Finasteride to Prevent Prostate Cancer: Should All Men or Only a High-Risk Subgroup Be Treated?

Andrew J. Vickers, Caroline J. Savage, and Hans Lilja

From the Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY.

Submitted April 17, 2009; accepted September 15, 2009; published online ahead of print at www.jco.org on February 1, 2010.

Supported in part by funds from David H. Koch provided through the Prostate Cancer Foundation, the Sidney Kimmel Center for Prostate and Urologic Cancers, and SPORE Grant No. P50-CA92629 from the National Cancer Institute.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

Corresponding author: Andrew J. Vickers, PhD, Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, 307 East 63rd St, New York, NY 10021; e-mail: vickersa@mskcc.org.

© 2010 by American Society of Clinical Oncology

0732-183X/10/2807-1112/\$20.00

DOI: 10.1200/JCO.2009.23.5572

ABSTRACT

Purpose

Finasteride has been shown to reduce the incidence of prostate cancer. Yet the use of finasteride remains low, likely because of the risk of adverse effects. We sought to determine whether prostate-specific antigen (PSA) levels could identify a high-risk subgroup for which the benefits of finasteride treatment outweigh the potential harms.

Patients and Methods

Raw data from the Prostate Cancer Prevention Trial were used to model chemopreventive treatment strategies: treat all men, treat no men, or treat a high-risk subgroup based on PSA level. We weighted the benefits (reduction in cancer rate) and harms (treatment rate) of each strategy using numbers-needed-to-treat thresholds—the maximum number of men a clinician would treat with finasteride to prevent one cancer.

Results

Of 9,058 men, 1,957 were diagnosed with prostate cancer during the 7-year study. For the end point of all cancers, including both for-cause and end-of-study biopsies, the optimal strategy is to treat all or nearly all men. To reduce risk of cancers detected through routine care, treating men with PSA > 1.3 or > 2 ng/mL is optimal. For example, treating only men with PSA > 2 ng/mL reduced the treatment rate by 83% and resulted in a cancer rate only 1.1% higher than treating all men.

Conclusion

Clinicians wishing to reduce the risk of any biopsy-detectable prostate cancer should recommend finasteride to all men. Clinicians who believe that it is unnecessary to prevent all cancers, but that preventing those readily detectable by screening would be desirable, would be best off recommending finasteride only to a high-risk subgroup.

J Clin Oncol 28:1112-1116. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Finasteride, a 5- α -reductase inhibitor, has been shown to be an effective chemopreventive agent for prostate cancer. In the Prostate Cancer Prevention Trial (PCPT), finasteride reduced the risk of prostate cancer by close to 25%.¹ Despite this landmark finding, use of finasteride to prevent cancer in the community remains low.²

One reason for initial caution was an apparent increase in high-grade disease in men taking finasteride: 37% (n = 280) of men taking finasteride versus 22% (n = 237) taking placebo had high biopsy Gleason grades. However, subsequent research has suggested that the relationship between finasteride and high-grade cancer was an artifact related to differential sampling of high-grade disease in small prostate volumes.³ In particular, analysis of radical prostatectomy specimens, which are not

subject to these sampling effects, suggests that finasteride does not induce high-grade disease.⁴

The low use of finasteride in the community may also be because most men are at low risk of morbidity or mortality from prostate cancer: a man has a less than 3% chance of dying from prostate cancer.⁵ For many men, potential adverse effects such as a reduction in libido, however mild,⁶ are experienced immediately and outweigh any reduction in what may seem like a rare and far-distant event.

These considerations may shift for a man who is informed that he is at high risk of prostate cancer. Furthermore, a formal economic analysis has found that finasteride is unlikely to be cost-effective for the entire male population, although it might be cost-effective in a subgroup of high-risk men.⁷ This warrants evaluation of the impact of finasteride in high-risk subgroups.

