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Prostate Cancer

Effect of Dutasteride on Prostate Biopsy Rates and the Diagnosis of Prostate Cancer in Men with Lower Urinary Tract Symptoms and Enlarged Prostates in the Combination of Avodart and Tamsulosin Trial

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Abstract

Background: A 23% relative risk reduction (RRR) in prostate cancer (PCa) was shown in men receiving dutasteride in the 4-yr Reduction by Dutasteride of Prostate Cancer Events study, in whom biopsies were protocol dependent.
Objective: Our aim was to explore PCa risk reduction in men with benign prostatic hyperplasia (BPH) from the Combination of Avodart and Tamsulosin (CombAT) study, in which biopsies were undertaken for cause.
Design, setting, and participants: CombAT was a 4-yr randomized double-blind parallel group study in 4844 men ≥50 yr of age with clinically diagnosed moderate to severe BPH, International Prostate Symptom Score ≥12, prostate volume ≥30 ml, and serum prostate-specific antigen (PSA) 1.5–10 ng/ml. Men underwent annual PSA measurement and digital rectal examination (DRE), and prostate biopsies were performed for cause.
Intervention: All patients took tamsulosin 0.4 mg/d, dutasteride 0.5 mg/d, or a combination of both.
Measurements: The primary end point was incidence of PCa. Secondary end points included postbaseline prostate biopsy rates and Gleason score of cancers.
Results and limitations: Dutasteride (alone or in combination with tamsulosin) was associated with a 40% RRR of PCa diagnosis compared with tamsulosin monotherapy (95% confidence interval, 16–57%; $p = 0.002$) and a 40% reduction in the likelihood of biopsy. There were similar reductions in low- and high-grade Gleason score cancers. The biopsy rate in the groups receiving dutasteride trended toward a higher diagnostic yield (combination: 29%, dutasteride: 28%, tamsulosin: 24%). One limitation was the lack of a standardized approach to PCa diagnosis and grading.
Conclusions: Dutasteride, alone or in combination with tamsulosin, significantly reduced the relative risk of PCa diagnosis in men with BPH undergoing annual DRE and PSA screening. Consistent with the increased usefulness of PSA for PCa detection, men receiving dutasteride had a numerically lower biopsy rate and higher yield of PCa on biopsy.
Trial registration: Clinicaltrials.gov identifier: NCT00090103 (http://www.clinicaltrials.gov/ct2/show/NCT00090103).

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1. Introduction

Clinical studies provide significant evidence supporting the use of 5α-reductase inhibitors (5-ARIs) to reduce the risk of prostate cancer (PCa). The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study showed a 23% relative risk reduction (RRR) of PCa with dutasteride in men at increased risk for PCa (prostate-specific antigen [PSA] ≥2.5 ng/ml) and negative baseline prostate biopsy [1]. In the Prostate Cancer Prevention Trial (PCPT), men treated with finasteride experienced a 24.8% reduction in the prevalence of PCa over 7 yr [2].

In clinical practice, men are typically monitored with annual PSA testing and digital rectal examination (DRE), and they only undergo prostate biopsy if indicated clinically. The Combination of Avodart and Tamsulosin (CombAT) trial provided an opportunity to investigate the effect of dutasteride on PCa risk reduction in a typical clinical setting. CombAT assessed whether dutasteride and tamsulosin combination therapy was superior to monotherapy in improving symptoms and long-term clinical outcomes in men with moderate to severe symptoms of benign prostatic hyperplasia (BPH) [3]. The purpose of the present study was to investigate the effect of dutasteride on the risk of PCa diagnosis in the CombAT trial.

2. Patients and methods

2.1. Study participants

CombAT recruited men ≥50 yr of age with a clinical diagnosis of BPH based on medical history and physical examination, International Prostate Symptom Score (IPSS) ≥12, prostate volume ≥30 ml by transrectal ultrasound (TRUS), total serum PSA 1.5–10.0 ng/ml, and urinary maximum flow rate >5 ml/s and ≤15 ml/s.

