng/ml or men taking 5-ARIs for benign conditions may benefit from a discussion of both the benefits and the potential risks. The actual recommendations are moderate, knowing that more data are needed. One of the ongoing studies, the REDUCE (Reduction by Dutasteride of Prostate Cancer Events) trial, is assessing the dual 5-ARI dutasteride in a population of men at elevated risk of being diagnosed with prostate cancer (PSA level 2.5–10 ng/ml with previously negative biopsy) and has the potential to further elucidate the preventive role of 5-ARIs. Until then, the actual data can be used to identify subgroups. Recently, Gong et al. tried to relate alcohol use and the risk of prostate cancer using the PCPT data. They concluded that heavy daily drinking increased the risk of high-grade prostate cancer and that it made finasteride ineffective in reducing prostate cancer risk. These subgroup analyses may help to tailor our recommendations.[33]

Conclusions 5-ARIs are a treatment option for prostate cancer prevention, but their use has to be discussed and benefit-risk ratio assessed in each individual patient.

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Czy inhibitory 5-α-reduktazy zapobiegają wystąpieniu raka stercza?

Wytyczne American Society of Clinical Oncology i American Urological Association oraz nowsze dane

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finasteryd, inhibitory 5-α-reduktazy, Prostate Cancer Prevention Trial (PCPT), rak gruczołu krokowego, zmniejszenie ryzyka

STRESZCZENIE

Ostatnio zostały opublikowane przez American Society of Clinical Oncology (ASCO) i American Urological Association (AUA) nowe wytyczne dotyczące użycia inhibitorów 5-α-reduktazy (*5-α-reductase inhibitors* – 5-ARIs) w chemoprewencji raka stercza, wzrosło zatem zainteresowanie zastosowaniem 5-ARIs. Analizowano aktualne dowody przemawiające za użyciem 5-ARIs w zapobieganiu raka gruczołu krokowego. Porównywano zatem nowe wytyczne ASCO i AUA z aktualnymi danymi dotyczącymi zastosowania 5-ARIs w zapobieganiu raka stercza. Aktualnie dyskusja o tym, czy zaleca się włączanie 5-ARIs w praktyce codziennej jako czynnika chemoprewencyjnego jest wciąż otwarta.

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Praca wpłynęła: 01.08.2009.
Przyjęta do druku: 01.08.2009.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2009;
119 (10): 648-653
Tłumaczył dr hab. med.
Jacek Jawień