We have previously shown that a single prostate-specific antigen (PSA) test strongly predicts subsequent prostate cancer in an unscreened population.⁸ This relationship was strengthened for advanced prostate cancers.⁹ Accordingly, we thought it would be possible to define a subgroup at high risk of prostate cancer on the basis of PSA level and possibly other risk factors such as age and family history. This high-risk group would potentially have greater-than-average benefit from treatment with finasteride. A chemoprevention strategy that focused on high-risk men might therefore change the balance between the benefits and harms of finasteride in favor of treatment. In this article, we compare using decision-analytic methods alternative approaches to prostate cancer prevention with finasteride: treating all, treating none, or treating a high-risk subgroup of the population.

PATIENTS AND METHODS

Raw data from the PCPT were obtained for follow-up through March 4, 2003. The PCPT study has been described previously.¹ In brief, men age 55 years and older, with no previous prostate cancer diagnosis, normal digital rectal exam (DRE), and baseline PSA of 3.0 ng/mL or less were randomly assigned to finasteride (5 mg/d) or placebo for 7 years. Men were followed with yearly PSA tests, and biopsies were recommended for men with PSAs higher than 4.0 ng/mL (adjusted in the finasteride arm to account for reduced prostate volume). After 7 years of therapy, all men who were not diagnosed with prostate cancer were asked to consent to an end-of-study biopsy. Written informed consent was obtained according to institutional guidelines. Only men who consented to a biopsy were included in these analyses. Human investigations were performed after approval by the local institution review board.

We hypothesized that the benefit of finasteride treatment, in terms of absolute risk reduction, would be greater among men with a higher risk of prostate cancer. We created logistic regression models to predict prostate cancer based on baseline PSA. PSA was entered with restricted cubic splines with knots at the tertiles. We created separate models for the finasteride and placebo groups and then calculated risk reduction associated with treatment as the difference in risk between groups at each PSA level. CIs were obtained using percentile methods from nonstratified bootstrap resampling with 1,000 replications. All analyses were repeated for two separate end points: risk of any cancer by the end of the study, including cancer on end-of-study biopsy, and risk of cancer found on for-cause biopsy, defined as any biopsy prompted by a PSA measurement above 4 ng/mL or an abnormal DRE.

We used a previously published decision-analytic method¹⁰ to evaluate the optimal chemoprevention strategy. In brief, we first divided PSA levels into approximate quintiles of risk. We then used each quintile as a binary cut point, assuming that men above the risk threshold would be treated, and those below would not. For example, using a PSA cut point of 1.3, we would include 2,838 of 4,687 patients in the control group with PSA ≤ 1.3 and 1,749 of 4,371 patients in the finasteride group with PSA > 1.3, for a total of 4,587 patients whose randomized allocation was consistent with a strategy of treating men with PSA > 1.3 with finasteride. At each quintile, we calculated the treatment rate and cancer rate among only those study participants whose randomized allocation was congruent with the particular treatment allocation.

To compare different treatment strategies, we then calculated a clinical net benefit. A net benefit is benefits minus harms: for chemoprevention, benefit is the reduction in the rate of cancer and harm is associated with giving treatment. Because events and treatments are not on the same scale, we use the numbers-needed-to-treat threshold (NNT_t) to combine them: the NNT_t is the maximum number of men that a doctor would treat with finasteride to prevent one cancer. The clinical net benefit can therefore be calculated as

$$\text{net benefit} = \text{reduction in event rate} - \text{treatment rate} \div \text{NNT}_t$$

In other words, the treatment rate is weighted by a factor related to the degree of harm associated with treatment. All analyses were conducted using STATA 10.0 (STATA, College Station, TX).

Table 1. Summary of Patient Characteristics

Characteristic	Placebo (n = 4,687)		Finasteride (n = 4,371)	
	No.	%	No.	%
Age, years				
Median	62		62	
Range	58-67		59-67	
PSA at baseline, ng/mL				
Median	1.1		1.1	
Range	0.7-1.8		0.7-1.8	
Family history of prostate cancer	794	17	714	16
Race				
White	4,382	93	4,059	93
African American	147	3	154	4
Other	158	3	158	4
Cancer				
For-cause biopsy	550	12	418	10
End-of-study biopsy	609	13	380	9
Total	1,159	25	798	18

NOTE. All values are median (interquartile range) or frequency (proportion). Abbreviation: PSA, prostate-specific antigen.

