



American Society of Clinical Oncology

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**Clinical Practice Guideline on the Use of
5-alpha Reductase Inhibitors for Prostate
Cancer Chemoprevention**

**American Society of Clinical
Oncology/American Urological Association**

Introduction

- ASCO Health Services Committee, ASCO Cancer Prevention Committee, and the American Urological Association (AUA) Practice Guidelines Committee jointly convened a panel of experts
- American Urological Association (AUA) and ASCO commissioned a Systematic Review, Wilt et al. “*5-alpha reductase inhibitors for prostate cancer chemoprevention: a systematic review of the evidence regarding effectiveness and adverse effects.*” (Cochrane Database of Systematic Reviews)

Guideline Methodology: Systematic Review

- Wilt et al. completed a review and analysis of data published through December 2006
 - ✓ MEDLINE
 - ✓ PreMedline
 - ✓ Cochrane Collaboration Library
 - ✓ Reviews
 - ✓ Personal files

*Additional search in April 2007 of MEDLINE/PreMEDLINE (yielded no relevant results)

Guideline Methodology (cont'd): Panel Members

Barnett Kramer, MD, <i>Co-Chair</i>	National Institutes of Health
Paul Schellhammer, MD, <i>Co-Chair</i>	Eastern Virginia Medical School
Stewart Justman, Ph.D., <i>Patient Representative</i>	University of Montana Liberal Studies
Peter C. Albertsen, MD	University of Connecticut Health Center
William J. Blot, PhD	International Epidemiology Institute
H. Ballentine Carter, MD	Johns Hopkins University
Joseph P. Costantino, PhD	National Surgical Adjuvant Breast and Bowel Project
Jonathan I. Epstein, MD	Johns Hopkins University

Guideline Methodology (cont'd): Panel Members

Paul Godley, MD, PhD	University of North Carolina Chapel Hill
Russell P. Harris, MD	University of North Carolina at Chapel Hill
Timothy J. Wilt, M.D., MPH	University of Minnesota School of Medicine
Janet Wittes, PhD	Statistics Collaborative
Robin Zon, MD	Michiana Hematology Oncology

2008 Recommendations for Use of 5- α Reductase Inhibitors for
Prostate Cancer Chemoprevention

Overarching Clinical Question

Should men routinely be offered a 5-Alpha
Reductase Inhibitor for the
chemoprevention of prostate cancer?

2008 Recommendations for Use of 5- α Reductase Inhibitors for Prostate Cancer Chemoprevention

Clinical Questions

- A. What is the impact of 5- α -reductase inhibitors on the risk of incident prostate cancer, prostate cancer mortality, and overall mortality? Do benefits and harms of 5- α -reductase inhibitors vary among identifiable subpopulations (e.g., age, race/ethnicity, family history, baseline risk for prostate cancer) and by type of 5- α -reductase inhibitor?

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Clinical Questions

- B. Do 5- α -reductase inhibitors have a differential effect on the development of different histologic grades or stages of prostate cancer? Are any such differences likely to modify the curability of prostate cancer when diagnosed? Is the Gleason histologic grading system for prostate cancer applicable to men who are receiving 5- α -reductase inhibitors or other interventions that target the androgen pathway?

2008 Recommendations for Use of 5- α Reductase Inhibitors for Prostate Cancer Chemoprevention

Clinical Questions

- C. What is the impact of 5- α -reductase inhibitors on the need for treatment for benign prostatic disease?
- D. What is the impact of 5- α -reductase inhibitors on quality of life? What are other potential harms and side effects of 5- α -reductase inhibitors? What are other potential benefits of, and indications for, 5- α -reductase inhibitor use (e.g., benign prostatic hyperplasia, male baldness)?
- E. How long should treatment continue for the best outcome (period vs. lifelong)?
- F. What are the future directions of research regarding 5- α -reductase inhibitors for the prevention of prostate cancer?

Primary Source of Evidence

- Prostate Cancer Prevention Trial (PCPT)
- N = 18,882
- Design – endpoint of period prevalence*
- Finasteride administered for 7 years
- Participant characteristics
 - No prior prostate cancer
 - Asymptomatic or, at most, mild lower urologic symptoms
 - PSA < 3 ng/ml
 - Normal DRE

***the proportion of randomized population trial period identified as having prostate cancer over trial period**

2008 Recommendations

Should men routinely be offered a 5- α -reductase inhibitor for the chemoprevention of prostate cancer?

- Asymptomatic men with a PSA ≤ 3.0 who are regularly screened with PSA or are anticipating undergoing annual PSA screening for early detection of prostate cancer may benefit from a discussion of the benefits of 5-ARIs for the prevention of prostate cancer and the potential risks (including the possibility of high-grade prostate cancer) to be able to make a better-informed decision.
- Men who are taking 5- α -reductase inhibitors for benign conditions such as LUTS would benefit from a similar discussion.