Patients with a history or evidence of PCa were excluded. However, patients with a suspicious ultrasound or DRE who had a negative biopsy during the preceding 6 mo and stable PSA were eligible. Additional exclusion criteria included a total serum PSA >10 ng/ml, previous prostatic surgery, history of acute urinary retention (AUR) within the 3 mo before study entry, or use of finasteride within 6 mo, dutasteride within 12 mo, or an α-blocker or phytotherapy within 2 wk before entry [3,4].

2.2. Study design

The CombAT study design has been reported [3]. This was a 4-yr multicenter randomized double-blind parallel group study. Eligible subjects were randomized to one of three treatment groups: combination therapy with dutasteride (0.5 mg) and tamsulosin (0.4 mg), dutasteride monotherapy (0.5 mg), or tamsulosin monotherapy (0.4 mg). The study was conducted in 35 countries; within each country/cluster, subjects were evenly distributed across the treatment groups.

TRUS-guided biopsy was performed based on the investigator's judgment of a clinically significant event, such as an adverse change in DRE, rise in PSA, or nodular areas detected on TRUS. A PSA value or change was not specified to guide biopsy decisions; the study thus reflects routine clinical practice regarding PCa detection.

Biopsy tissue was evaluated by local pathology laboratories. Upon positive biopsy, Gleason score and biopsy characteristics were recorded; Gleason scores were also noted for cancer diagnosed during BPH-related prostatic surgery.

2.3. End points and statistical analyses

The primary end point of the CombAT study at year 4 was the time to AUR or BPH-related surgery. The primary end point at year 2 was a change in the IPSS.

Detection of PCa was investigated as an adverse event. Time to first PCa diagnosis was summarized by treatment group using product-limited estimates calculated by the Kaplan-Meier method and displayed graphically as Kaplan-Meier curves. Comparisons of combination therapy versus monotherapy were performed using a log-rank test. Relative risk estimates for treatment effect and corresponding 95% confidence intervals (CIs) were calculated using a Cox univariate proportional hazard model.

Additional comparisons represent post hoc analyses based on the safety data set for the intent-to-treat population (all subjects randomized to treatment; $n = 4844$). Gleason scores were compared between the treatment groups using the F test. Baseline characteristics of men with and without PCa were compared using the Wilcoxon rank sum test for age, PSA, prostate volume, IPSS, and body mass index; race and family history were compared using the Fisher exact test. Characteristics of positive biopsies were compared using the F test.

The post hoc analysis included pooled data from the dutasteride arms. Values are reported in the results as medians with interquartile ranges, except where indicated. A p value of 0.05 designates statistical significance.

3. Results

3.1. Subject disposition and demographics

Demographic characteristics of the patient population have been reported [5]. Briefly, 4844 men with symptomatic BPH were randomized to treatment, and 3195 (66%) completed the month 48 visit. Key PCa-related characteristics at baseline were similar between treatment groups (Table 1).

Table 1 – Baseline participant characteristics by treatment group

Parameter	Combination ($n = 1610$)	Dutasteride ($n = 1623$)	Tamsulosin ($n = 1611$)
Age, yr	66 (61–71)	66 (61–71)	66 (61–71)
White race, n (%)	1421 (88)	1433 (88)	1405 (87)
Family history of PCa, n (%)	137 (9)	151 (10)	129 (8)
Serum PSA, ng/ml	3.4 (2.4–5.1)	3.4 (2.3–5.1)	3.6 (2.4–5.2)
Total prostate volume, ml	48.9 (39.2–63.2)	48.4 (38.5–63.2)	49.6 (38.6–65.0)
IPSS	16 (12–21)	16 (12–20)	16 (12–20)
BMI, kg/m^2 [3]	26.9 (24.7–29.6)	26.7 (24.6–29.4)	26.9 (24.8–29.4)

BMI = body mass index; IPSS = International Prostate Symptom Score; PCa = prostate cancer; PSA = prostate-specific antigen.
Values reported as medians (interquartile range), except where indicated; differences among groups were not statistically significant ($p > 0.05$).