RESULTS

Of 9,058 men included in our analysis, 1,957 were diagnosed with prostate cancer during the 7-year study: 798 (18.3%) men in the finasteride group and 1,159 (24.7%) men in the placebo group. Baseline PSA, age, race, and family history were similar in finasteride and placebo groups (Table 1).

The overall risk of being diagnosed with cancer during the 7-year study was 21.6% (95% CI, 20.8% to 22.5%). In both groups, approximately half the cancers were detected by a biopsy performed for cause (an elevated PSA and/or abnormal DRE result): 52% (n = 418) and 47% (n = 550) for the finasteride and control groups, respectively; the rest were detected by an end-of-study biopsy. Excluding end-of-study biopsies reduced the cumulative risk of cancer diagnosis during the 7-year study to 10.7% (95% CI, 10.1% to 11.3%). In comparison, Surveillance, Epidemiology, and End Results (SEER) -Medicare estimates the 10-year probability of developing prostate cancer in a 65-year-old man to be 8.1%.¹¹

Fig 1. Absolute risk reduction of all cancers between placebo and finasteride groups predicted by prostate-specific antigen (PSA) at baseline.

Fig 2. Absolute risk reduction of for-cause-detected cancers between placebo and finasteride groups predicted by prostate-specific antigen (PSA) at baseline.

PSA levels were significantly associated with the outcome of all cancers and for-cause cancers ($P < .001$ for both). We calculated predictive accuracy of the models to predict both outcomes: for the prediction of all cancers, the area under the curve (AUC) was 0.663; the AUC for for-cause detected cancer was higher at 0.745.

Figure 1 shows the absolute risk reduction of any cancer for finasteride treatment compared with that in the control group, by baseline PSA. The absolute risk difference initially rises linearly with baseline PSA, suggesting a constant relative risk, but then flattens at high risk. Figure 2 shows the absolute risk reduction of finasteride treatment using cancer detected by for-cause biopsy as the outcome. Absolute risk reduction continues to increase with rising baseline risk.

We divided the data into approximate quintiles according to baseline PSA and determined the clinical net benefit of treating by each of these cut points. For the outcome of all cancers detected (Table 2), it is difficult to justify stratifying the population into risk groups and treating only those at high risk. Given an extremely conservative clinician—one who would treat no more than 10 men to prevent one

cancer—the highest clinical net benefit is obtained from treating only the highest quintile of the population. For all other levels of NNT thresholds, the optimal strategy is to treat either all men at risk or all but the lowest risk quintile.

In contrast, when considering only cancers detected by a for-cause biopsy, there is a clear case for recommending finasteride to some, but not all, men (Table 3): across a range of NNT thresholds, the optimal strategy is to treat either 20% or 40% of the men with the highest PSA level. Providing finasteride to men with a PSA > 1.3 ng/mL reduced the treatment rate by 62% compared with treating all men, with only a small increase in the event rate (from 9.6% to 9.9%). Restricting use of finasteride only to men with a PSA of ≥ 2 ng/mL would, in comparison to treating all men, reduce the treatment rate by 83% and increase the event rate by only 1.1%. This is clearly a preferable strategy except in the unusual case of a clinician who would treat 80 or more men in order to prevent one cancer. Using baseline PSA to decide treatment, one would recommend finasteride to men with PSA > 1.3 ng/mL if it were considered worthwhile to treat at least 30 men in order to prevent one cancer and to men with PSA > 2 ng/mL if it were worth treating between 20 and 25 men. Finasteride should not be used where the NNT threshold is below 20.