Findings

- In a group of 1000 men, treatment with finasteride reduced cases of prostate cancer from 60 to 45; a decrease of 15 cases
- In a group of 1000, treatment with finasteride increased cases of high-grade (Gleason score 8-10) from 18 to 21; an increase of 3 cases
- Both courses above are seven years
- NNT to prevent one case of prostate cancer by treating for 7 years with finasteride = 71

Clinical Questions and Findings

- **Question A:** What is impact on risk of incident prostate cancer, prostate cancer mortality, and/or overall mortality? Are there differences by identifiable subpopulations?
- **Response/Evidence:** Decrease in risk of incident prostate cancer
 - Relative decrease in period prevalence = 26%
 - Absolute risk reduction = 1.4%
- Trials not powered to show mortality difference, no difference found
- No differences found among different races/ethnicities*, ages, baseline risks or family histories of prostate cancer

*The participants of the PCPT, however, were 92% non-Hispanic white

Clinical Questions and Findings

- **Question B:** Are there differential effects on differences in grades/stages? What is applicability of Gleason histologic grading system?
- **Response/evidence:**
 - Secondary analysis of PCPT found increase of 3 cases of high-grade prostate cancer per 1000 men
 - Difference of opinion on explanation of this finding
 - Until the explanation of finding known, decisions regarding the natural history of the disease and decisions regarding treatment interventions should be based on the histologic information obtained on biopsy regardless of 5-ARI status

Clinical Questions and Findings

- **Question C:** What is impact on treatment for benign prostatic disease
- **Response/evidence:**
 - 5-ARIs are established, FDA-approved treatments for symptomatic benign prostatic hyperplasia (BPH).
 - From PCPT
 - Reduces urinary retention – RR = .67
 - Reduces transurethral resection of the prostate (TURP)

Clinical Questions and Findings

- **Question D:** What is impact on QOL? What are other potential benefits/harms, other indications
- **Response/evidence:**
 - Potential Harms:
 - Erectile Dysfunction – 2-4% increase
 - Decreases in ejaculate volume – 1.3-2.9%
 - Gynecomastia – 1.6-3.11%
 - Decreased libido – 1-4%
 - Sexual dysfunction decreases over time
 - Decrease in PSA
 - Male Pattern Baldness – ≥ 50 years, 50% decrease in PSA and 1 mg similar to 5 mgs at 1 year follow-up (single study).

Clinical Questions and Findings

- **Question E:** What is optimal treatment duration?
- **Response/evidence:**
 - Guideline recommends seven year duration for primary prevention for Finasteride (PCPT)
 - Trial using four year administration of dutasteride is ongoing (REDUCE trial)

Please note

- All the men in the PCPT were receiving regular screening for prostate cancer. The impact of 5-alpha reductase inhibitors, including finasteride, on the risk of developing prostate cancer in men who are not being actively screened is therefore not known.

Future Directions of Research on 5-ARIs

- Establish effect on prostate cancer morbidity and mortality
- Establishing optimal dose – 1 mg versus 5 mg
- Find appropriate PSA cut-points for men taking 5-ARIs which would trigger a biopsy
- Establish the role of 5-ARIs for men not actively receiving screening
- Establish the most effective means of communication for men considering the use of a 5-ARI
- Create risk stratification models incorporating molecular data

Interpretive Summary

For the man who wishes periodic monitoring (opportunistic or organized screening), 5-ARI therapy over a 7-year period reduces the period prevalence of for-cause cancer diagnoses by about 25% (relative risk reduction) for an absolute risk reduction of about 1.4%.

Interpretive Summary, cont'd.

Although the majority of the Panel judged that the observed higher incidence of high-grade (Gleason 8-10) cancer in the finasteride group is likely due to confounding factors, the increased incidence of high-grade cancer as a result of induction by the drug cannot be excluded with certainty. Further benefits accruing from the drug are reduction of the risk of urinary retention and need for surgical intervention. Harms include sexual side effects, which usually diminish with time.

Strategies to Improve Doctor-Patient Communication

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;

Strategies to Improve Doctor-Patient Communication, cont'd.

3. Communicate that no information on the long-term effects of 5-ARIs on prostate cancer incidence exists beyond about seven 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 side effects; and
5. Inform men of the likely improvement in lower urinary tract symptoms.

Limitations in Current Literature

- Only one large completed trial that was directly relevant to this guideline – Prostate Cancer Prevention Trial (PCPT)
- PCPT powered to measure incidence, not mortality
- Proportion of prostate cancers decreased by finasteride that are “clinically meaningful” (i.e. morbid and/or life-threatening) is currently unknown
- 92% of PCPT participants were non-Hispanic white
- Changes that occur in standards for PSA thresholds, criteria for biopsy, and biopsy methods

Additional ASCO Resources

- This full text of the guideline, this slide set, and a doctor-patient discussion guide are available at: <http://www.asco.org/guidelines/5ari/>
- Access the cancer.net website for a Patient Guide and other patient-friendly information at <http://www.cancer.net>



ASCO Guidelines

It is important to realize that many management questions have not been comprehensively addressed in randomized trials and guidelines cannot always account for individual variation among patients. A guideline is not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results. Accordingly, ASCO considers adherence to this guideline to be voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, the guideline describes administration of therapies in clinical practice; it cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease and setting for which better therapy is needed. Because guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.