Table 2 – Postbaseline biopsies by treatment group, including reasons for biopsy

	Combination	Dutasteride	Tamsulosin
Subjects with postbaseline biopsies, *n* (%)	115 (7.1)	143 (8.8)	214 (13.3)
No. of postbaseline prostate biopsies*	123	163	253
Reason for biopsy, *n* (%)**			
PSA	90 (73.2)	113 (69.3)	203 (80.2)
TRUS	10 (8.1)	8 (4.9)	10 (4.0)
DRE	20 (16.3)	33 (20.2)	30 (11.9)
Other	2 (1.6)	8 (4.9)	9 (3.6)
Missing	1 (0.8)	1 (0.6)	1 (0.4)

DRE = digital rectal examination; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.
* Subjects may have undergone more than one biopsy.
** Percentages are based on the number of postbaseline biopsies.

3.2. Postbaseline prostate biopsy rates

Over 4 yr, 539 for-cause prostate biopsies were performed in 472 subjects, with 60 patients having more than one biopsy. More men in the tamsulosin group underwent prostate biopsy (214 of 1611: 13.3%) than in the combination group (115 of 1610: 7.1%; $p < 0.0001$) or dutasteride group (143 of 1623: 8.8%; $p < 0.0001$); men who received dutasteride alone or in combination had a 40% reduction in the likelihood of biopsy (95% CI, 29–49%; $p < 0.0001$). Most men were referred for biopsy based on elevated serum PSA (Table 2).

3.3. Prostate cancer detection

PCa was detected in 37 of 1610 men in the combination group (2.3%), 42 of 1623 in the dutasteride group (2.6%), and 63 of 1611 in the tamsulosin group (3.9%); 34, 39, and 55 of the cancers, respectively, were found in men with a baseline serum PSA $\geq$2.5 ng/ml. Most PCa cases were diagnosed on for-cause biopsy rather than as a result of BPH-related surgery; PCa was detected during BPH-related surgery in three, two, and eight men from the dutasteride, combination, and tamsulosin groups, respectively.

Among patients who underwent for-cause biopsies, 29% (33 of 115) were positive for PCa in the combination group, 28% (40 of 143) in the dutasteride group, and 24% (51 of 214) in the tamsulosin group ($p = 0.54$). Of these men, PSA was the indication for biopsy in 67% (22 of 33) in the combination group, 55% (22 of 40) in the dutasteride group, and 80% (41 of 51) in the tamsulosin group. DRE triggered biopsies in 15% (5 of 33), 28% (11 of 40), and 10% (5 of 51), respectively.

Time to PCa diagnosis was longer in favor of the combination and dutasteride groups compared with the tamsulosin group (combination vs tamsulosin, $p = 0.006$; dutasteride vs tamsulosin, $p = 0.021$); the combination and the dutasteride groups were similar (Fig. 1). Pooling the dutasteride arms, there was a 1.5% absolute risk reduction and a 40% RRR versus tamsulosin (95% CI, 16–57%; $p = 0.002$). The PCa RRR was 43% (95% CI, 15–62%) for combination therapy versus tamsulosin monotherapy and 37% (95% CI, 6–57%) for dutasteride versus tamsulosin.

3.4. Gleason scores for prostate cancer diagnoses

Gleason scores were available for 94% (134 of 142) of PCa cases (35 combination, 41 dutasteride, 58 tamsulosin). Mean Gleason scores were 6.3 ± 1.09 in the combination group, 6.8 ± 1.12 in the dutasteride group, and 6.7 ± 1.29 in the tamsulosin group ($p = 0.12$). Over the 4-yr study there were numerically fewer Gleason score 7 and Gleason score 8–10 tumors in the dutasteride groups combined, compared with the tamsulosin group (Fig. 2). These results were similar when examined by time period for years 1–2 and years 3–4.