We conducted an exploratory analysis to determine whether additional information such as age, family history, or race could improve risk stratification. The additional information only marginally improved the predictive accuracy above that of PSA alone (AUC of 0.674 v 0.663 and 0.754 v 0.745 for models predicting all cancer or for-cause cancers, respectively). Moreover, the conclusion of which treatment strategy was optimal did not change with the additional information. We found no strong reason to use a multivariable model to predict baseline risk in lieu of the simpler approach of stratifying according to baseline PSA.

DISCUSSION

The results of our analysis indicate that risk group stratification for treatment with finasteride is unlikely to be beneficial for preventing all prostate cancers detectable at biopsy. However, if we use as an end

Table 2. Percentage of Men Treated and Percentage With Outcome of All Cancers, According to Treatment Strategies Based on Baseline PSA Cut Points

Treatment	Treatment Rate (%)	Event Rate (%)	Reduction in Event Rate With Treatment (%)	No. Needed to Treat Threshold						
				10	15	20	25	30	35	50
None	0.00	24.73	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
PSA										
> 2	16.84	23.26	1.46	-2.19	3.42	6.23	7.91	9.03	9.84	11.28
> 1.3	38.13	21.74	2.99	-8.20	4.51	10.86	14.67	17.22	19.03	22.30
> 0.9	57.20	20.46	4.27	-14.52	4.55	14.08	19.80	23.61	26.34	31.24
> 0.6	81.00	18.84	5.89	-22.12	4.88	18.38	26.49	31.89	35.74	42.69
All	100.00	18.26	6.47	-35.29	-1.95	14.71	24.71	31.38	36.14	44.71

NOTE. Percentage of men treated and percentage with outcome of all cancers, according to treatment strategies based on baseline PSA cut points. Clinical net benefit, the number of cancers prevented per 1,000 men treated adjusted for the number of treatments, is shown at various numbers needed to treat thresholds for each PSA cut point. The highest clinical net benefit, indicating the optimal strategy, is bolded. As an example, the strategy of treating men with finasteride only if baseline PSA > 0.9 ng/mL would lead to 57.2% of the population being treated and would reduce the rate of prostate cancer by 4.27% compared with no chemoprevention. If it is thought worth treating, say, no more than 35 men to prevent one cancer, this gives a net benefit of $4.27\% - 57.2\% \div 35 = 0.02634$, or 26.34 per thousand. In other words, the strategy of treating only if PSA > 0.9 ng/mL is the equivalent of a strategy that reduced the rate of cancer by about 26 per thousand without requiring any finasteride treatment. The key point is that, for a number needed to treat threshold of 35, a different strategy, treating all men, has a higher net benefit. Therefore, for patients and clinicians who think it would be worth treating 35 men with finasteride to prevent one cancer, the optimal clinical strategy is to offer all men chemoprevention, irrespective of PSA level.

Abbreviation: PSA, prostate-specific antigen.

Table 3. Percentage of Men Treated and Percentage With Outcome of For-Cause Detected Cancer, According to Treatment Strategies Based on Baseline PSA Cut Points

Treatment Strategy	Treatment Rate (%)	Event Rate (%)	Reduction in Event Rate With Treatment (%)	No. Needed to Treat Threshold						
				10	15	20	25	30	35	50
None	0.00	11.73	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
PSA										
> 2	16.84	10.65	1.09	−5.96	−0.35	2.46	4.14	5.26	6.07	7.51
> 1.3	38.13	9.90	1.84	−19.76	−7.05	−0.69	3.12	5.66	7.48	10.74
> 0.9	57.20	9.79	1.94	−37.77	−18.70	−9.17	−3.45	0.36	3.09	7.99
> 0.6	81.00	9.62	2.11	−59.86	−32.86	−19.36	−11.26	−5.86	−2.00	4.94
All	100.00	9.56	2.17	−78.28	−44.95	−28.28	−18.28	−11.62	−6.86	1.72

NOTE. Percentage of men treated and percentage with outcome of for-cause detected cancer, according to treatment strategies based on baseline PSA cut points. Clinical net benefit, the number of cancers prevented per 1,000 men treated adjusted for the number of treatments, is shown at various numbers needed to treat thresholds for each PSA cut point. The highest clinical net benefit, indicating the optimal strategy, is bolded. As an example, the strategy of treating men with finasteride only if baseline PSA > 1.3 ng/ml would lead to 38.13% of the population being treated and would reduce the rate of prostate cancer by 1.84% compared with no chemoprevention. If it is thought worth treating, say, no more than 35 men to prevent one cancer, this gives a net benefit of 1.84% − 38.13% ÷ 35 = 0.0748 (after rounding), or 7.48 per thousand. In other words, the strategy of treating only if PSA > 1.3 ng/ml is the equivalent of a strategy that reduced the rate of cancer by about 7.5 per thousand without requiring any finasteride treatment. The key point is that, for a number needed to treat threshold of 35, this strategy has the highest net benefit. Therefore, for patients and clinicians who think it would be worth treating 35 men with finasteride to prevent one cancer, the optimal clinical strategy is to offer finasteride only to men with a PSA > 1.3 ng/ml. Abbreviation: PSA, prostate-specific antigen.

point cancers that would be found in routine clinical care—biopsy following an elevated PSA or abnormal DRE—we found that the optimal strategy is to treat a subgroup of men at high risk rather than the whole at-risk population. Accordingly, the interpretation of our results, whether finasteride should be used as a chemopreventive for all men or for just a higher risk subgroup, depends on the relative clinical significance of cancers found during the end-of-study biopsy.

One view is that such cancers are no less clinically relevant than those found following an elevated PSA or abnormal DRE. In this view, an important proportion of these cancers would grow and cause symptoms, even if they were not detected by usual screening procedures during the course of the study. Thus, cancers found at end-of-study biopsy constitute a false negative for screening. An alternative view is that few of these cancers are clinically relevant, that is, if a cancer is not large enough to be found by screening, it is unlikely to become apparent during a man's lifetime in the absence of screening. Accordingly, the majority of the cancers found by end-of-study biopsy constituted overdiagnosis.

There are several lines of evidence in favor of this second point of view. The first comes from our own PCPT data: the rate of high-grade cancer was dramatically higher in for-cause biopsies in comparison with end-of-study biopsies. Using data from the control group to avoid the oversampling problems associated with finasteride, only 1.4% of end-of-study biopsies had a Gleason score of 8 or higher compared with 9.9% of for-cause biopsies, a seven-fold difference. This is of particular relevance, given recent data from untreated men suggesting that high Gleason score is the major determinant of prostate cancer–specific mortality.¹² A second line of evidence comes from the European Randomized Trial of Screening for Prostate Cancer (ERSPC). Schröder et al¹³ have used estimates from the PCPT data to calculate that, had all men in the ERSPC Rotterdam section been biopsied at study entry, 3,472 prostate cancers would have been detected. However, with 12 years of follow-up, only 620 screen-detected and 80 interval cancers have been found. It is difficult to see a cancer as being clinically relevant if it does not emerge during more than 10 years of follow-up. Third, data from an unscreened Swedish cohort has shown a strong association between PSA and subsequent prostate cancer. In particular, in a subset analysis of

men with prostate cancers of unquestionable clinical significance—clinical stage T3 or T4 or metastatic disease—PSA had a high predictive accuracy (concordance index of 0.848).⁸ This suggests that low-PSA tumors are unlikely to become clinically relevant.

An additional reason to focus on for-cause biopsies concerns the value of finasteride for preventing morbidity related to treatment, even if the treatment is for cancers of low malignant potential. Because it is screen-detected cancers that lead to treatment—necessary or otherwise—it is the effects of finasteride on cancers detected by screening that should interest us.

One argument against focusing on the for-cause biopsies is that finasteride lowers PSA. Accordingly, the apparent effects of finasteride may simply be a case of verification bias¹⁴: some men who have cancer and have PSA levels that would be slightly over the biopsy threshold have PSA lowered by finasteride, are not biopsied, and are therefore not counted as cancer cases. However, if this were the case, we would expect there to be a smaller difference in cancer rates for end-of-study biopsies in comparison to the for-cause biopsies, yet the opposite was true (relative risk ≈ 0.65 and 0.8 respectively).