3.5. Comparison of baseline characteristics of men with and without prostate cancer

Baseline characteristics were similar between men who did and did not have PCa diagnosed during the study (Table 3);

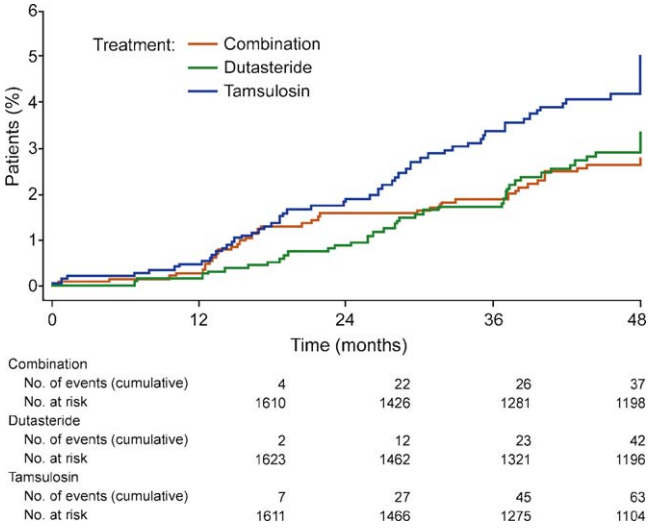

Fig. 1 – Time to prostate cancer adverse effect by treatment group. Kaplan-Meier graph for time to prostate cancer diagnosis by treatment group. Time to prostate cancer was significantly longer for combination therapy versus tamsulosin monotherapy ($p = 0.006$) and dutasteride monotherapy versus tamsulosin monotherapy ($p = 0.021$). The relative risk reduction (RRR) was 43% for combination versus tamsulosin (95% confidence interval [CI], 15–62%) and 37% for dutasteride versus tamsulosin (95% CI, 6–57%). When results from the dutasteride arms were pooled, there was a 1.5% absolute risk reduction and a 40% RRR versus tamsulosin (95% CI, 16–57%; $p = 0.002$).