Finasteride has two additional benefits that we did not formally model in this study. First, finasteride improves the accuracy of the PSA test,¹⁵ suggesting that it should be used more widely in men undergoing PSA screening. However, we found large differences in clinical net benefit between the optimal strategy identified for preventing for-cause cancer and a more expanded use of finasteride. For example, if a physician would treat no more than 30 patients with finasteride to prevent one cancer, the optimal strategy is to prescribe finasteride to men with PSA > 1.3 ng/mL. To expand finasteride treatment to men with PSA > 0.9 ng/mL would be the equivalent of treating an additional 150 men per 1,000 with no additional for-cause cancers prevented. It is unclear whether the salutary effects of finasteride on the PSA test warrant such a large increase in treatment rates. A second benefit of finasteride that we did not model is that it is of proven value for treating benign prostate enlargement.¹⁶ We believe that this is not pertinent to the aim of this article: we focus on prevention of prostate cancer. Any clinical reason to take finasteride for treatment of benign disease would override considerations of chemoprevention.

The harms of finasteride are open to debate, which is why we report results for a range of NNT thresholds. The primary adverse effect is decreased sexual function. The authors of the PCPT reported a carefully conducted, longitudinal study of sexual function during the trial.⁶ Finasteride was associated with statistically significant but small reductions in sexual functioning. After 6 months of treatment, patients taking finasteride scored 3.2 points lower than controls from a mean close to 50 on a 100-point sexual functioning scale; this difference was slightly attenuated over time. Although it is clearly a small effect, we do not think it can be ignored. As a simple illustration, if we were prepared to treat 20 patients with finasteride to prevent one prostate cancer, the total effect on sexual function (20×3) would be the equivalent of making one patient totally impotent; suffice it to say that total impotence is far from an inevitable result of treatment for prostate cancer.

Our study has several strengths. First, we analyzed raw data from a randomized trial. This allows us to draw conclusions that do not depend on assumptions about the relationship between absolute and relative risk.¹⁷ Second, we simulated the effects of various chemoprevention strategies at the population level. Third, in contrast to a previous paper examining the association between baseline risk and the effect of finasteride,¹⁸ we focus on absolute rather than relative risk reduction, because it is only the former that can be used to make medical decisions. Fourth, we used a decision-analytic approach that allows us to directly compare the clinical impact of different strategies and determine which would be optimal.

That said, our study has several limitations. Our follow-up remains relatively limited, and we have yet to obtain a full picture of the study cohort, particularly in terms of the clinical effects of prostate cancer. A tumor in the prostate is not in itself a medical problem, even if it can and often does lead to iatrogenic morbidity. It is arguable that our end point, like that of the PCPT, is essentially a surrogate outcome. In this respect, it is better to have a stronger surrogate than a weaker one. There is widespread agreement that tumors with high Gleason scores are a strong indication of a poor clinical outcome, and there is little doubt that it would be of value to prevent such tumors. Yet because of differential biopsy sampling in finasteride-treated prostates,

we were unable to model the effects of treatment on high Gleason score disease.

In conclusion, clinicians wishing to reduce the risk of any biopsy-detectable prostate cancer should recommend finasteride to all men. Clinicians who believe that it is unnecessary to prevent all cancers, but that preventing those readily detectable by screening would be desirable, would be best off recommending finasteride only to a high-risk subgroup. Depending on clinicians' or patients' views about the harms of finasteride, high risk could be defined by either 2 ng/mL or 1.3 ng/mL, constituting either approximately 20% or 40% of the population of eligible age.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** Hans Lilja, Arctic Partners Oy **Honoraria:** Andrew J. Vickers, GlaxoSmithKline; Hans Lilja, GlaxoSmithKline **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Andrew J. Vickers, Hans Lilja
Financial support: Andrew J. Vickers, Hans Lilja
Administrative support: Caroline J. Savage
Collection and assembly of data: Andrew J. Vickers, Caroline J. Savage
Data analysis and interpretation: Andrew J. Vickers, Caroline J. Savage
Manuscript writing: Andrew J. Vickers, Caroline J. Savage
Final approval of manuscript: Andrew J. Vickers, Caroline J. Savage