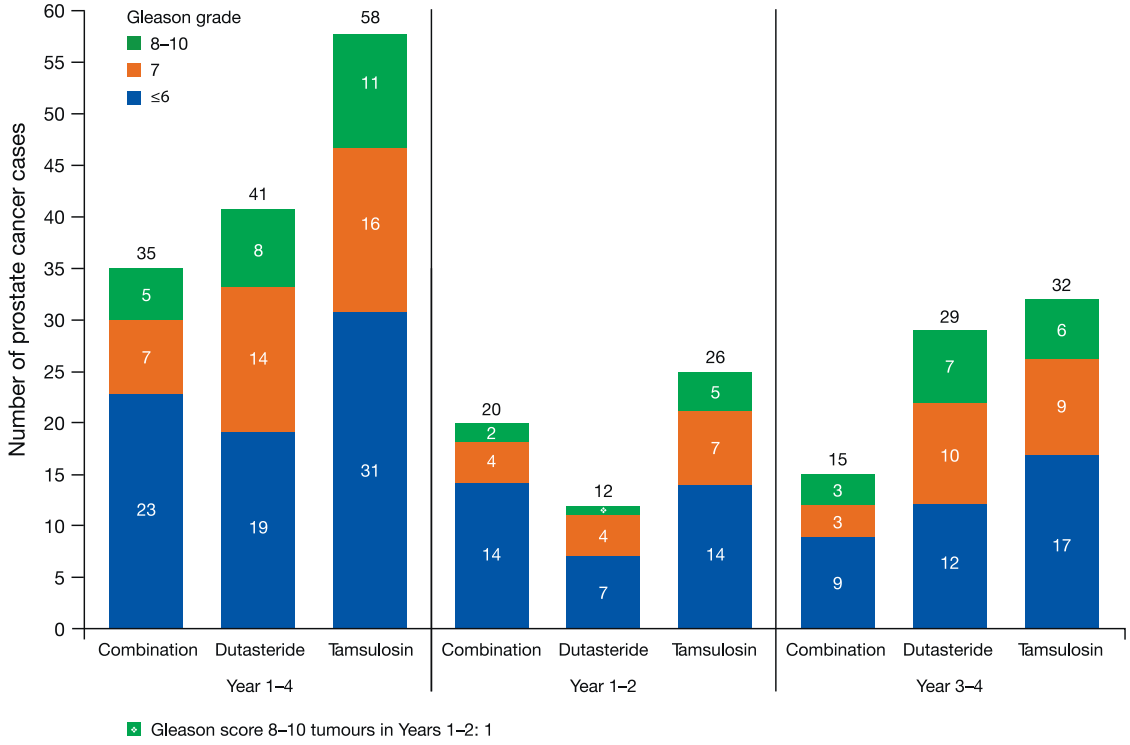

Fig. 2 – Gleason score of prostate cancer diagnosed in the CombAT study. Number of prostate cancer cases and Gleason score distribution by treatment group and time period. Numbers above bars indicate total number of cancers detected by treatment group; numbers within bars report occurrence by Gleason score.

Table 3 – Baseline characteristics of men with and without a diagnosis of prostate cancer

Parameter	Subjects diagnosed with PCa ($n = 142$)	Subjects not diagnosed with PCa ($n = 4702$)	p value
Age, yr	66.5 (61–73)	66 (61–71)	0.16
Family history of PCa, %	11	9	0.45
White race, %	87	88	0.79
Serum PSA, ng/ml	4.7 (3.45–6.85)	3.4 (2.3–5.1)	<0.0001
Total prostate volume, ml	47.7 (37.1–58.9)	49.0 (38.8–64.0)	0.16
IPSS	16 (12–19)	16 (12–20)	0.20
BMI, kg/m^2 [3]	26.9 (24.8–29.2)	26.8 (24.7–29.4)	0.97

BMI = body mass index; IPSS = International Prostate Symptom Score; PCa = prostate cancer; PSA = prostate-specific antigen.
Values reported as medians (interquartile range), except where indicated. Continuous parameters compared using the Wilcoxon rank sum test; categorical parameters compared using the Fisher exact test.

however, baseline PSA levels were higher in men diagnosed with PCa compared with men not diagnosed with PCa (4.7 ng/ml vs 3.4 ng/ml; $p < 0.0001$), with no differences between treatment groups.

3.6. *Characteristics of positive prostate cancer biopsies*

The mean number of cores obtained at biopsy was similar in all treatment groups (combination: 10.4 ± 3.95, dutasteride: 11.3 ± 6.20, tamsulosin: 11.0 ± 5.82; $p = 0.76$), and the mean number of positive cores was also similar (combination: 3.2 ± 3.09, dutasteride: 3.2 ± 2.67, tamsulosin: 3.1 ± 2.27; $p = 0.98$). Mean percentage core involvement with cancer was numerically greater in the combination and dutasteride groups than in the tamsulosin group (27.7% ± 25.41 and 26.7% ± 26.38 vs 21.3% ± 19.33; $p = 0.46$).

4. Discussion

In this group of men with BPH, treatment with dutasteride alone or in combination with tamsulosin resulted in a 40% RRR in PCa diagnosis compared with tamsulosin monotherapy over the 4-yr study (combination therapy vs tamsulosin: 43%, $p = 0.006$; dutasteride monotherapy vs tamsulosin: 37%, $p = 0.021$; Fig. 1). This reduction in PCa with dutasteride, alone or in combination, was evident across all Gleason scores.

The CombAT study provides additional insight into the effects of dutasteride on PCa risk reduction and PSA utility. Similar to the present analysis, the effect of dutasteride on PCa rates was investigated in men from three large phase 3 BPH trials [6]. In these trials, men with BPH who received dutasteride experienced a 51% RRR in PCa versus placebo

over 27 mo. Men in both the CombAT and phase 3 BPH trials experienced significant reductions in the relative risk of biopsy-detectable PCa; however, the corresponding absolute risk reductions were low (1.3–1.6%). In the REDUCE study and PCPT, the larger 5–6% absolute risk reductions in biopsy-detectable PCa likely reflect the study design in which all subjects received a biopsy [1,2].

Results from the REDUCE study and PCPT have raised questions related to the diagnosis of high-grade tumors in men taking a 5-ARI. Initial results from the 7-yr PCPT demonstrated an increased prevalence of Gleason score 7–10 PCa in men treated with finasteride compared with placebo [2]. There was no significant increase in Gleason score 7–10 tumors in the REDUCE study; however, there was an increase in Gleason 8–10 tumors over the 4-yr study period [1]. In the CombAT study, the reduction in PCa with combination therapy and dutasteride monotherapy versus tamsulosin in the CombAT study was evident across all Gleason scores (Fig. 2). Thus the CombAT findings suggest that dutasteride had a beneficial effect on at least some high-grade cancers, similar to what has been seen in logistic regression analyses accounting for prostate volume and other potential sources of bias in both the REDUCE and PCPT trials [1,7–9].

Men treated with dutasteride (alone or in combination) in the CombAT study underwent fewer biopsies. Therefore the reduction in PCa in the dutasteride arms of CombAT was largely due to a reduction in biopsies. To interpret the significance of PCa risk reduction with dutasteride in CombAT, it is important to note the improved usefulness of PSA to detect PCa in men taking 5-ARIs [10–12]. Although the diagnosis of PCa in CombAT was lower in men treated with dutasteride (alone or in combination), the chances of cancer detection on PSA-driven biopsies were numerically higher in the dutasteride arms (28–29%) than in the tamsulosin arm (24%). The reduced indication for biopsy may have resulted from the effect of dutasteride on the volume and behavior of cancer, leading to decreased secretion of PSA from such cancers and a reduced chance of an abnormal DRE. In men whose PSA was rising in the dutasteride arm, the likelihood of PCa detection on biopsy increased.

The CombAT study population consisted of men with moderate to severe symptoms of BPH; therefore, these findings are most relevant to a comparable patient population. Men eligible for CombAT were also at an increased risk for PCa based on a baseline PSA level of $\geq$1.5 ng/ml. This level was recently reported as marking an above-average risk for PCa diagnosis over 4 yr because men with PSA $\geq$1.5 ng/ml were at significantly greater risk compared with men with baseline PSA $<$ 1.5 ng/ml (odds ratio: 7.47; $p < 0.001$) [13]. Therefore findings from CombAT might also be considered within the context of men with an above-average baseline risk of PCa.

The CombAT study design allowed investigation of PCa risk reduction in a typical clinical scenario, in which men were screened annually (PSA measurement and DRE) and PCa was primarily detected in for-cause biopsies. However, investigation of PCa risk reduction in this setting has a few limitations. Participants were evaluated at study entry for clinically detectable PCa; however, there was no baseline biopsy to rule out otherwise undiagnosed PCa. At autopsy, approximately 50% of men >50 yr have PCa [14]. Therefore some men entered the CombAT study with undiagnosed biopsy-detectable PCa; the presumption is that cancers discovered in CombAT were likely present at baseline (some were potentially biopsy detectable, whereas others were likely small and unlikely to have been detected on biopsy). Based on PCa doubling times, it is also unlikely that a new cancer would form and become biopsy detectable within the 4-yr study period. Thus the RRR seen with dutasteride probably resulted from prevention of PCa growth and/or shrinkage of existing cancers.

CombAT did not have a standardized approach to diagnose and grade PCa, either through biopsy methodology or central review of biopsy samples. Because this was a global trial, different approaches may have been used to determine what PSA change was an indication for biopsy. CombAT also did not include a placebo group. Although tamsulosin is not expected to have an effect on PCa detection, the reduction in PCa diagnosis is relative to the tamsulosin arm rather than a placebo group.