REFERENCES

- Thompson IM, Goodman PJ, Tangen CM, et al: The influence of finasteride on the development of prostate cancer. *N Engl J Med* 349:215-224, 2003
- Goetzl MA, Holzbeierlein JM: Finasteride as a chemopreventive agent in prostate cancer: Impact of the PCPT on urologic practice. *Nat Clin Pract Urol* 3:422-429, 2006
- Kulkarni GS, Al-Azab R, Lockwood G, et al: Evidence for a biopsy derived grade artifact among larger prostate glands. *J Urol* 175:505-509, 2006
- Lucia MS, Epstein JI, Goodman PJ, et al: Finasteride and high-grade prostate cancer in the Prostate Cancer Prevention Trial. *J Natl Cancer Inst* 99:1375-1383, 2007
- Jemal A, Siegel R, Ward E, et al: Cancer statistics, 2009. *CA Cancer J Clin* 59:225-49, 2009
- Moinpour CM, Darke AK, Donaldson GW, et al: Longitudinal analysis of sexual function reported by men in the Prostate Cancer Prevention Trial. *J Natl Cancer Inst* 99:1025-1035, 2007
- Svatek RS, Lee JJ, Roehrborn CG, et al: Cost-effectiveness of prostate cancer chemoprevention: A quality of life-years analysis. *Cancer* 112:1058-1065, 2008
- Lilja H, Ulmert D, Björk T, et al: Long-term prediction of prostate cancer up to 25 years before diagnosis of prostate cancer using prostate kallikreins measured at age 44 to 50 years. *J Clin Oncol* 25:431-436, 2007
- Ulmert D, Cronin AM, Björk T, et al: Prostate-specific antigen at or before age 50 as a predictor of advanced prostate cancer diagnosed up to 25 years later: A case-control study. *BMC Med* 6:6, 2008
- Vickers AJ, Kramer BS, Baker SG: Selecting patients for randomized trials: a systematic approach based on risk group. *Trials* 7:30, 2006
- Fast Stats: An interactive tool for access to SEER cancer statistics: Surveillance Research Program, National Cancer Institute. <http://seer.cancer.gov/faststats>
- Kattan MW, Cuzick J, Fisher G, et al: Nomogram incorporating PSA level to predict cancer-specific survival for men with clinically localized prostate cancer managed without curative intent. *Cancer* 112:69-74, 2008
- Schröder FH, Bangma CH, Roobol MJ: Is it necessary to detect all prostate cancers in men with serum PSA levels < 3.0 ng/mL? A comparison of biopsy results of PCPT and outcome-related information from ERSPC. *Eur Urol* 53:901-908, 2008
- Cronin AM, Vickers AJ: Statistical methods to correct for verification bias in diagnostic studies are inadequate when there are few false negatives: A simulation study. *BMC Med Res Methodol* 8:75, 2008
- Thompson IM, Chi C, Ankerst DP, et al: Effect of finasteride on the sensitivity of PSA for detecting prostate cancer. *J Natl Cancer Inst* 98:1128-1133, 2006
- Naslund MJ, Miner M: A review of the clinical efficacy and safety of 5alpha-reductase inhibitors for the enlarged prostate. *Clin Ther* 29:17-25, 2007
- Baker SG, Kramer BS, Corle D: The fallacy of enrolling only high-risk subjects in cancer prevention trials: Is there a "free lunch"? *BMC Med Res Methodol* 4:24, 2004
- Thompson IM, Tangen CM, Parnes HL, et al: Does the level of prostate cancer risk affect cancer prevention with finasteride? *Urology* 71:854-857, 2008