5. Conclusions

This study offers useful insight into PCa detection in a common clinical situation where men with BPH undergo annual PSA and DRE screening. Dutasteride treatment, either alone or in combination with tamsulosin, was associated with a reduction in the number of PCa biopsies and a 40% RRR of PCa versus tamsulosin with similar reductions in low- and high-grade tumors.

These data support the value of dutasteride in daily clinical practice. Beyond the reduction in PCa detection, the improvement in PSA performance with dutasteride treatment may also result in a lower rate of unnecessary biopsies, a higher biopsy diagnostic yield, and easier identification of cancers likely to be relevant to the practicing clinician.

Author contributions: Claus Roehrborn had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Roehrborn, Andriole, Wilson, Castro, Rittmaster.
Acquisition of data: Roehrborn, Andriole, Wilson, Castro, Rittmaster.
Analysis and interpretation of data: Roehrborn, Andriole, Wilson, Castro, Rittmaster.
Drafting of the manuscript: Roehrborn, Andriole, Wilson, Castro, Rittmaster.
Critical revision of the manuscript for important intellectual content: Roehrborn, Andriole, Wilson, Castro, Rittmaster.
Statistical analysis: Wilson.
Obtaining funding: Rittmaster.
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Supervision: Castro, Rittmaster.
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References

[1] Andriole GL, Bostwick DG, Brawley OW, et al. Effect of dutasteride on the risk of prostate cancer. N Engl J Med 2010;362:1192–202.
[2] Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. N Engl J Med 2003;349:215–24.
[3] Siami P, Roehrborn CG, Barkin J, et al. Combination therapy with dutasteride and tamsulosin in men with moderate-to-severe benign prostatic hyperplasia and prostate enlargement: the CombAT (Combination of Avodart and Tamsulosin) trial rationale and study design. Contemp Clin Trials 2007;28:770–9.
[4] Roehrborn CG, Boyle P, Nickel JC, Hoefner K, Andriole G. Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. Urology 2002;60:434–41.
[5] Roehrborn CG, Siami P, Barkin J, et al. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. Eur Urol 2010;57:123–31.
[6] Andriole GL, Roehrborn C, Schulman C, et al. Effect of dutasteride on the detection of prostate cancer in men with benign prostatic hyperplasia. Urology 2004;64:537–41, discussion 542–3.
[7] Lucia MS, Epstein JI, Goodman PJ, et al. Finasteride and high-grade prostate cancer in the Prostate Cancer Prevention Trial. J Natl Cancer Inst 2007;99:1375–83.
[8] Cohen YC, Liu KS, Heyden NL, et al. Detection bias due to the effect of finasteride on prostate volume: a modeling approach for analysis of the Prostate Cancer Prevention Trial. J Natl Cancer Inst 2007;99:1366–74.
[9] Pinsky P, Parnes H, Ford L. Estimating rates of true high-grade disease in the prostate cancer prevention trial. Cancer Prev Res (Phila) 2008;1:182–6.
[10] Andriole GL, Bostwick DG, Brawley O, et al. The utility of PSA for detection of prostate cancer in men treated with dutasteride: results from the REduction by DUtasteride of prostate Cancer Events (REDUCE) study. J Mens Health 2009;6:269.
[11] Thompson IM, Chi C, Ankerst DP, et al. Effect of finasteride on the sensitivity of PSA for detecting prostate cancer. J Natl Cancer Inst 2006;98:1128–33.
[12] Etzioni RD, Howlader N, Shaw PA, et al. Long-term effects of finasteride on prostate specific antigen levels: results from the prostate cancer prevention trial. J Urol 2005;174:877–81.
[13] Schroder FH, Roobol MJ, Andriole GL, Fleshner N. Defining increased future risk for prostate cancer: evidence from a population based screening cohort. J Urol 2009;181:69–74, discussion 74.
[14] Sakr WA, Grignon DJ, Crissman JD, et al. High grade prostatic intraepithelial neoplasia (HGPIN) and prostatic adenocarcinoma between the ages of 20–69: an autopsy study of 249 cases. In Vivo 1994;8:439–43.